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Emerging and Practical Concepts and Controversies in Leukemias

24 April 2021

Virtual Breakout: Pediatric Leukemia Patients

APTITUDE HEALTH

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Welcome and Meeting Overview

Franco Locatelli

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Meet the Faculty

Franco Locatelli
Head of Department of Paediatric Haematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Rome. and Full Professor of Pediatrics at the Sapienza University of Rome, Italy

Lia Gore, MD
Professor and Chief of Pediatric Hematology/ Oncology/Bone Marrow Transplant
Children's Hospital Colorado and the University of Colorado School of Medicine

Oscar González Ramella, MD, PhD
Professor, Physician in Pediatric Oncology and Hematology; Chair of the Bone Marrow Transplantation Unit at Hospital Civil of Guadalajara, Jalisco, Mexico

Adriana Seber, MD
Coordinator of Pediatric Bone Marrow Transplantation Team at Hospital Samaritano Higienópolis, São Paulo, Brazil

Carlos Andrés Portilla, MD
Coordinator of Pediatric Hematology and Oncology Unit, Centro Médico Imbanaco, Cali, Colombia

María Sara Felice, MD, PhD
Director, Acute Leukemia And Lymphoma, Hospital Garrahan, Buenos Aires, Argentina

Objectives of the Program

- Understand current treatment patterns for ALL including incorporation of new technologies
- Uncover when genomic testing is being done for ALL, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in ALL as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring ALL
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies in ALL
- Review promising novel and emerging therapies in ALL

Virtual Breakout: Pediatric ALL Patients (Day 2)

Chair: Franco Locatelli

TIME UTC-3	TITLE	SPEAKER
10.00 – 10.15	Session open • Educational ARS questions for the audience	Franco Locatelli
10.15 – 10.35	First-line treatment of pediatric ALL • Presentation (15 min) • Q&A (5 min)	Lia Gore
10.35 – 10.55	Current treatment options for relapsed ALL in children including HSCT; COVID-19 considerations and vaccinations • Presentation (15 min) • Q&A (5 min)	Franco Locatelli
10.55 – 11.15	Bispecifics for pediatric ALL, focus on frontline therapy • Presentation (15 min) • Q&A (5 min)	Lia Gore
11.15 – 11.45	Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: María Sara Felice (ARG), Oscar González Ramella (MEX), Adriana Seber (BRA), Carlos Andres Portilla (COL)	Luisina Peruzzo Jorge Ramirez Melo Gustavo Zamperlini
11.45 – 12.30	Interactive Q&A and session close • Educational ARS questions for the audience	Franco Locatelli

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Educational ARS Questions

Franco Locatelli

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Q

Educational Questions Pediatric ALL

Question 1: Which of the following subsets of 1st relapse ALL patients can be considered at very high risk?

a) All patients with B-ALL relapsing within 18 months from diagnosis
b) All patients with MLL-rearranged leukemia
c) All patients with hypodiploidy
d) Each of the 3 previous subsets

Q

Educational Questions Pediatric ALL

Question 2: Which assertion is correct for children with B-ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment
b) Inotuzumab dosage is 3 mg/m^2
c) TBI-based conditioning regimen should be preferentially used in children above the age of 4 years
d) None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

Q

Educational Questions Pediatric ALL

Question 3: 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

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First-line treatment of pediatric ALL

Lia Gore

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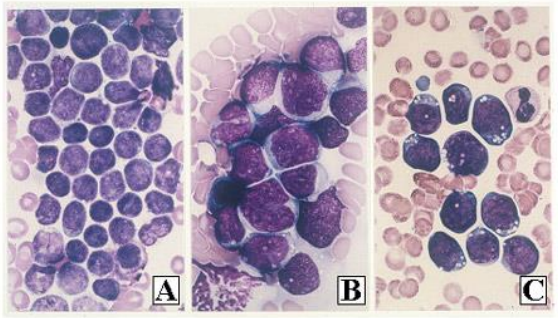
First-Line Therapy for Pediatric Acute Lymphoblastic Leukemia



Prof Lia Gore, MD

Chief, Pediatric Hematology/Oncology/Bone Marrow Transplant-Cellular Therapeutics

University of Colorado School of Medicine and Children's Hospital Colorado

Success in Treating the Most Common Childhood Cancer

- 1948 – first case of temporary remission reported by Farber et al
- Successive generations of treatment show improved outcomes
- Current regimens offer survival of 90%–99% for most patients

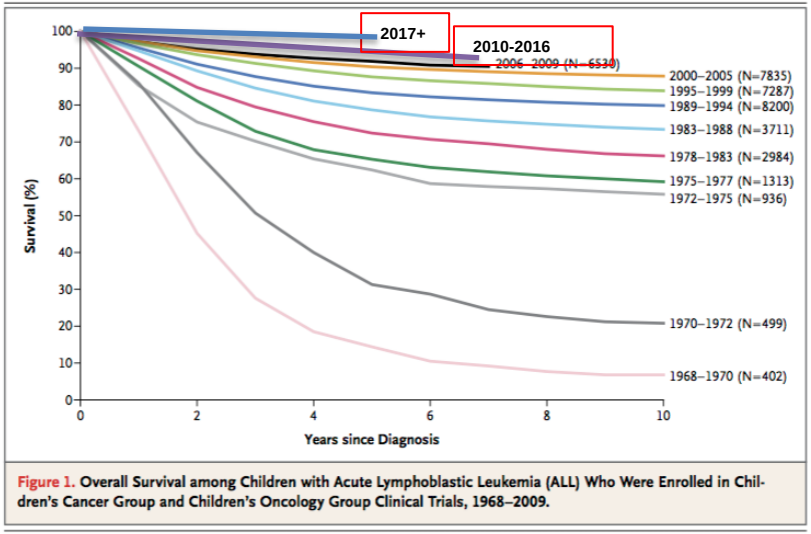
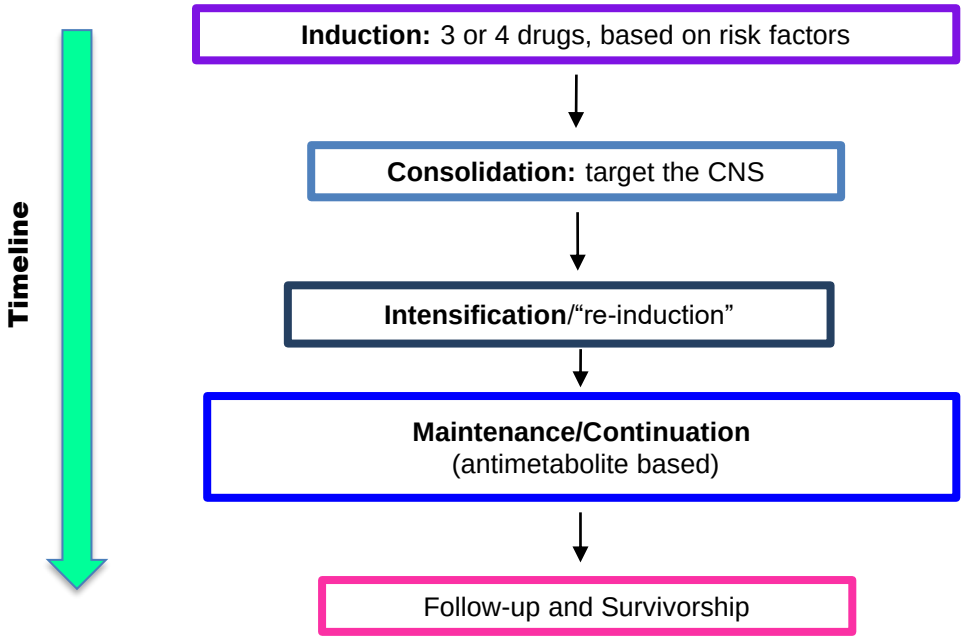


Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

Hunger SP, Mullighan CG. *N Engl J Med.* 2015;373(16):1541-1552.

Simplified Treatment of ALL at Diagnosis



COG Classification Table*

Risk Group	SR-Favorable (SR-Fav)	SR-Average (AR)		HR-Favorable (HR-Fav)	High Risk[1] (HR)					Very-High Risk (VHR)
Projected 5-year EFS	>95%	85-95%		>94%	65-92%					<65%
NCI Risk Group	SR	SR	SR	HR <10yr	SR	SR	SR	HR (except HR-Fav)	HR	HR
CNS[1]	1/2	1/2	1	1	2	Any	Any	Any	Any	Any
Cytogenetics[2]	Fav	Fav	Neut	Fav	Neut	Unfav	Any	Any	Any	Any[3]
Day 8 PB MRD (%)	<1	≥1	Any	n/a	Any	Any	Any	n/a	n/a	n/a
EOI MRD (%)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	≥0.01[4]	<0.01	≥0.01[4]	≥0.01
EOC MRD (%)	n/a	n/a	n/a	n/a	n/a	n/a	Any	n/a	<0.01	≥0.01
Total pt accrual/yr	521	348		38	598					24
Fraction of patients (%)[5]	30	20		2	35					1

*BFM has similar classification categories; efforts to facilitate data comparisons when possible.

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SR, standard risk; HR, high risk; EFS, event-free survival; CNS, central nervous system; PB, peripheral blood; MRD, minimal residual disease; EOI, end of induction; EOC, end of consolidation.

Hunger SP, et al. *Pediatr Blood Cancer.* 2013;60(6):957-963.

Outcomes for Patients With Favorable Genetics and CNS1 in Current COG Trials

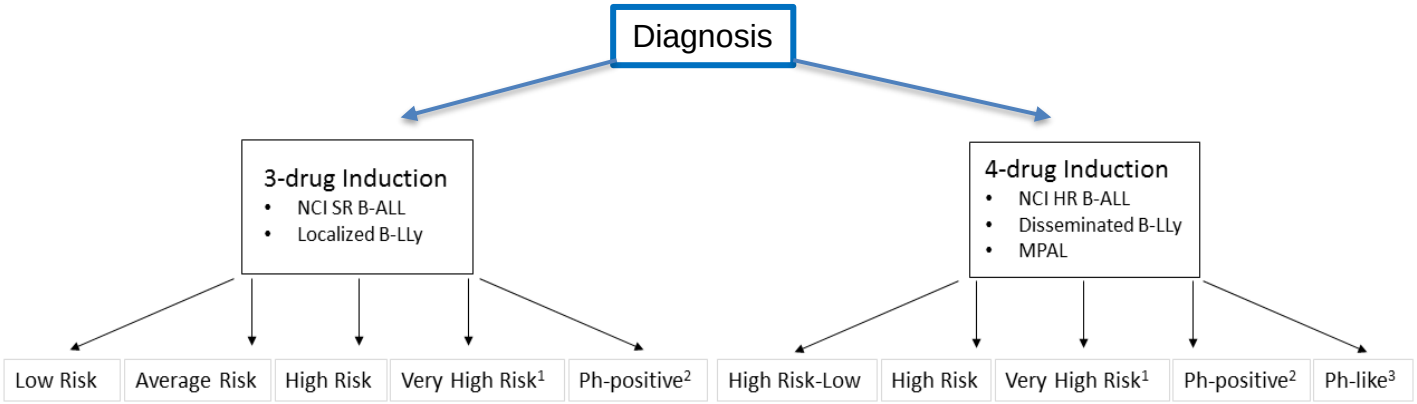
NCI Risk	Day 8 MRD	Day 29 MRD	5-Year EFS	5-Year OS	n
Standard	<1%	<0.01%	95.7%	99.1%	1129
Standard	≥1%	<0.01%	91.7%	99.4%	170
Standard	Any	≥0.01%	88.1%	96.8%	369
High	<1%	<0.01%	94.9%	98.1%	243
High	≥1%	<0.01%	93.6%	95.5%	50
High	Any	≥0.01%	75.4%	90.4%	121

	Age <10 yr N = 107 (44%)	**Age ≥10 yr** N = 136 (56%)	***P* Value**
5-year EFS	98.0%	92.4%	.126
5-year OS	98.7%	97.8%	.411

CHILDREN'S ONCOLOGY GROUP

Raetz E, et al. ASH 2015. Abstract 807.

Overall Schematic of Current ALL Therapy



Risk stratification is based on
biologic and genetic features at diagnosis and
response to induction chemotherapy.
These are the best predictors of outcome for all patients.

Induction

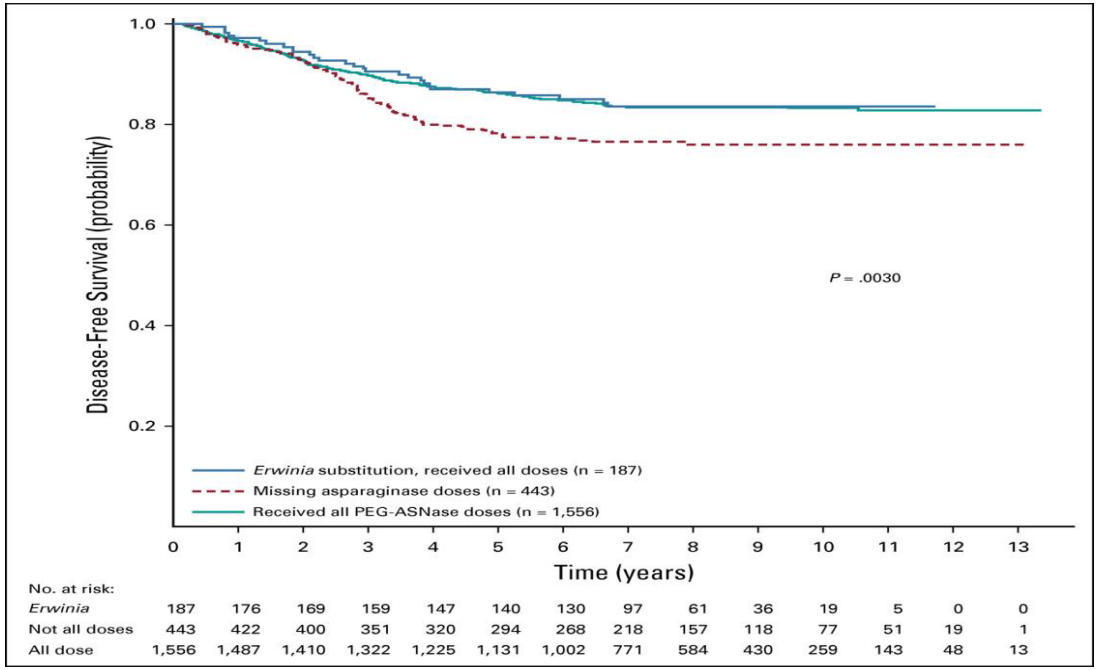
- **3-drug induction** = steroid, VCR, ASP
  - NCI Standard Risk
    - Except CNS3, testicular disease, steroid pretreatment
  - Localized B-lymphoblastic lymphoma (B-LLy)
- **4-drug induction** = steroid, VCR, ASP, + daunorubicin
  - NCI High Risk
  - NCI Standard Risk with CNS3, testicular, steroid pretreatment
  - Disseminated B-LLy
  - MPAL

Post-induction risk-stratification is based on response to induction.

Observations on the History of Frontline ALL Therapy

- Induction with steroids, vincristine, and asparaginase are key elements that, to date, cannot be removed from therapy
  - Asparaginase intensification improves outcomes in most risk groups, T-, B-, and LLy (multiple iBFM, DFCI, POG, COG trials: Amylon 1999; Silverman 2001; Pession 2005; Pieters 2011; Gupta 2020), but not in SR-low (Mattano 2014), and is not without toxicity
  - Prednisone pre-phase separates out good responders (Schrappe 1998)
- Daunorubicin increases survival for HR patients (Gaynon 1988; Nachman 1997, 1998; Veerman 2009)
- Intensified consolidation not needed for excellent outcomes in SR patients (Maloney 2013, 2019)
- Pulses of maintenance therapy cure more patients (HR = 0.54) (Conter 2007; De Moerloose 2010)
  - Type of steroid (dexamethasone vs prednisone) matters (Mitchell 2005; Larson 2016)
  - 6MP and 6TG are both effective in maintenance (Harms 2003), but 6TG leads to more VOD/SOS (Stork 2010)
- CNS therapy is essential for cure
  - Intrathecal therapy can replace cranial irradiation (Clarke 2003)
  - 24 Gy is not better than 18 Gy (Steinherz 1989; Schrappe 1998)
  - IT methotrexate can also decrease marrow relapse (Clarke 2003)
- Modern combination regimens equalize outcomes for most patients with B- and T-cell ALL
- TKIs have changed the outcome for Ph+ disease and eliminated HSCT in CR 1 for the majority of patients
- Infants with *KMT2A* rearrangements have a dismal prognosis with any regimen tested to date

Asparaginase Intensity but Not Product in HR Patients Affects Outcomes

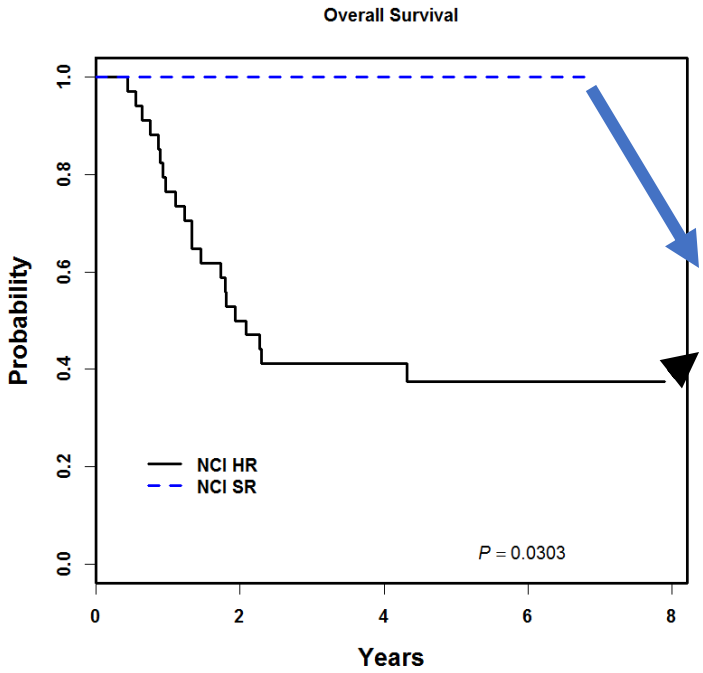


Gupta S, et al. *J Clin Oncol.* 2020;38(17):1897-1905.

3 vs 4 Drugs: Adding Daunorubicin

Evidence	Study/Trial	Daunorubicin Dose	Additional Information
Standard of Care	1. Veerman (2009) DCOG-ALL-9 2. Gaynon (1988) CCG-193P 3. Nachman (1997) 4. Nachman (1998) 5. Buchmann (2003) POG	25 mg/m^2	1. Dexamethasone. IT during induction. No infant data. HD MTX plus 2 intensification phases 2. Prednisone. CNS prophylaxis given. No infant data 3. Prednisone. IT cytarabine on day 0. No infant data 4. Prednisone. IT cytarabine on day 0. No infant data 5. Prednisone. All patients had initial therapy and developed first relapse. Infant (<1 yr) data (n = 14)
Evidence	**Study/Trial**	**Daunorubicin Dose**	**Additional Information**
Infant ALL	1. Lauer (1998) POG 8398 2. Reaman (1999) CCG-107/1883 3. Saltzer (2014) 4. Pieters (2019)	1. 0.83 mg/kg IV days 2, 8, 15, 22 2. 12.5 (<3 mo) or 25 mg/m^2 (4-11 mo) IV/week 3. 15 mg/m^2 (<7d); 20 mg/m^2 (7d to <6 mo); 22.5 mg/m^2 (6-12 mo) IV on days 8,9	1. Infants grouped <6 mo (60%) and >6 mo (40%). CNS prophylaxis given (triples) 2. Infants grouped <3 mo, 3-5 mo, 6 to <1 yr. Given intrathecal Ara-C and MTX 3. IT MTX d1, IT HC/Ara-C d15, IT MTX/HC d29
Evidence	**Study/Trial**	**Daunorubicin Dose**	**Additional Information**
Dex > Pred	1. Larson (2016) AALL0232	25 mg/m^2	Dexamethasone had superior outcome in younger children (1-9 yr) compared with prednisone. Older patients had more toxicity with Dex than Pred

Overall Survival After Induction Failure, by (M3) Marrow Status



	5-yr OS ± SE
AALL0331 (SR)	100%
AALL0232 (HR)	37.4% ± 10.5%

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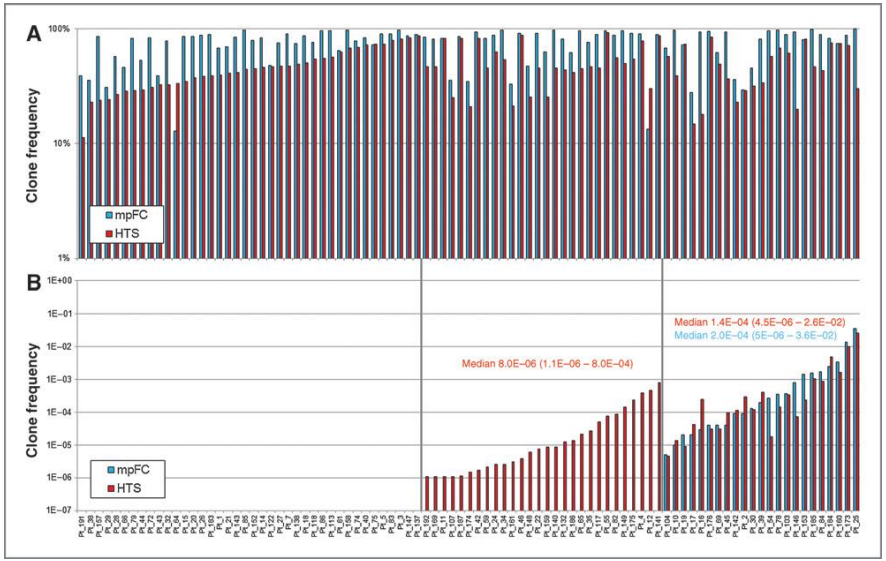
AALL0232 PI: Eric Larsen, MD
AALL0331 PI: Kelly Maloney, MD

Improving MRD Detection by Next- Generation/High-Throughput Sequencing (HTS)



Wu D, et al. *Clin Cancer Res*. 2014;20(17):4540-4548.

- HTS of clonotypic Ig/TCR rearrangements detects MRD at ~1/1,000,000 sensitivity
- Pilot study of ~300 pts from AALL0331 showed that 20% had no detectable residual clonal sequence at any level at day 29
  - HTS-neg pts had a 5-yr EFS of 98.1% and OS 100%
- Includes pts with and without favorable genetics

Kirsch SIOP 2016 and Wood ASH 2016.

Role of End-of-Induction HTS-MRD

- Conservatively estimating true EFS of HTS–MRD-undetectable patients at 96%, and accounting for 20% of AR patients, EFS of patients with detectable HTS-MRD should be ~88%
  - Wood/UW cohort – 87.4% EFS for an approximately equivalent population
- Patients with non-informative HTS had a 5-year EFS of 78.5% (included NCI HR patients)
- From COG 0331 (SR) and 0232 (HR) samples, HTS detected dominant clone in 93.2% of patients
  - Among SR patients, 19.9% had no detectable residual clonal sequence at any level at EOI; these patients had an outstanding EFS of 98.1% ± 0.2%
- Proportion of undetectable samples did not vary between cytogenetic risk groups (so, likely similar among SR/AR patients)

HTS-MRD, minimal residual disease assessed by high-throughput sequencing.

Observations on the History of Frontline ALL Therapy

- Cytogenetic and molecular abnormalities/variations matter
  - *KMT2A*, Ph+/*BCR-ABL*, Ph-like, *ETV6-RUNX1*, triple trisomy, high hyperdiploidy iAMP21, *TCF-PBX1*, *CRLF2*, and severe hypodiploidy all confer different prognostic implications
    - Impact of advancing technology on treatment and outcomes
    - Changing role of HSCT in the frontline
- MRD matters[1-3]
  - Lower is better; none is best – but by what method?
- Many patients with ALL can be cured with simple therapy[4,5]
  - 4–6 weeks of 3-drug induction
  - Appropriate CNS prophylaxis
  - Pulses of maintenance therapy
- Escalating MTX improves outcomes for some patients
- Addition of rituximab (GRAALL 2005) improves outcomes for adults[6]; pediatric outcomes unknown
- Adding anthracycline during induction plus 4 weeks of CPM/Ara-C/6-MP consolidation therapy or 8 weeks of delayed intensification (Protocol IIa + IIb) cures another ~10% of patients
- A major cause of morbidity and mortality in children with ALL is treatment-related toxicity and late effects. **HOW DO WE REDUCE TOXICITY YET MAINTAIN GOOD OUTCOMES??**

AR, average risk; SR, standard risk.

1. van Dongen 1998; 2. Coustan-Smith 2000; 3. Borowitz 2008; 4. Kirsch SIOP 2016; 5. Wood ASH 2016; 6. Maury 2016.

What About Lymphoblastic Lymphoma?

ALL-focused regimens are often used to treat HR B-cell or T-cell ALL and lymphoblastic lymphoma – often on the same protocol or on an arm of an ALL protocol

- Several trials have compared various ALL or lymphoma regimens
  1. LSA212 vs COMP (non-daunorubicin regimen)
  2. LSA212 vs A-COP+ (adriamycin)
  3. Daunorubicin in NHL-BFM-86 was the same in both arms

Regimen Used	Daunorubicin Dose (Regimen)	Other Drugs Used During Induction (Regimen)
1. NHL-BFM-86	1. 30 mg/m^2 weekly	1. Prednisone, vincristine, L-asparagine with MTX
2. NHL-BFM-95	2. 30 mg/m^2 weekly	2. Prednisone, vincristine, L-asparagine with MTX, 6-MP, Ara-C, cyclophosphamide
3. UKCCSG 86	3. 45 mg/m^2 days 1, 2 (weekly)	3. Prednisone, vincristine, L-asparagine with MTX
4. LSA212	4. 60 mg/m^2 days 12, 13	4. Prednisone, vincristine, L-asparagine with Ara-C and cyclophosphamide

- Many study investigators anticipate that the LLy arm will not achieve statistical significance for an endpoint, but data are gathered and reported in final outcomes
- Data collected and reported on these trials support the findings of ALL outcomes with some differences
  - To date, there is no equivalent to MRD as a prognostic indicator in ALL
  - Most patients with LLy do quite well with combination regimens as above

Continued Need to Improve AR/SR ALL Outcomes

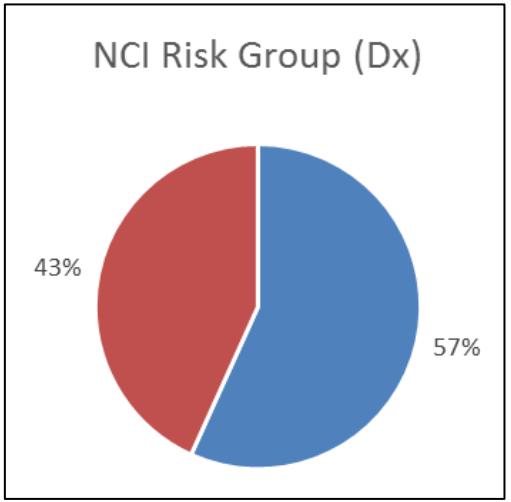
- ~600 NCI HR and ~1200 NCI SR patients enroll on COG trials each year

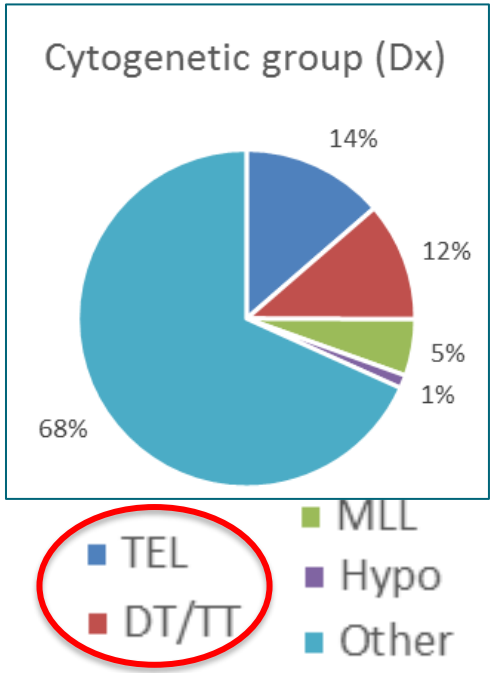
- Despite better outcome, SR pts contribute about half of treatment failures
  - 5-year EFS rate 77% for HR ALL (AALL0232) and 89% for SR ALL (AALL0331)
  - For every 1000 B-ALL patients, there are ~77 events among HR patients and ~73 events among SR patients

- Improving EFS for SR (and particularly AR) patients will therefore significantly reduce the overall burden of relapse in ALL

AR, average risk; SR, standard risk.

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





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Brown PA, et al. on COG AALL1331.

Status of Immunotherapy for ALL in the Frontline

- Cooperative groups worldwide 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
  - Biologic and genetic features of leukemia cells
  - Response kinetics
  - Surrogate and biomarkers of efficacy

Clinical Trial Questions in COG: Introduction of Molecularly or Immunologically Targeted Therapy in B-ALL

	Risk Group	Projected 5-yr DFS	Therapeutic Question	COG Study Number
33%	SR-Favorable	>95%	Standard therapy with 2-year duration of maintenance therapy for boys and girls	AALL173 and AALL173 2
2%	HR-Favorable	>94%		
32%	SR-Avg & High	~89%	Blinatumomab	AALL1731
27%	High Risk	~80%	Inotuzumab	AALL1732
2%	Very High Risk	<50%	CD19 CAR T-cell therapy	AALL1721
5%	Ph+, Ph-like	60%–85%	Molecularly targeted therapy	AALL1631 and 1521

Randomized

- **All patients on AALL1731 and AALL1732 receive q12-week pulses of VCR/steroid**
- **All boys and girls on AALL1731 and AALL1732 receive therapy for 2 years from the phase that starts after consolidation**

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International Cooperation Is Essential


Cancer Center
UNIVERSITY OF COLORADO

Global Leukemia Academy

Current treatment options for relapsed ALL in children, including HSCT; COVID-19 considerations and vaccinations

Franco Locatelli

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Current treatment options for relapsed ALL in children, including HSCT; COVID-19 considerations and vaccinations

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Disclosures

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

Relapsed ALL in Childhood:
Background

RELAPSE RATE:

Approximately 15%–20% of children with ALL relapse after standard treatment[1]

PROGNOSIS OF RELAPSED ALL LARGELY DEPENDS ON[2-6]

- ✓ Time from diagnosis to relapse
- ✓ Site of relapse
- ✓ Blast immune-phenotype

Almost all children with relapsed T-ALL and 2/3 of those with BCP-ALL are candidates for alloHSCT after a second morphologic complete remission (M1 marrow) is achieved[7-8]

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplant.

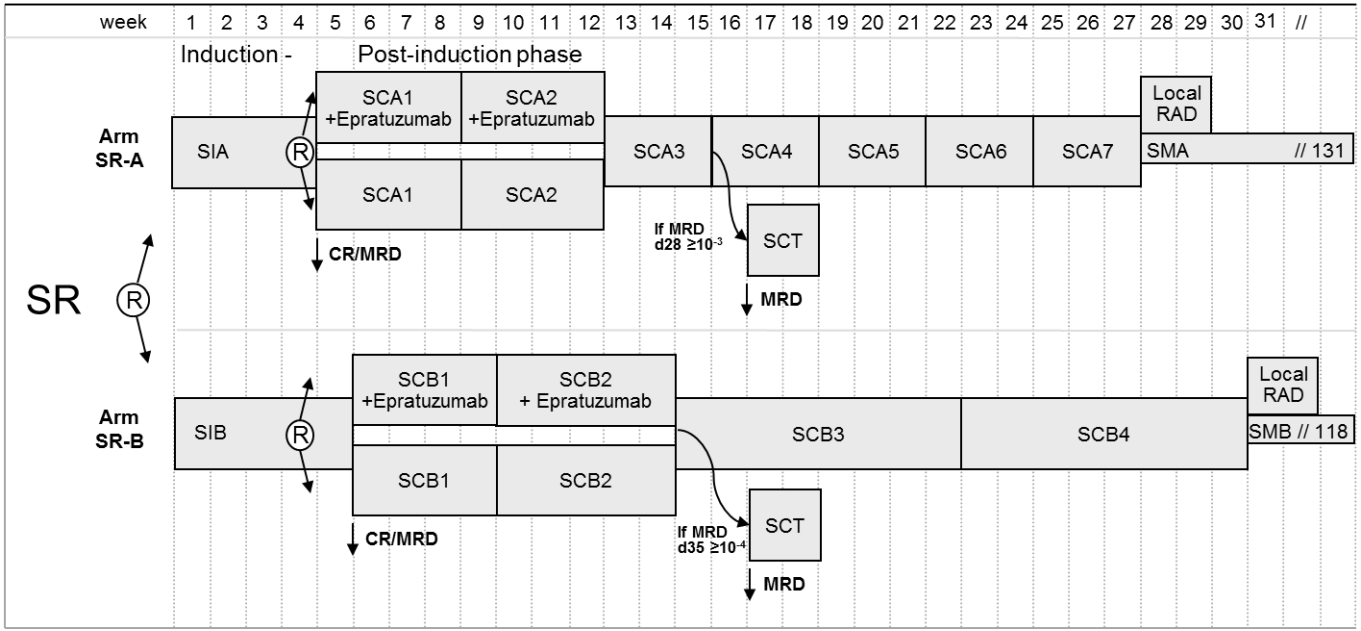
1. Hunger SP, Mullighan CG. *N Engl J Med.* 2015;373:1541-1552; 2. Chessells JM, et al. *Br J Haematol*. 2003;123:396-405; 3. Irving JA, et al. *Blood.* 2016;128:911-922; 4. Krentz S, et al. *Leukemia.* 2013;27:295-304; 5. Malempati S, et al. *J Clin Oncol.* 2007;25:5800-5807; 6. Schrappe M, et al. *N Engl J Med.* 2012;366:1371-1381; 7. Locatelli F, et al. *Blood.* 2012;120:2807-2816; 8. Peters C, et al. *J Clin Oncol.* 2015;33:1265-1274.

IntReALL:
Definition of Strategy Groups SR and HR

Immuno-phenotype	B-cell precursor			(pre) T		
Time Point/Site	Extra-med. isolated	Bone marrow combined	Bone marrow isolated	Extra-med. isolated	Bone marrow combined	Bone marrow isolated
Very early	**HR**	**HR**	**HR**	**HR**	**HR**	**HR**
Early	**SR**	**SR**	**HR**	**SR**	**HR**	**HR**
Late*	**SR**	**SR**	**SR**	**SR**	**HR**	**HR**

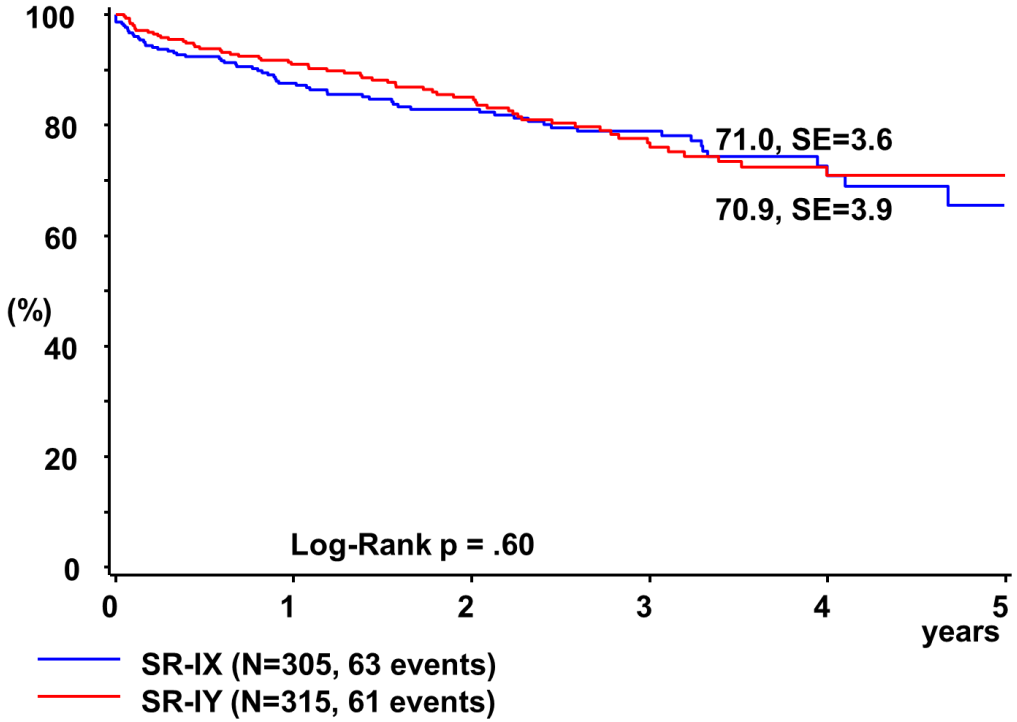
*Late defined as: >6 months after cessation of frontline therapy, ie, >30 months after initial diagnosis.
SR, standard-risk group; HR, high-risk group.
ClinicalTrials.gov NCT03590171

IntReALL SR 2010:
Treatment Schedule Overview

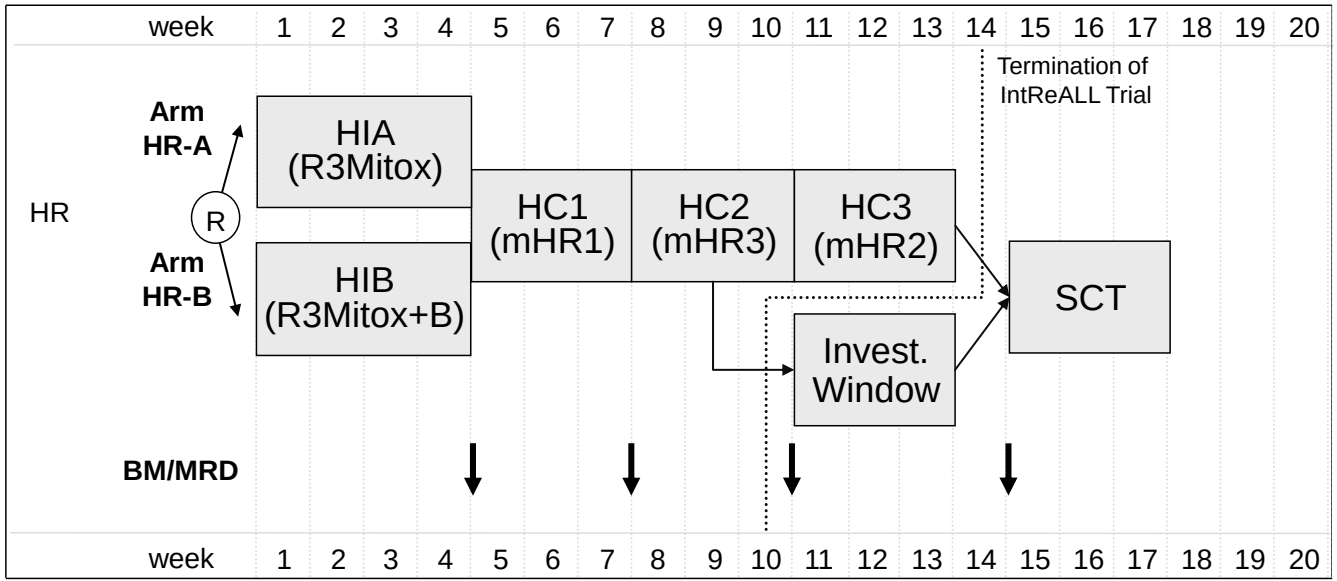


Arrow down (↓), bone marrow puncture with CR/MRD assessment.
MRD, minimal residual disease; R, randomization; RAD, irradiation, if indicated; SCA/B, SR consolidation arm A/B; SCT, stem cell transplantation; SIA/B, SR induction arm A/B; SMA/B, SR maintenance arm A/B; SR, standard-risk group.
ClinicalTrials.gov NCT01802814.

IntReALL SR 2010:
EFS by First Randomization (4 years, 10/2020)



IntReALL HR 2010:
Design



HR, high-risk group; R, randomization, HIA/B, high-risk induction arm A/B; R3Mitox, ALL-R3 mitoxantrone regimen; B, bortezomib; HC, high-risk consolidation; SCT, stem cell transplantation; BM, bone marrow; MRD, minimal residual disease.
ClinicalTrials.gov NCT03590171.

IntReALL-BCP 2020:
New Risk-Stratification

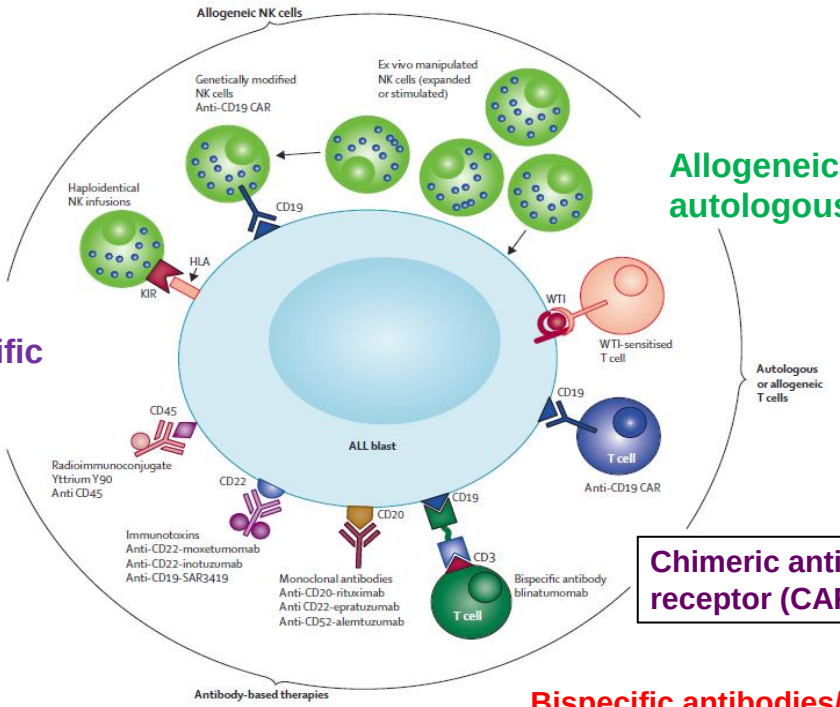
VHR (15%) Eligible for allo-HSCT or consolidation therapy

- ***TP53* alteration**
- **Hypodiploidy**
- **T(1;19)/(17;19)**
- **MLL/AF4**
- **Very early relapse (<18 mo)**

SR (60%) Late isolated or combined medullary/extramedullary relapse (allo-HSCT depending on MRD response at the end of induction)

HR (25%) Early isolated or combined medullary/extramedullary relapse (all these patients are candidates to receive allo-HSCT as final consolidation)

New Immunologic Approaches Under Investigation in Childhood ALL



Allogeneic and autologous NK cells

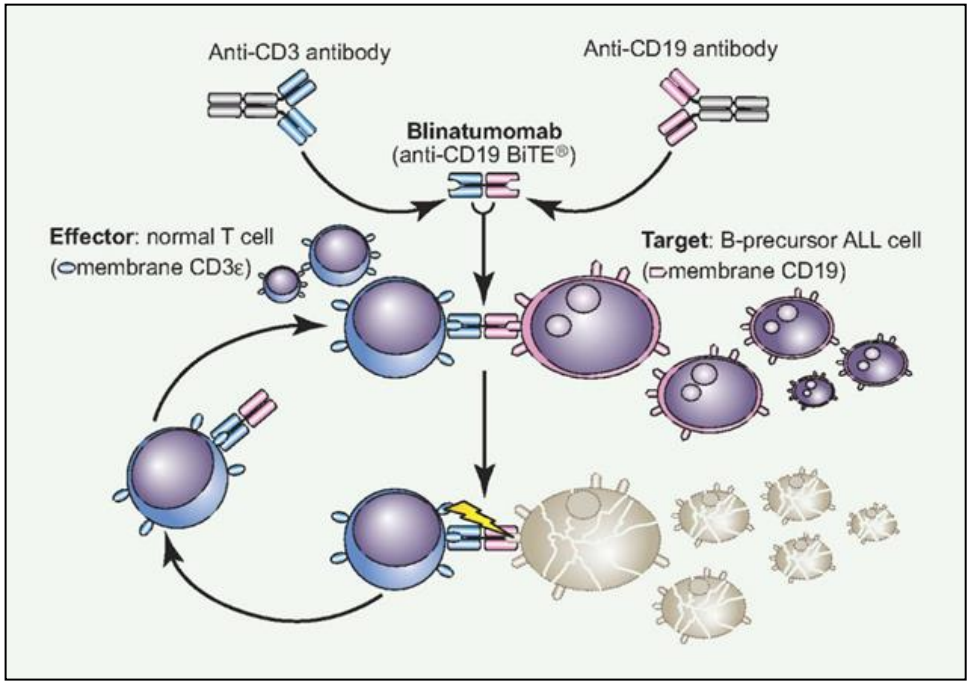
Immunotoxin-specific antibodies

Chimeric antigen receptor (CAR) T cells

Bispecific antibodies/antibody constructs

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

Blinatumomab (CD19 BiTE)



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

In multiple-relapsed/refractory setting (pediatrics)[1]

- CR 35%–40%
- MRD-negative CR 20%–25%

In MRD-positive setting (adults)[2]

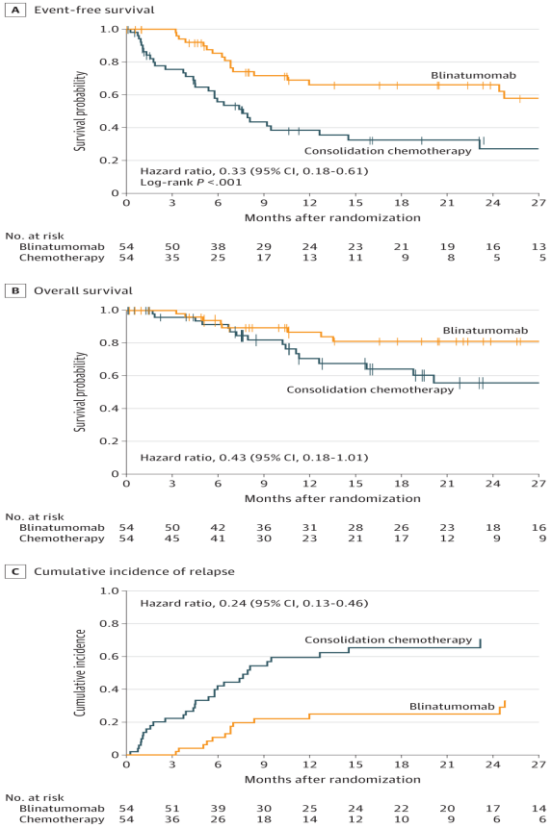
- 80% MRD clearance
- 60% subsequent DFS (bridge to HSCT)

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

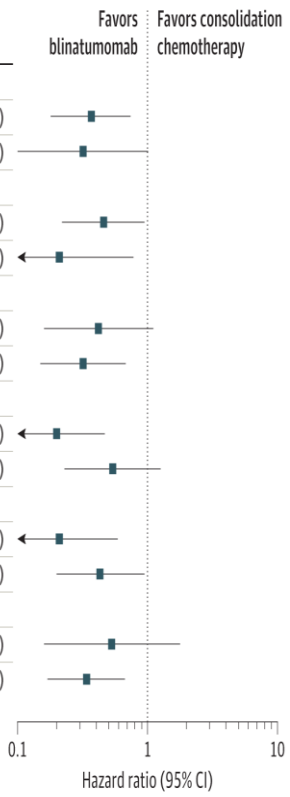
JAMA Network™

From: Locatelli F, et al. **Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial**

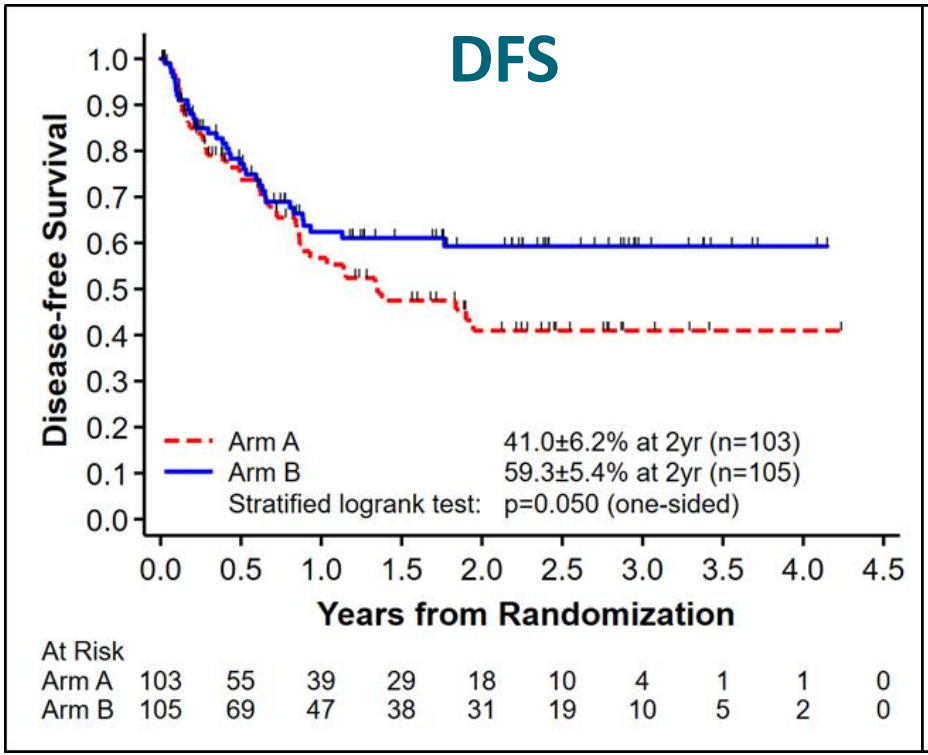
JAMA. 2021;325:843-854. doi:10.1001/jama.2021.0987

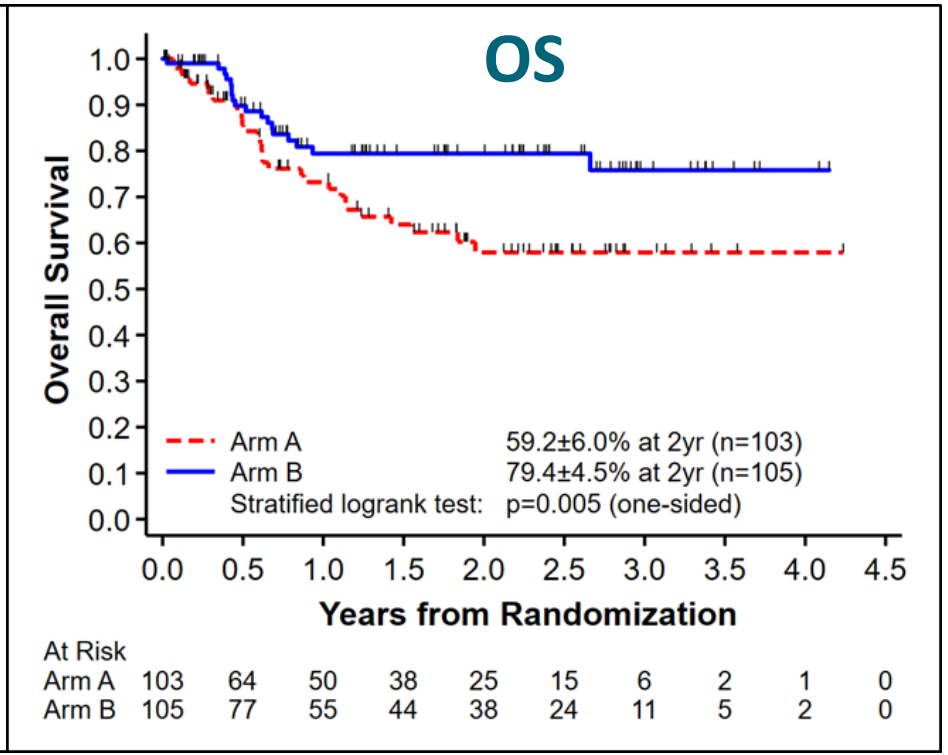


Subgroup	No. of events/No. treated (%) Blinatumomab	Consolidation chemotherapy	Hazard ratio (95% CI)
Age, y			
1-9	12/39 (30.8)	23/38 (60.5)	0.37 (0.18-0.74)
>9	5/15 (33.3)	8/16 (50.0)	0.32 (0.10-1.01)
Minimal residual disease at end of induction			
$<10^{-3}$ Blast cells	12/35 (34.3)	19/34 (55.9)	0.46 (0.22-0.95)
$\geq 10^{-3}$ Blast cells	3/15 (20.0)	9/16 (56.3)	0.21 (0.05-0.78)
Minimal residual disease before treatment start			
$<10^{-4}$ Blast cells	6/25 (24.0)	13/26 (50.0)	0.42 (0.16-1.11)
$\geq 10^{-4}$ Blast cells	11/29 (37.9)	18/28 (64.3)	0.32 (0.15-0.68)
Sex			
Male	9/30 (30.0)	14/22 (63.6)	0.20 (0.08-0.47)
Female	8/24 (33.3)	17/32 (53.1)	0.54 (0.23-1.26)
Time to relapse, mo			
<18	6/19 (31.6)	14/22 (63.6)	0.21 (0.07-0.59)
≥18 and ≤30	10/32 (31.3)	17/28 (60.7)	0.43 (0.20-0.95)
Extramedullary disease at relapse			
Yes	4/10 (40.0)	8/14 (57.1)	0.53 (0.16-1.78)
No	13/44 (29.5)	23/40 (57.5)	0.34 (0.17-0.67)



Survival: Arm A (chemotherapy) vs Arm B (blinatumomab)

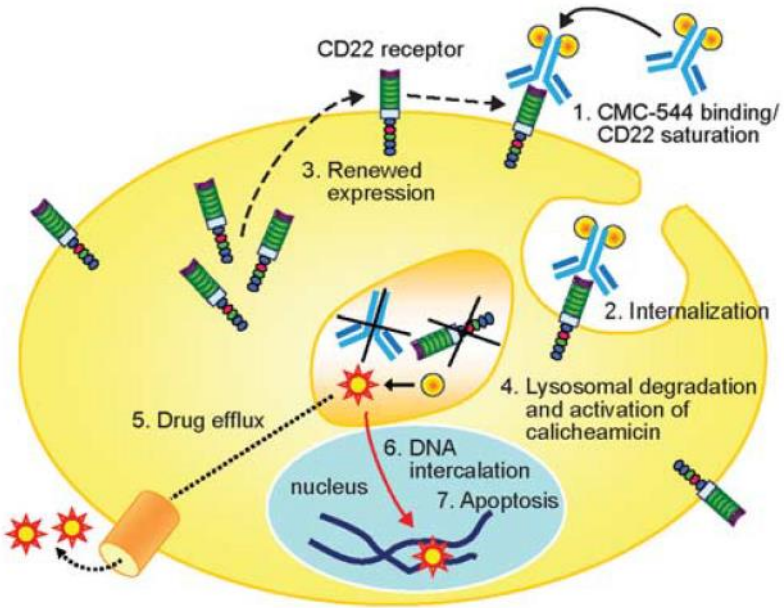




Median follow-up 1.4 years

Locatelli F, et al. *JAMA.* 2021;325:843-854.

Inotuzumab Ozogamicin (CMC-544)



Proposed mechanism of action of CMC-544:

1. Binding of CMC-544 to CD22 receptors at the cell surface of target cells
2. Internalization of the CMC-544–CD22 receptor complex
3. Renewed expression of CD22 receptors at the cell surface, which enables binding and internalization of new CMC-544 leading to intracellular accumulation of calicheamicin
4. Fusion of the CMC-544–containing endosome with a lysosome, which will lead to degradation of the acid-labile linker, and release of inactive calicheamicin. Via a thiol-modification step, active calicheamicin is formed
5. Active calicheamicin may be removed from the cell by drug efflux pumps
6. DNA intercalation and ds DNA break formation by free calicheamicin entering the nucleus
7. Apoptosis induction due to irreversible DNA damage

de Vries JF, et al. *Leukemia*. 2012;26:255-264.

Patient Characteristics

Characteristic	n=25
Age, years; median (range)	11 (1.7–16.9)
Age category, n (%)	
>1– ≤2 years	1 (4)
>2– ≤6 years	4 (16)
>6 years	20 (80)
Gender, n (%)	
Male	17 (68)
Female	8 (32)
Bone marrow status at screening, n (%)	
M3	22 (88)
M2	3 (12)
White blood cell count at screening, per L; median (range)	3.5×10^9 ($0.19–8.59 \times 10^9$)
Disease status at enrolment	
1st relapse after HSCT	7 (28)
≥2nd relapse	15 (60)
Refractory	3 (12)

Characteristic	n=25
Number of prior treatments; median (range)	2 (2–7)
Specific elements of prior treatment, n (%)	
Prior HSCT	14 (56)
Prior blinatumomab	6 (24)
Prior CAR-T	1 (4)
CD22 expression at screening	
CD22-positive ALL cells, MFI; median (range)	2768 (505–8370)
CD22-positive blasts; % (range)	98 (53–100)
Cytogenetic subtype, n (%)[a]	
Hypodiploid	4 (16)
Hyperdiploid	13 (52)
t[1;19](q23;p13)	2 (8)
t[4;11](q21;q23)	1 (4)
Normal cytogenetics	4 (16)
Not done	1 (4)

[a]Note: patients can have both hypodiploidy and a translocation

ALL, acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell; HSCT, hematopoietic stem cell transplant; MFI, mean fluorescence intensity

Brivio E, et al. *Blood.* 2020;137:1582-1590.

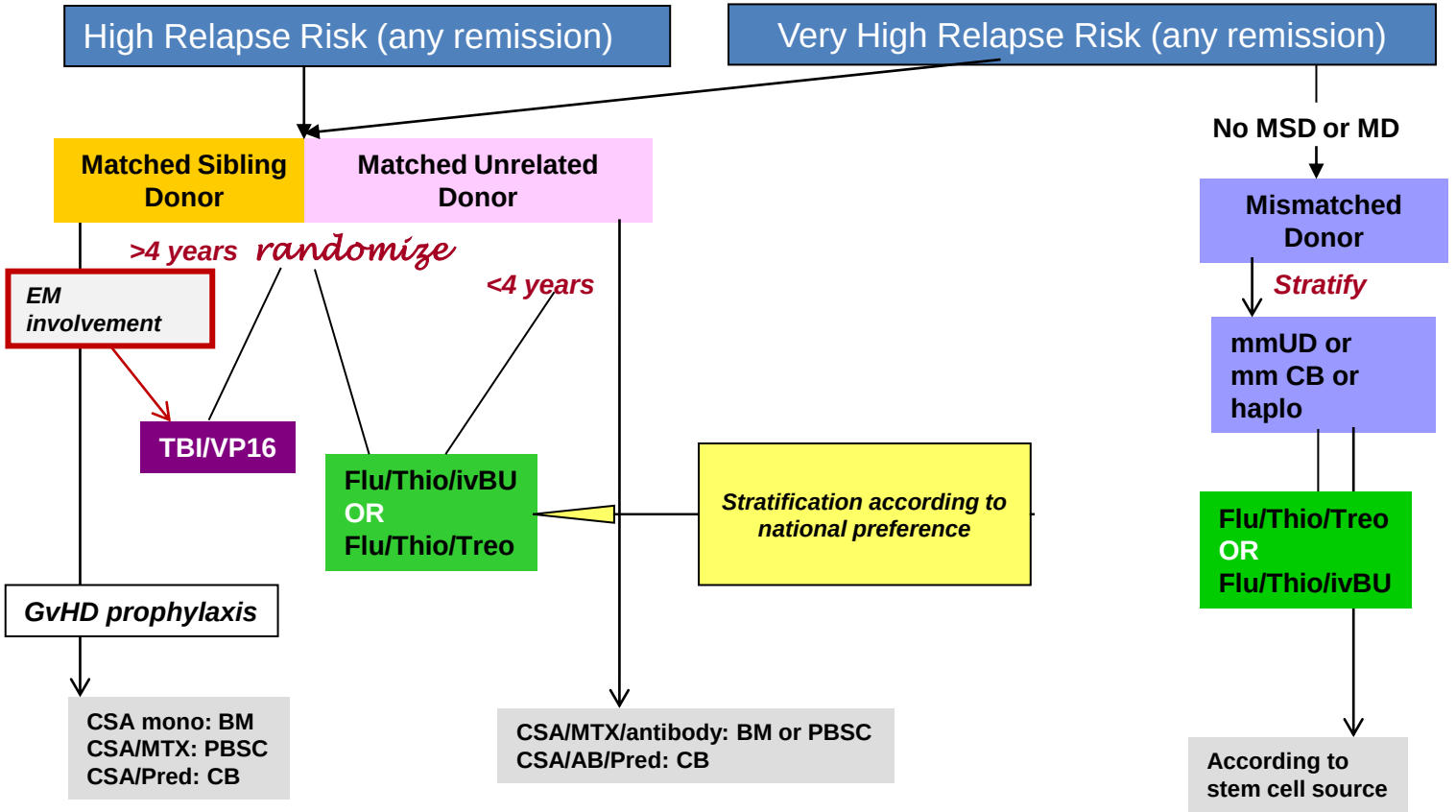
Results (n = 20)

ORR After 1 Course	80% 75% at DL1 85% at DL2 (CR n = 15, CRp n = 1, CRi n = 4)
Achievement of MRD negativity	79% (n = 15)
Median FU	13.3 mo (range 1.1−14.0)
Median duration of response	8 mo (range 1.1−14.0)
6-mo EFS/OS	63.3% (95% CI: 45.8−87.6) 66.7% (95% CI 47.9-93.0)
12-mo EFS/OS	33.4% (95% CI: 16.5−67.4) 38.7% (95% CI: 21.3–70.4)

- 8 patients received a consolidation treatment with HSCT (n = 6) or CAR T cells (n = 2; median of 61 days [range 23-125] after the last InO dose)
- 2/13 patients with available samples showed CD22 negativity at relapse

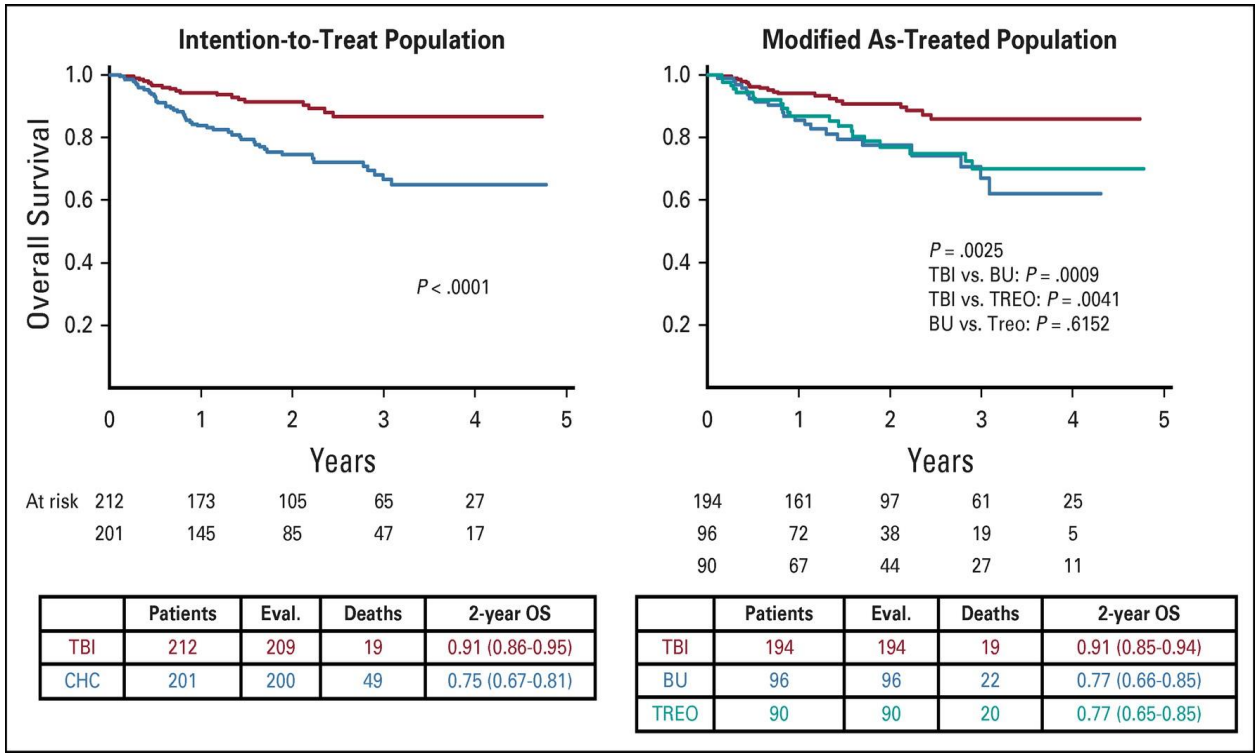
Brivio E, et al. ASH 2019. Abstract 2629.

The Role of the Conditioning Regimen in HSCT for Childhood ALL: The FORUM Trial



Peters C, et al. *J Clin Oncol*. 2021;39(4):295-307.

Primary Endpoint: Overall Survival

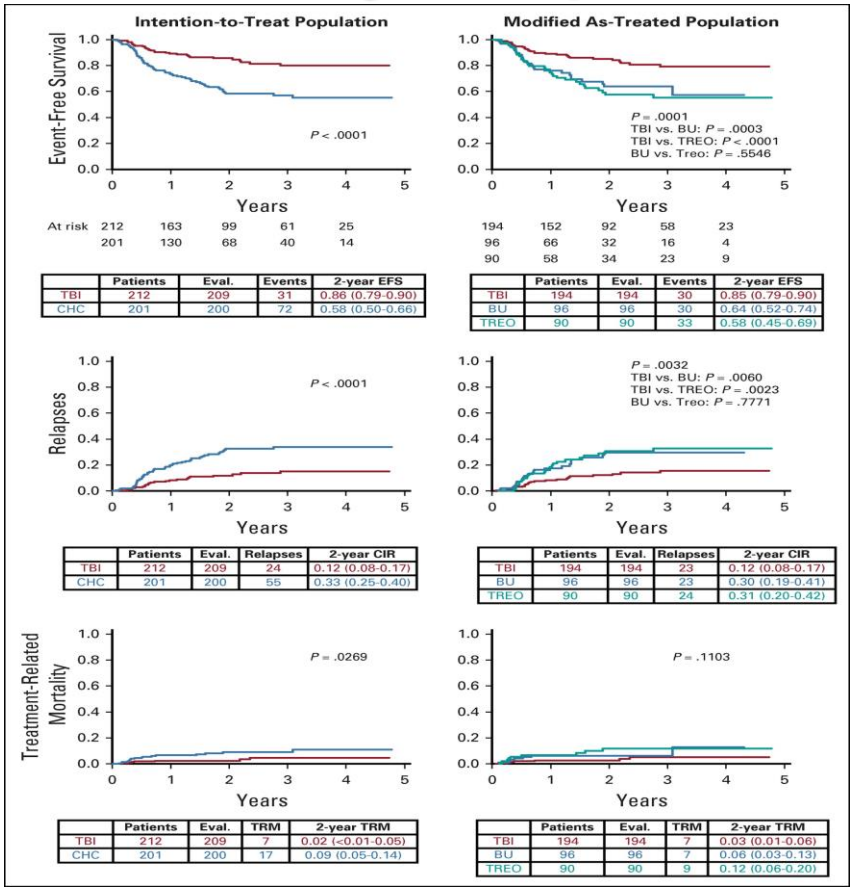


	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

BU, busulfan; CHC, chemo-conditioning; CIR, cumulative incidence of relapse; EFS, event-free survival; OS, overall survival; TBI, total body irradiation; TREO, treosulfan; TRM, treatment-related mortality.
Peters C, et al. *J Clin Oncol.* 2021;39(4):295-307.

Secondary Endpoints

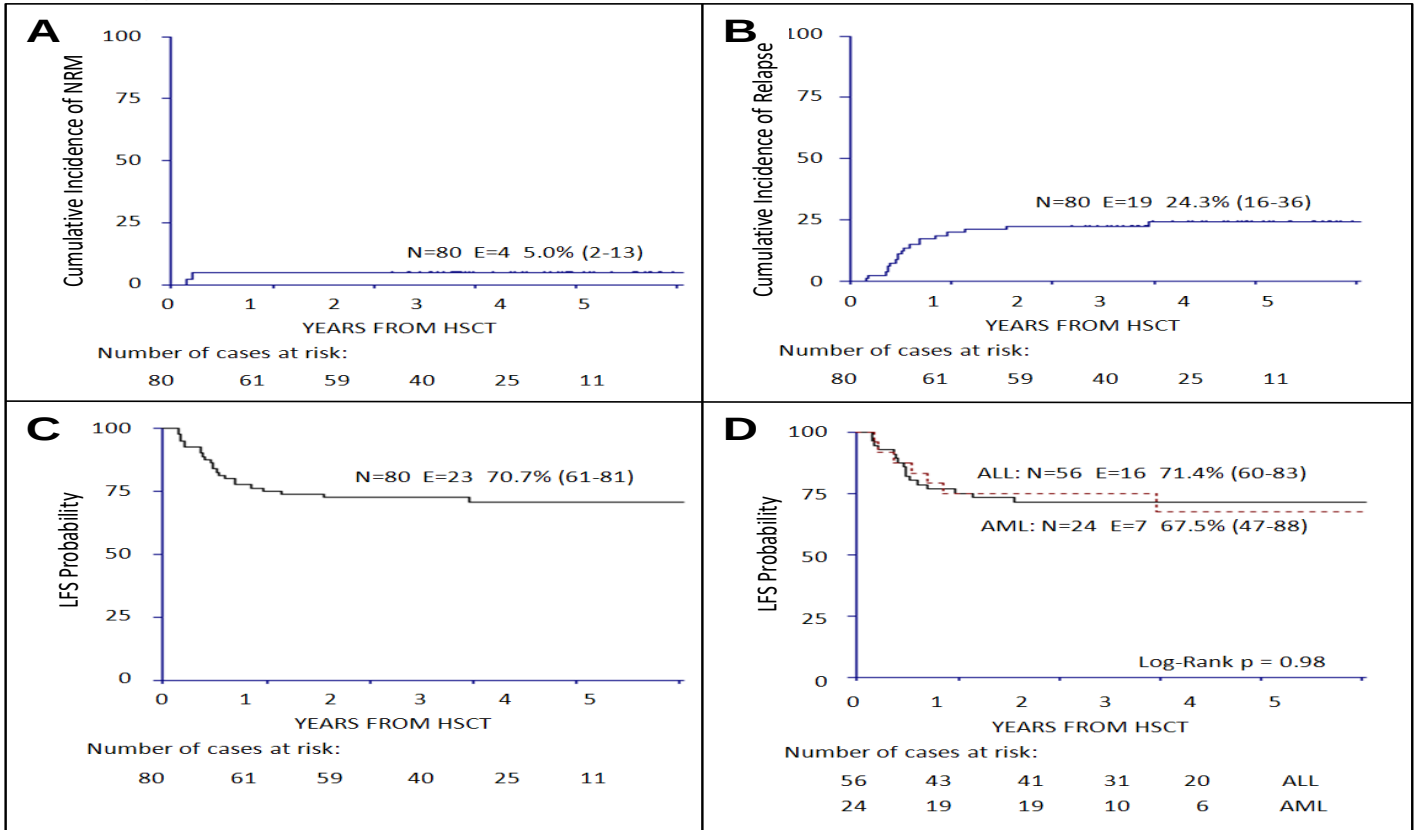


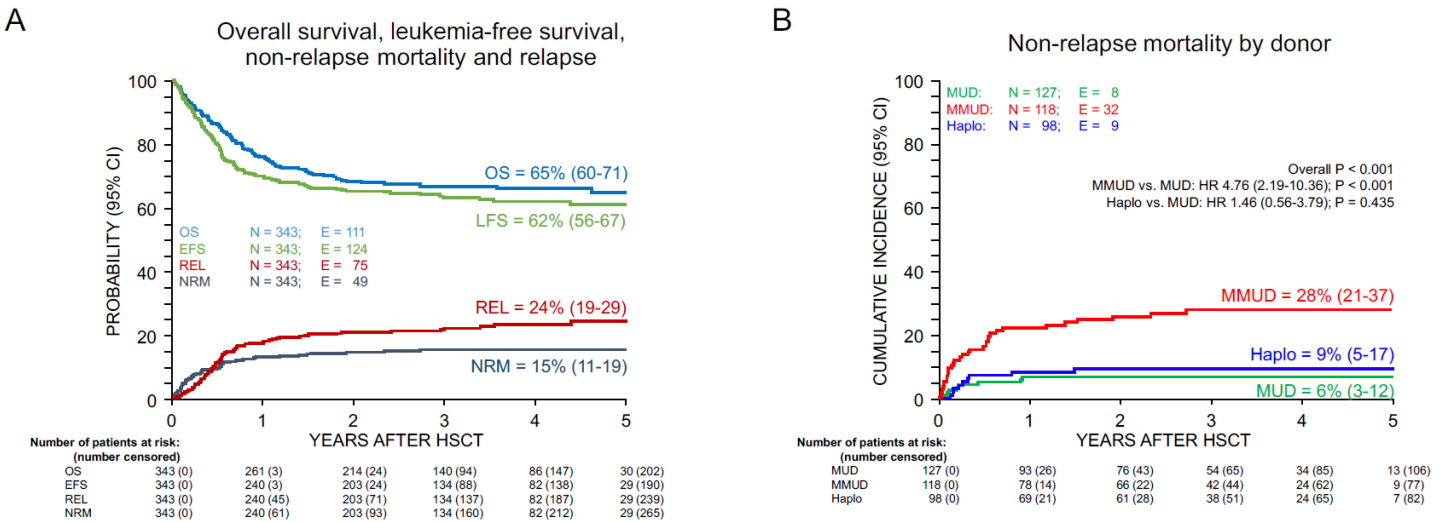
BU, busulfan; CHC, chemo-conditioning; CIR, cumulative incidence of relapse; EFS, event-free survival; OS, overall survival; TBI, total body irradiation; TREO, treosulfan; TRM, treatment-related mortality.
Peters C, et al. *J Clin Oncol.* 2021;39(4):295-307.

Regular Article blood

Outcome of children with acute leukemia given HLA-haploidentical HSCT after αβ T-cell and B-cell depletion

Franco Locatelli,[1,2] Pietro Merli,[1] Daria Pagliara,[1] Giuseppina Li Pira,[1] Michela Falco,[3] Daniela Pende,[4] Roberto Rondelli,[5] Barbarella Lucarelli,[1] Letizia Pomponia Brescia,[1] Riccardo Masetti,[5] Giuseppe Maria Milano,[1] Valentina Bertaina,[1] Mattia Algeri,[1] Rita Maria Pinto,[1] Luisa Strocchio,[1] Raffaella Meazza,[4] Lavinia Grapulin,[6] Rupert Handgretinger,[7] Alessandro Moretta,[8] Alice Bertaina,[1,*] and Lorenzo Moretta[9,*]

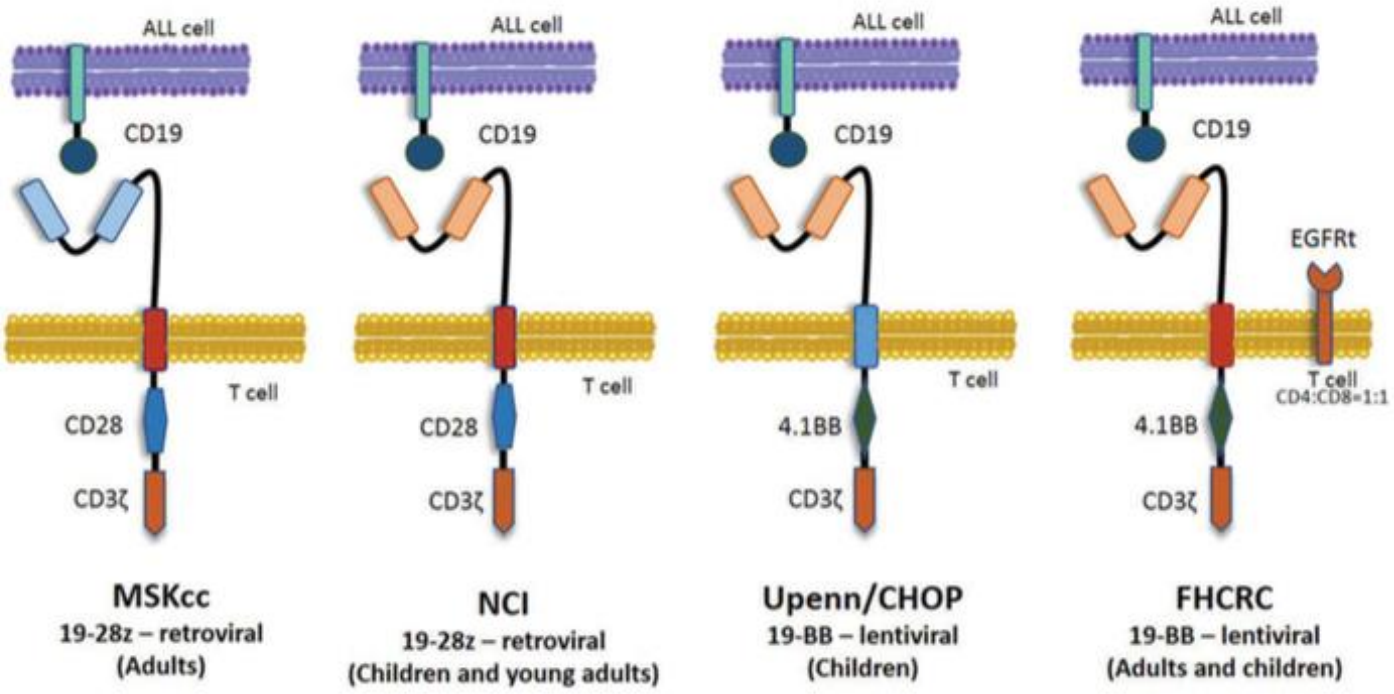




Bertaina A, et al. *Blood*. 2018;132:2594-2607.

Published Constructs of Second-Generation CD19 CARs for ALL

CAR design important for persistence and sustained efficacy



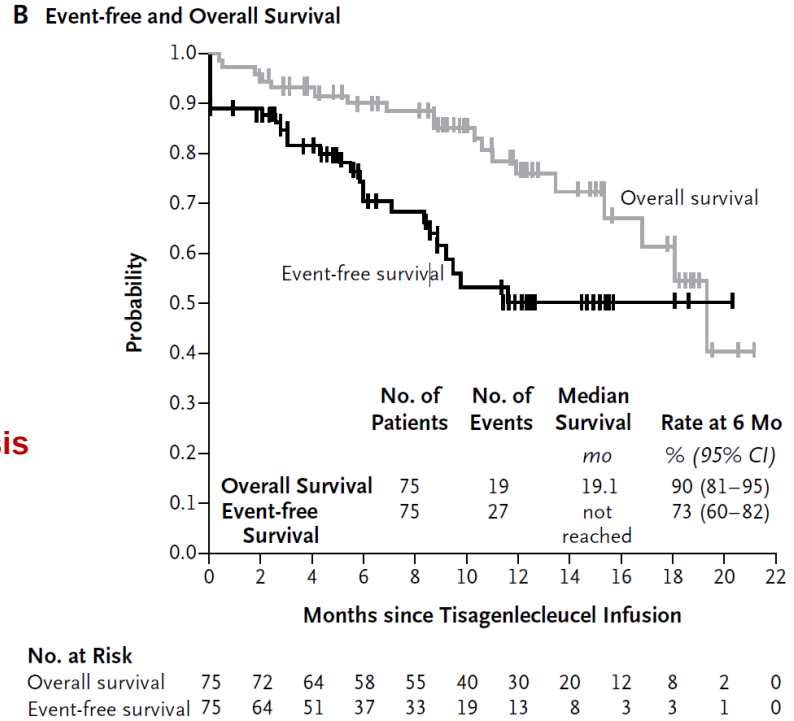
Del Bufalo F, Locatelli F, et al. *Expert Rev Clin Immunol.* 2019;15:497-509.

Summary of ELIANA Study

ORIGINAL ARTICLE

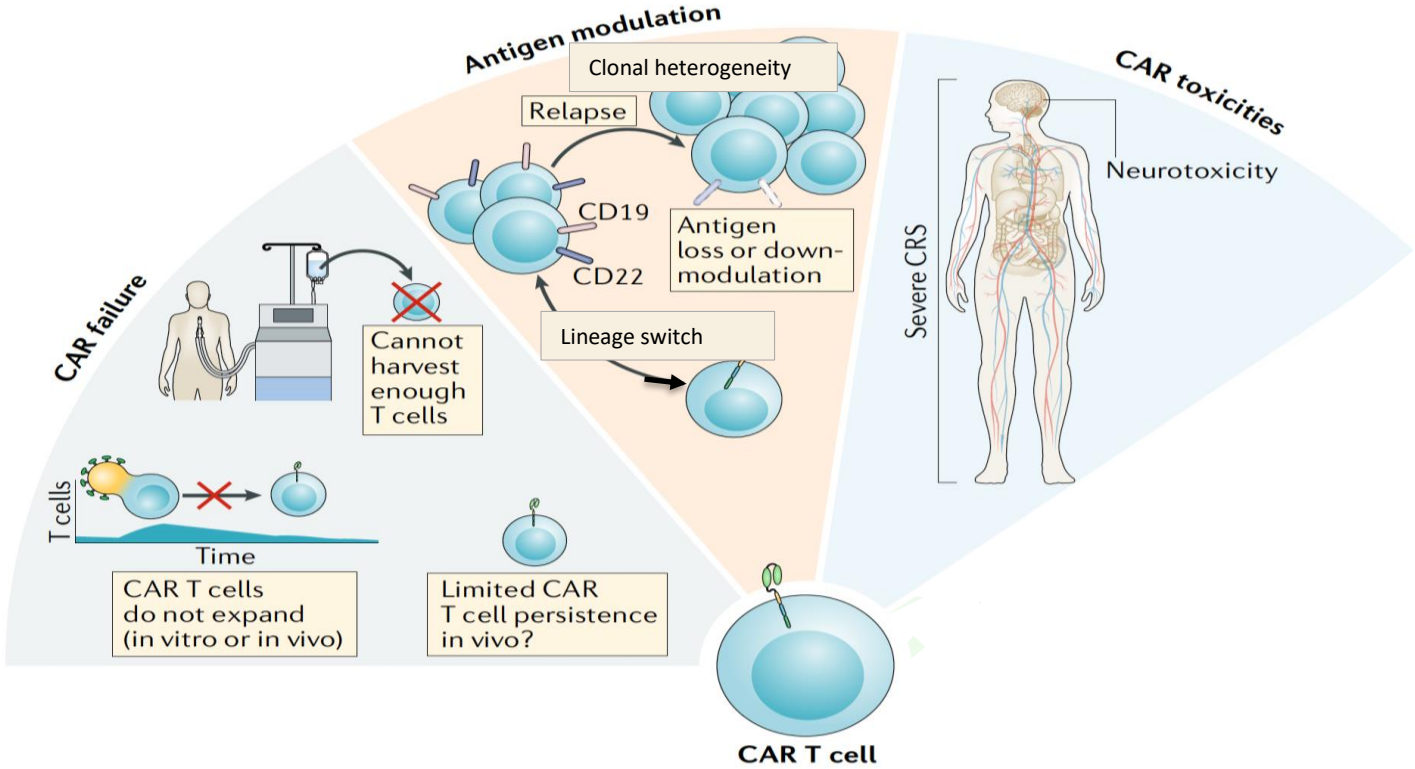
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

- 92 patients enrolled, 75 treated
- 73% of grade 3–4 AEs related to CAR T
- **81% → CR/CRi, all MRD negative; 66% in intention-to-treat analysis**
- 1-year EFS at 50%; no relapses after this
- **Demonstrates feasibility of delivery in multiple centers**
- **FDA approval for R/R pediatric ALL: August 2017**
- **Also approved in the EU, Canada, and Switzerland**



Maude SL, et al. *N Engl J Med*. 2018;378:439-448; KYMRIAH™ (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.

Current Limitations of CAR T Cells



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

Results: Patient Baseline Characteristics

Baseline Characteristic	Pediatric ALL (N = 255)
Median age, years (range)	13.2 (0.41-26.17)
<3 years	15 (5.9)
Male/Female, n (%)	150 (58.8)/105 (41.2)
Disease status at CT, n (%)	
Primary refractory/relapse	159 (62.3)
Morphologic CR	95 (37.2)
Unknown	1 (0.5)
≥5% blasts in marrow prior to CT, n (%)	84 (33)
MRD negative/positive prior to CT[a], %	46/53
Median time from leukapheresis acceptance to infusion, days (range)	33 (21-91)
Median time of follow-up since infusion, month (range)	13.4 (3.5-27.9)

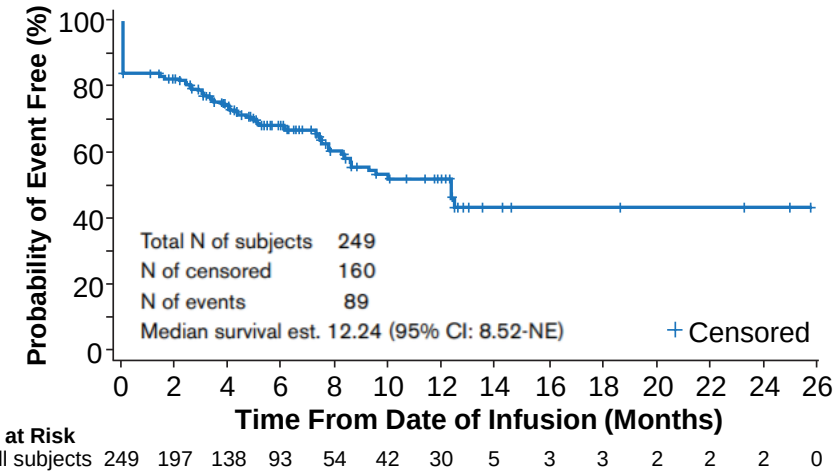
Baseline Characteristic	Pediatric ALL (N = 255)
Prior CNS involvement, n (%)	24 (9.4)
Number of prior therapies, median (range)	3 (0-15)
Prior alloSCT, n (%)	71 (27.8)
Prior blinatumomab, n (%)	38 (14.9)
Prior inotuzumab, n (%)	27 (10.6)
Down syndrome, n (%)	12 (4.7)

- Median time from ALL diagnosis to CAR T-cell infusion was 32 months
- The median follow-up of patients with ALL was 13.4 months

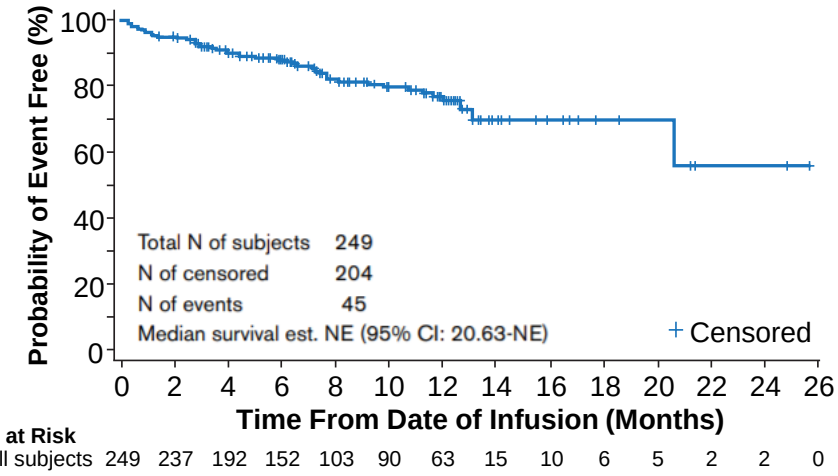
Pasquini MC, et al. *Blood Adv*. 2020;4:5414-5424.

Results: Event-Free and Overall Survival

EFS Rates Among All Infused Patients, % (95% CI) N = 249	
6 months	68.6 (62.0-74.4)
12 months	52.4 (43.4-60.7)



OS Rates Among All Infused Patients, % (95% CI) N = 249	
6 months	88.5 (83.6-92.0)
12 months	77.2 (69.8-83.1)



34 (16.1%) patients went on to HSCT after tisagenlecleucel while in remission

EFS, event-free survival; HSCT, hematopoietic stem cell transplant; OS, overall survival.

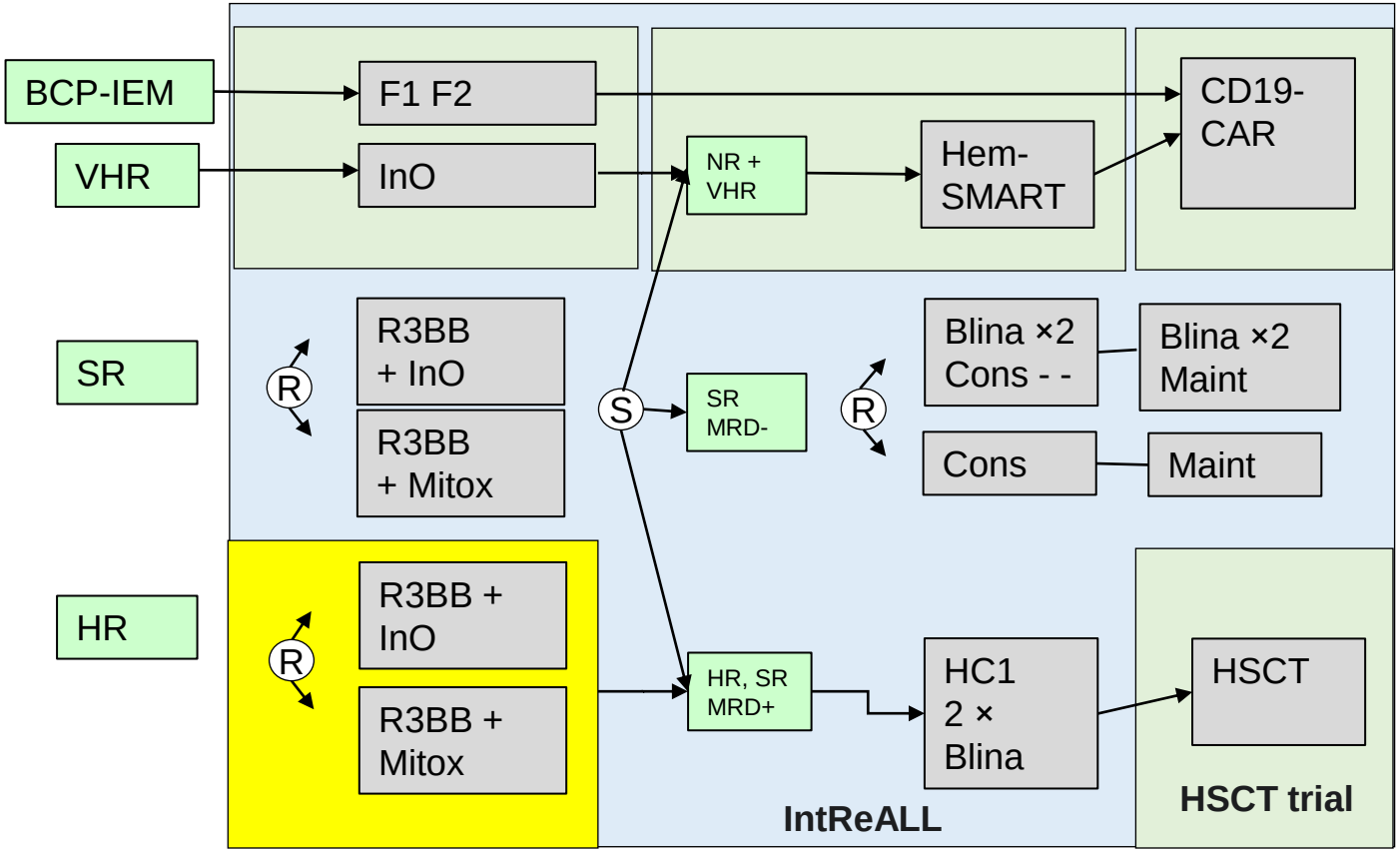
Pasquini MC, et al. *Blood Adv*. 2020;4:5414-5424.

Results: Efficacy and Safety by Subgroup Analyses

Percentage, (95% CI)	<3 Years	Down Syndrome	Prior CNS Involvement	Prior Blinatumomab	Prior Inotuzumab	Primary Refractory	MRD Negative
Efficacy/safety sets, N	15/15	12/12	23/24	37/38	26/27	37/38	42/44
CR (BOR)	86.7 (59.5-98.3)	100 (73.5-100)	82.6 (61.2-95.0)	78.4 (61.8-95.0)	65.4 (44.3-82.8)	86.5 (71.2-95.5)	97.6 (87.4-99.9)
DOR at 6 months	*	*	*	67.2 (42.5-83.1)	*	*	85.9 (69.2-93.9)
OS at 6 months	*	100 (NE-NE)	79.7 (54.1-92.0)	88.5 (72.1-95.5)	64.2 (42.5-79.5)	87.8 (70.5-95.3)	97.1 (81.4-99.6)
CRS (grade ≥3)	6.7 (0.2-31.9)	16.7 (2.1-48.4)	25.0 (9.8-46.7)	13.2 (4.4-28.1)	7.4 (0.9-24.3)	10.5 (2.9-24.8)	0 (0.0-8.0)
Neurotoxicity (grade ≥3)	13.3 (1.7-40.5)	16.7 (2.1-48.4)	8.3 (1.0-27.0)	7.9 (1.7-21.4)	11.1 (2.4-29.2)	7.9 (1.7-21.4)	2.3 (0.1-12.0)

*Number of patients at risk is <10.
BOR, best overall response; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete remission; CNS, central nervous system; CRS, cytokine release syndrome; DOR, duration of remission; MRD, minimal residual disease; NE, not estimable; OS, overall survival.
Pasquini MC, et al. *Blood Adv*. 2020;4:5414-5424.

Design IntReALL-BCP 2020 Updated



Final Considerations

- Although leukemia recurrence remains the main cause of treatment failure in childhood ALL, the chance of rescuing relapsed patients is increasing over time
- Immunotherapy is changing the therapeutic scenario of relapsed patients with childhood BCP-ALL
- Patients with T-ALL have much more limited benefit from immunotherapy, and rescue strategy for relapsed patients still represents an unmet medical need
- Future studies are warranted to more precisely define the role of immunotherapy options with the respective pros and limitations, also in comparison with the standard of care, still represented by allogeneic HSCT

Global Leukemia Academy

Bispecifics for pediatric ALL, focus on frontline therapy

Lia Gore

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

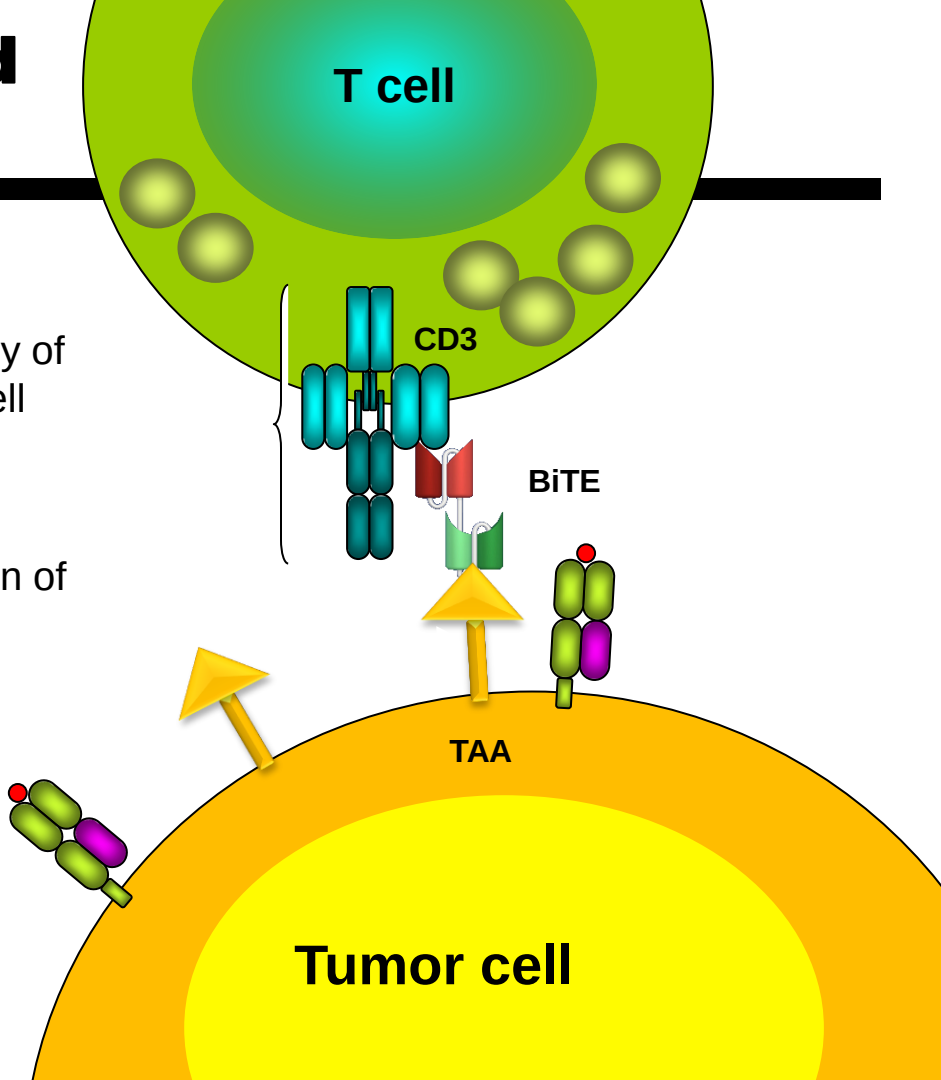
- Definition of a “bispecific” = bispecific T-cell engager
- Mechanism of action
- Review of recent trial results in pediatric relapsed ALL
- **Future considerations**

What a BiTE® Is and How BiTEs Work

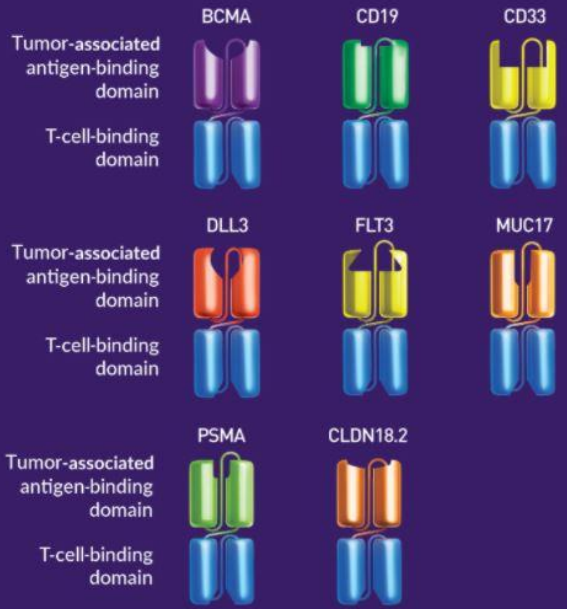
Act independently of specificity of T-cell receptor (TCR)

Allow T cell recognition of tumor-associated surface antigen (TAA)

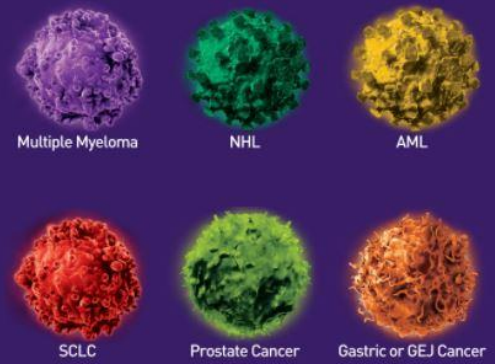
Do not require MHC Class I and/or peptide antigen



BiTE® molecules under clinical investigation include the following targets[1,4,5]:



The BiTE® platform is being investigated across a broad set of cancers[4]



BiTE® molecules are designed to bring T-cell innovation to more patients

- Designed to target tumor-associated antigens[1]
- Designed to lead to off-the-shelf therapies without the need for ex vivo manipulation of patients' cells[1,2]
- Investigated for use as monotherapies and in combination with other treatments[3,6,7]

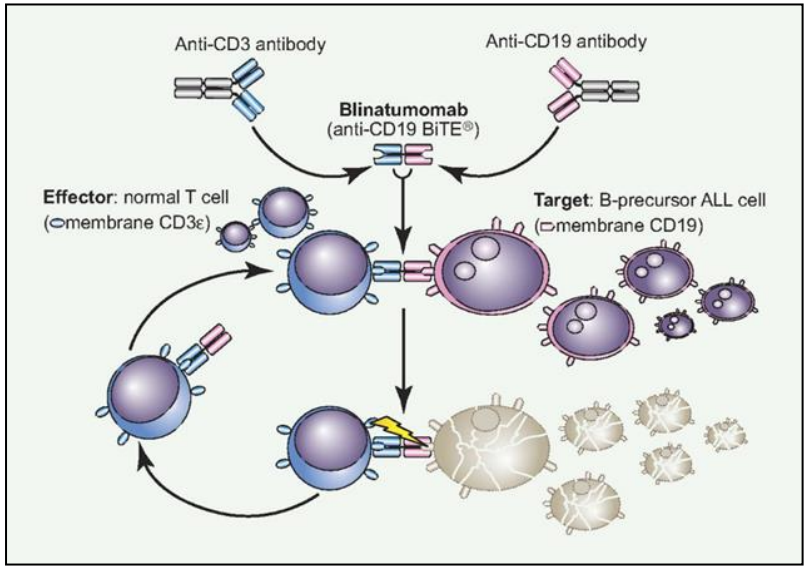
The BiTE® immuno-oncology platform has been studied in thousands of patients, many of whom have been followed for up to 5 years.[8,9]

With the BiTE® immuno-oncology platform, Amgen is driven to push the boundaries of science for patients with cancer by:

- Leveraging innovative trial designs[10]
- Investigating clinically relevant endpoints and outcomes[11-13]

Source: www.amgen.com

Blinatumomab (CD19 BiTE)



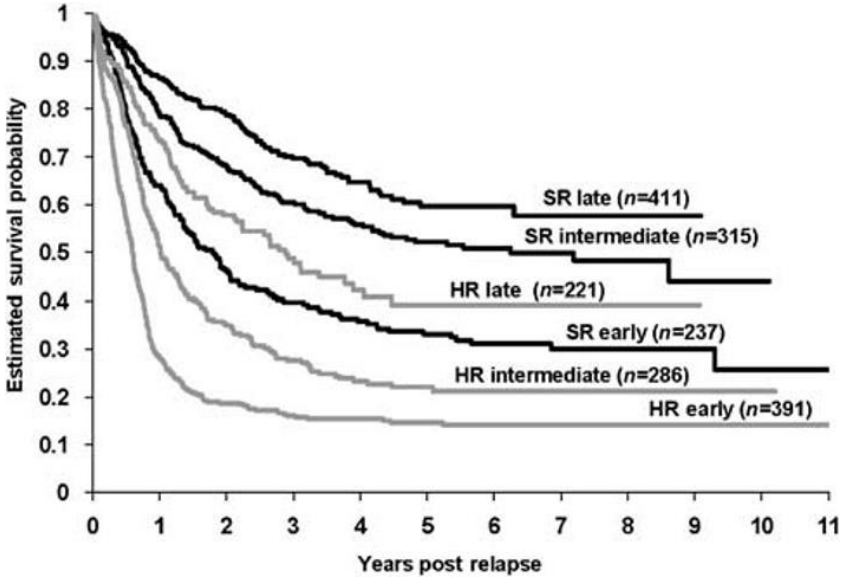
Brown P. *Blood.* 2018;131(14):1497-1498.

- In multiple-relapsed/ 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)

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

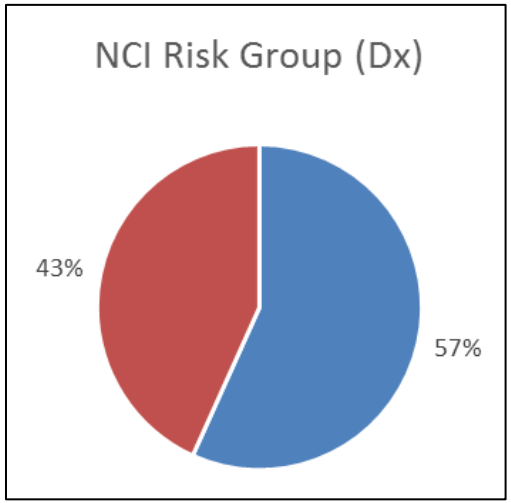
Success in Treating the Most Common Childhood Cancer

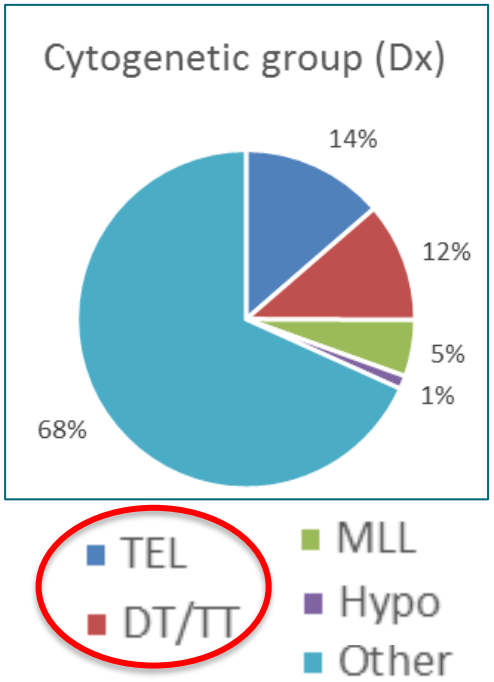
- Current regimens offer survival of 90%–99% for most patients
- Patients with some subtypes and relapsed disease do not have such hopeful outcomes



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

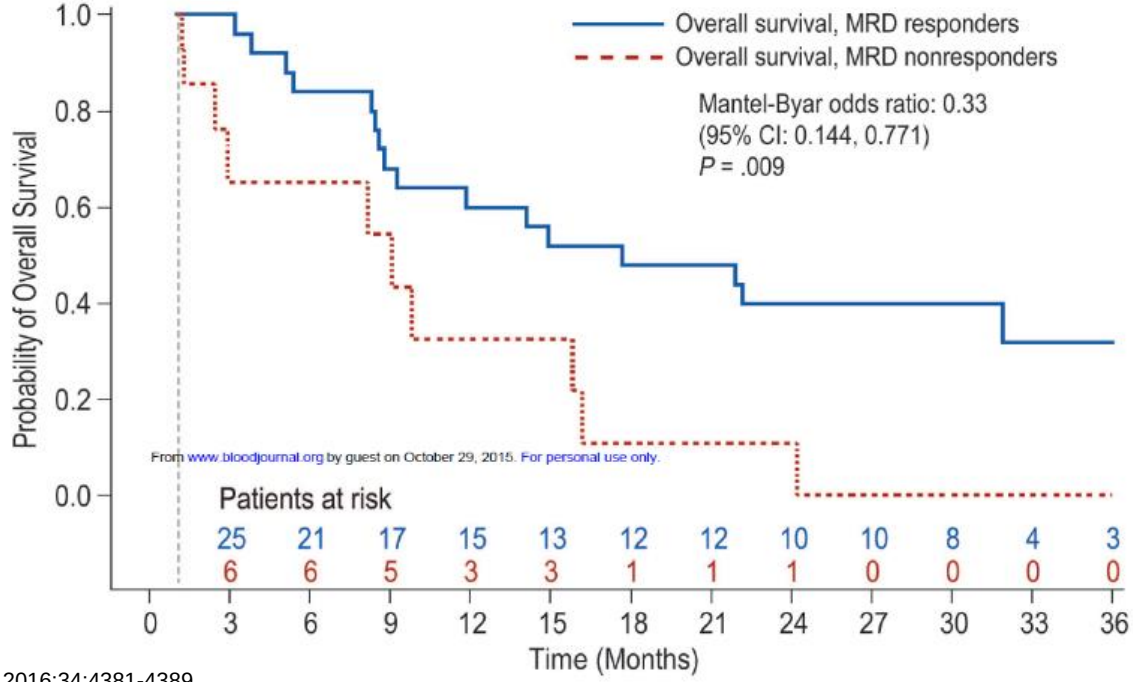
Standard- and Low-Risk ALL Remain Major Contributors to Relapse





Brown PA, et al. on COG AALL1331.

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



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

Toxicities of Special Interest With BiTEs (and CAR T Cells)

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

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 antigen-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?

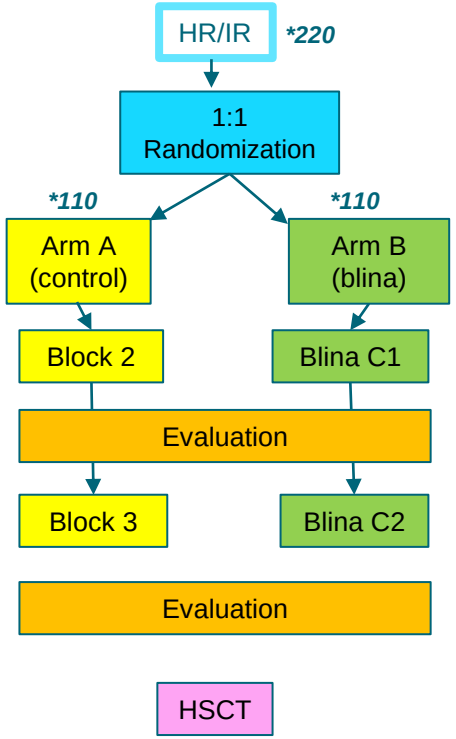
AALL1331 Schematic

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)

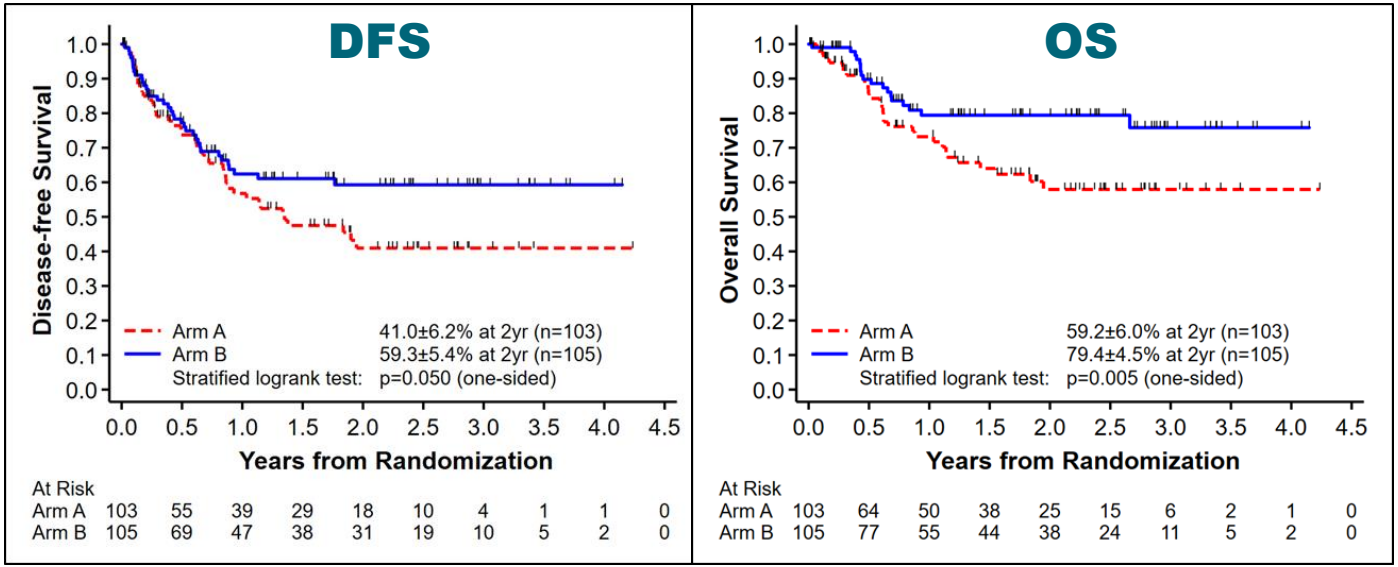
- ***First patient randomized Jan 2015***
- ***Randomization halted September 2019 (95% projected accrual)***

CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. *JAMA*. 2021;325(9):833-842.

Survival

Arm A (Chemotherapy) vs Arm B (Blinatumomab)

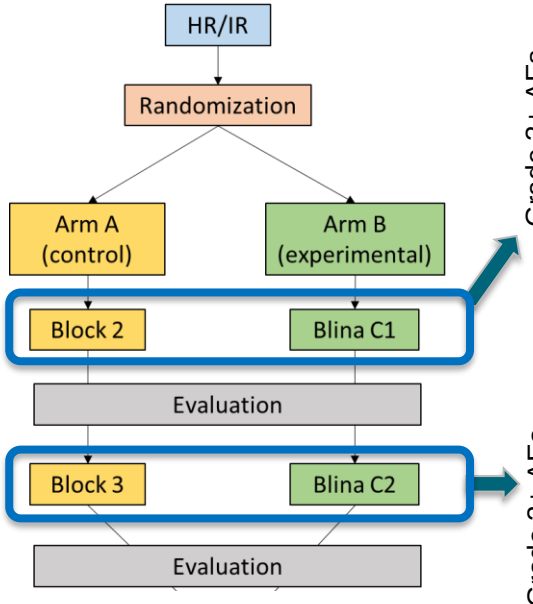


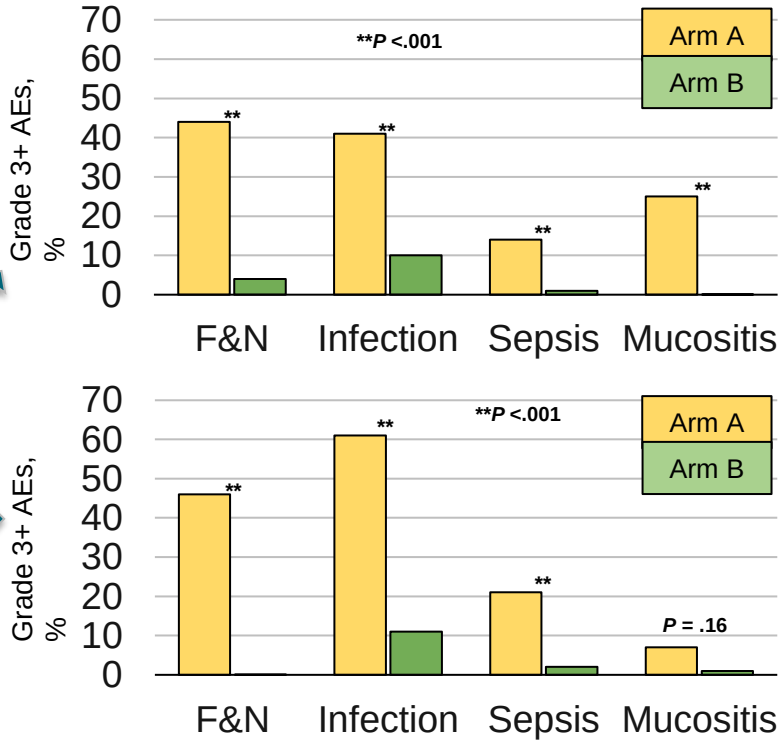
Median follow-up 1.4 years

CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. *JAMA*. 2021;325(9):833-842.

Adverse Events on COG AALL1331





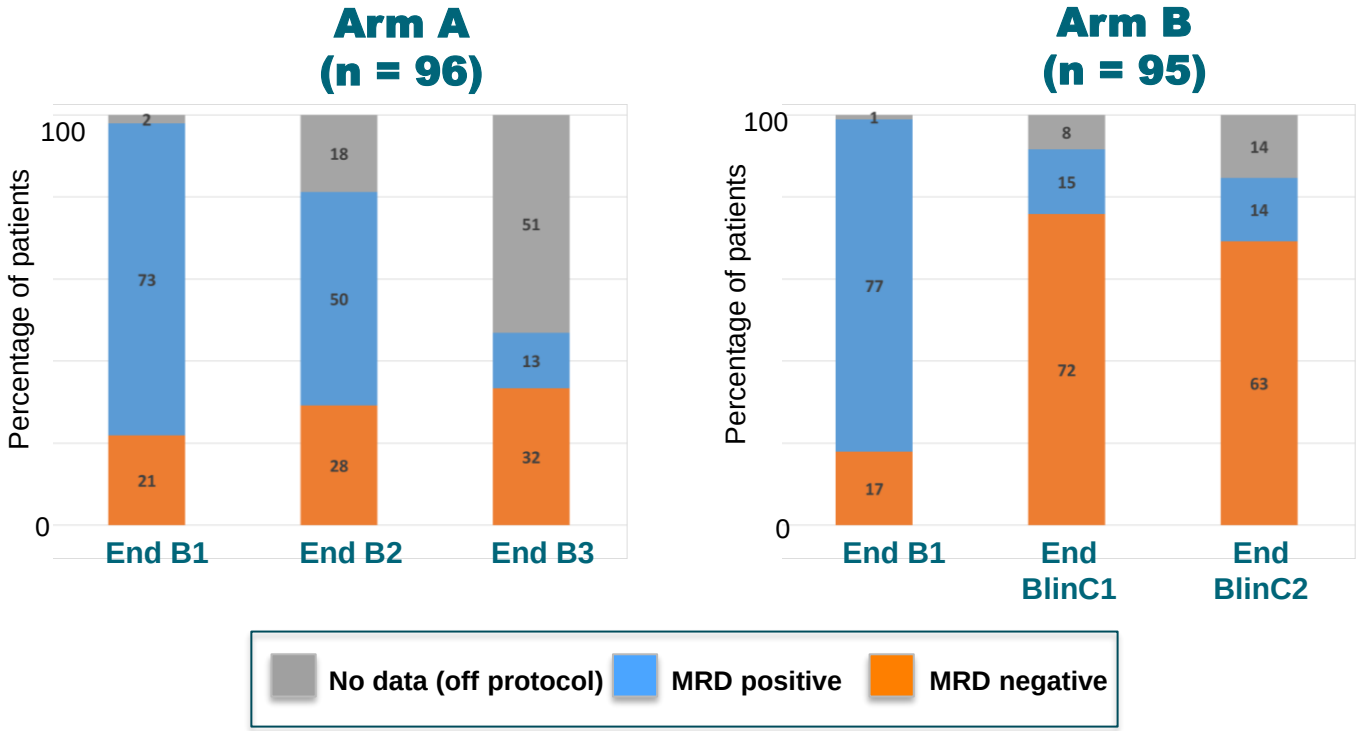
- *N = 4 post-induction grade 5 AEs on Arm A (all infections)*
- *N = 0 on Arm B*
- *Ages of Arm A deaths: 2, 17, 23, and 26 years old (AYA skewed)*
- *NOTE: AE rates significantly higher in AYA (Hogan, et al. ASH Abstract 2018)*

CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. *JAMA*. 2021;325(9):833-842.

MRD Clearance on COG AALL1331

High-Risk Arms



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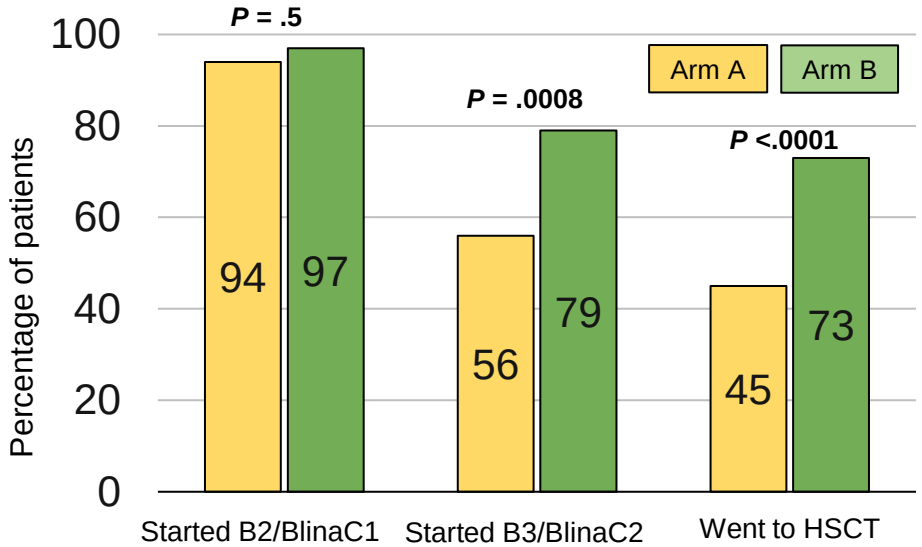
AALL1331: Ability of HR Patients to Proceed to Transplant

Arm A (Chemo) vs Arm B (Blina)



A significant contributor to the improved survival for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may be the **ability of blinatumomab to successfully bridge to HSCT**

CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. *JAMA*. 2021;325(9):833-842.

Status of Immunotherapy for ALL in the 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 Trials for ALL With BiTEs

	Trial	Disease	Primary Objective	Status
B-ALL	AALL1731	Newly diagnosed SR B-ALL	Randomized trial of blinatumomab added to standard chemotherapy	Open
B-ALL	IntReALL BCP 2020	Newly diagnosed SR and HR B-ALL	Randomized trial of blinatumomab added to standard chemotherapy	
Relapse	AALL1331	First-relapse B-ALL	Randomized trial of blinatumomab vs chemotherapy	Recently completed*
Relapse	AALL1821	First-relapse B-ALL	Safety and efficacy of blinatumomab + nivolumab	Open

- There are over 50 different bispecific antibodies being tested in clinical trials. To date, only blinatumomab has been used in children with ALL
- Other targets for ALL could include bispecifics targeting CD20 and BCMA
  - Multiple companies, including Roche, Regeneron, AbbVie, and others, have products in development

Current/Recent Considerations With Bispecific T-Cell Engagers

- Current products all have very short half-lives, necessitating prolonged continuous infusion
  - Prolonged-half-life compounds in development
- Concerns over selection pressure that result 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?

Q

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

Q

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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

Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients

Panelists: María Sara Felice (ARG), Oscar González Ramella (MEX), Adriana Seber (BRA), Carlos Andres Portilla (COL)

APTITUDE HEALTH®

AYA patient with severe morbidity and 2 relapses

Luisina Peruzzo, MD
Hematology Oncology Department
Buenos Aires, Argentina

OUTCOME

4-year-old boy
Pre–B-ALL
RT-PCR: BCR/ABL p210
BCR/ABL p190 MLL/AF4
TEL/AML1 E2A/PBX1 negative
MLPA: *IKZF1* not deleted

PGR
MRD D15: not evaluable (0,16% blasts)
MRD D33: negative
MRD day 78: not evaluable

2010

SAE DURING INDUCTION
Febrile neutropenia

1st RELAPSE

Hematological
60 months from **CR1**
Pre–B-ALL

1 BLOCK → **CR2**
1B protocol
2 BLOCK (75%)
6 BLOCK: RDT + MAINTENANCE

2015

SAE AFTER FIRST BLOCK

- Septic shock of enteral origin (*E. coli*)
- Arm cellulite, necrotizing myositis and osteomyelitis by *Klebsiella P.*
- Massive bleeding, cardio-respiratory arrest

MRD TP1, TP2, TP3, and TP4: negative

2nd RELAPSE

Hematological
70 months from **CR2**
Pre–B-ALL

2021

OUTCOME

4-year-old boy
Pre–B-ALL
RT-PCR: BCR/ABL p210
BCR/ABL p190 MLL/AF4
TEL/AML1 E2A/PBX1 negative
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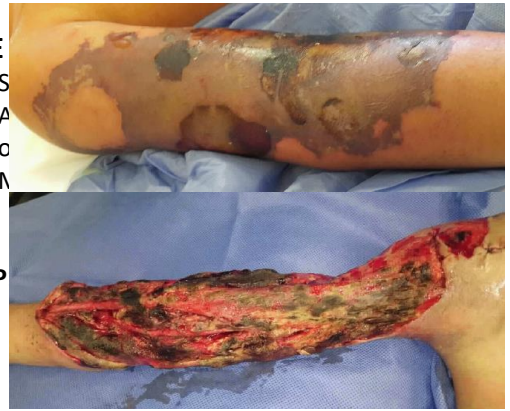
2015

SAE
- S
- A
  o
- N

MRD TP



2nd RELAPSE

Hematological
70 months from **CR2**
Pre–B-ALL

2021

Q

QUESTION

Possible treatment options

1. Palliative care?
2. Third-line chemotherapy, followed by HSCT?
3. Immunotherapy?
4. Repeat any of the previous schedules of chemotherapy?

OUTCOME

4-year-old boy
Pre–B-ALL
RT-PCR: BCR/ABL p210
BCR/ABL p190 MLL/AF4
TEL/AML1 E2A/PBX1 negative
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SAE AFTER FIRST BLOCK

- Septic shock of enteral origin (*E. coli*)
- Arm cellulite, necrotizing myositis and osteomyelitis by *Klebsiella P.*
- Massive bleeding, cardio-respiratory arrest

MRD TP1, TP2, TP3, and TP4: negative

2nd RELAPSE

Hematological
70 months from **CR2**
Pre–B-ALL

3rd line
Clofarabine
Cyclophosphamide
Cytarabine
(CYCLET)
CR3

2021

SAE after CYCLET block

- Febrile neutropenia
- Respiratory infection due to adenovirus
- BK virus hemorrhagic cystitis

MRD TP1: 0.12%, TP2: negative

OUTCOME

4-year-old boy
Pre–B-ALL
RT-PCR: BCR/ABL p210
BCR/ABL p190 MLL/AF4
TEL/AML1 E2A/PBX1 negative
MLPA: *IKZF1* not deleted

PGR
MRD D15: not evaluable (0,16% blasts)
MRD D33: negative
MRD day 78: not evaluable

2010

1st RELAPSE

Hematological
60 months from **CR1**
Pre–B-ALL

1 BLOCK → **CR2**
1B protocol
2 BLOCK (75%)
6 BLOCK: RDT + MAINTENANCE

2015

2nd RELAPSE

Hematological
70 months from **CR2**
Pre–B-ALL

3rd line
Clofarabine
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CR3

2021

SAE DURING INDUCTION
Febrile neutropenia

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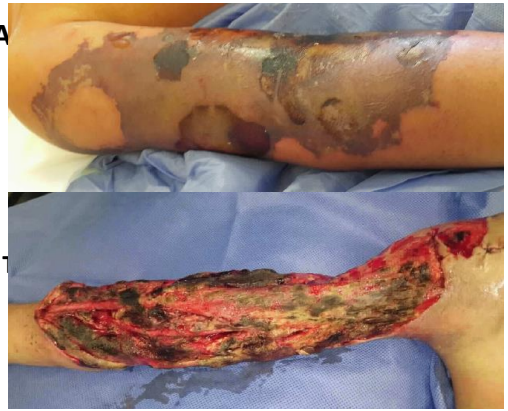

MRD T

SAE after CYCLET block
- Febrile neutropenia
- Respiratory infection due to adenovirus
- BK virus hemorrhagic cystitis

MRD TP1: 0.12%, TP2: negative

THANKS FOR YOUR ATTENTION

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ALL Patient Case

Jorge Ramirez Melo

Oscar González Ramella

Hospital Civil de Guadalajara

Mexico

Case Presentation (1/2)

Male, 14 years old

Previously healthy

No family history of cancer or other pathologies

8 days of pain in the legs, of progressive intensity without improvement with the administration of intramuscular analgesic treatment

Review of systems: decreased activity level

Physical examination: hepatomegaly and decreased strength in lower limbs 4/5

Laboratory work-up
Leukocytes 89,840, Hgb 12.3, Platelets 8450
Cr 1.07, UNB 9.3, Urea 19, K 5, P 0.9, Ca 7.4

Diagnostic images
Chest X-ray without mediastinal mass
Abdominal X-ray: osteolytic bone lesions in lumbar spine and pelvis

Case Presentation (2/2)

High-risk lymphoblastic leukemia

1. Age
2. Hyperleukocytosis
3. Extramedullary infiltration: osteolytic bone lesions

Immunophenotype: 87.3% lymphoid blasts

Cytogenetics: karyotype diploid cells in 100%, DNA index 1, FISH negative for all leukemia translocations

LCR: CNS stage 1

Total Therapy XV

MRD of day 14: 0.68%

He received remission induction therapy until day 20 before complication

Clinical Evolution (1/2)

Hospitalized for abdominal pain

Diagnosis:
Neutropenic colitis
Febrile neutropenia
Mucositis grade II

The next day he was transferred to intensive care

He presented symptomatic bradycardia

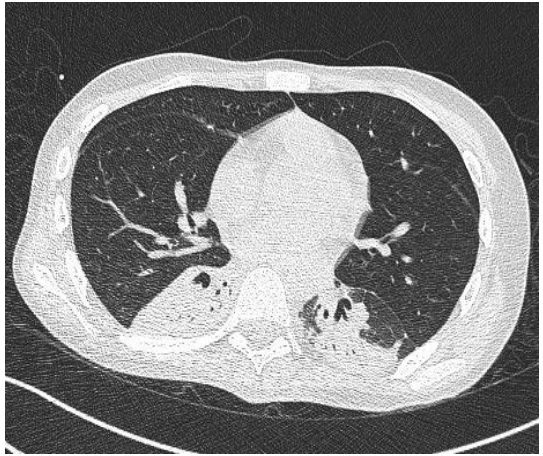
EKG: long QT syndrome

Echocardiogram: signs of pulmonary hypertension, pulmonary thromboembolism

Treatment: vasopressors, non-invasive mechanical ventilation, digoxin, sildenafil, metoprolol

Catheter-related thrombophlebitis in the right arm

Anticoagulation could not be started (platelets 20,000)



Q

Question

According to the clinical evolution and the thorax CT image, what would be your diagnosis for this ALL patient's complication?

a) Gram-negative pneumonia
b) Severe pancreatitis
c) SARS-CoV-2 infection
d) Chemotherapy-related pneumonitis
e) None of the above

Clinical Evolution (2/2)

20 days of steroid, without anticoagulation or chemotherapy

The patient was discharged to his home for 2 days, and then he was admitted to our service

Hgb 9.2, platelets 411,600, leukocytes 2000, neutrophils 1590

He received the second phase of IR with cytarabine 50 mg/m^2; cyclophosphamide was omitted

Negative MRD (<0.01% blasts) at the end of IR

Discussion

High-risk ALL with positive EMR at day 14 in patients with multiple comorbidities: heart failure, long QT syndrome, pulmonary thromboembolism, SARS-CoV-2 infection

1. Need of chemotherapy intensification in this particular case?

2. The need for anticoagulation or clinical guides for SARS-CoV-2 infection in patients with thrombocytopenia and ALL?

3. Role of immunotherapy for this patient?

4. Any experiences of the panelists with ALL patients with COVID infection?

ALL Patient Cases

Gustavo Zamperlini, MD

Hospital Samaritano

São Paulo/SP, Brazil

CASE 1: PATIENT HISTORY AND FRONTLINE THERAPY

- White Brazilian boy
- In September 2012, 3 years of age
  - Fever and pallor
  - Pancytopenia
  - Acute lymphoblastic leukemia: CD34, CD38, CD19++, CD22+, CD10+
- Risk assessment
  - CNS1; karyotype 46XY; BCR/ABL negative
- Frontline therapy
  - ReLLA – Intermediate Risk (St. Jude Total XV-based protocol)
  - Rash and urticaria after the last PegASP dose during induction; MRD negative
  - End of treatment: March 2015
- Combined testicular and marrow (70% blasts) relapse: July 2020, 10 years of age

RELAPSED/REFRACTORY SETTING

- Late combined testicular and bone marrow relapse
- Second-line therapy
  - High-risk arm ReLLA protocol (4-drug–based induction)
  - PegASP: arthralgia and rash after the second dose; L-asp assay = no activity
  - Orchiectomy of the left testis
  - MRD persistently positive after induction (0.03%) and consolidation (0.02%)
  - No matched related or unrelated donor
- Further therapies
  - Blinatumomab 15 µg/m^2/day for 28 days
  - MRD negative after the first cycle
  - January 2021: haploidentical T-cell replete transplant – Flu/TBI 1200 cGy + testicular boost
  - GVHD prophylaxis: post-transplant Cy, CSA, MMF

DISCUSSION

- What is the best protocol to reinduce patients who cannot receive asparaginase?
- What is the best anthracycline? Is mitoxantrone the best drug?
- What is the role of blinatumomab in extramedullary relapse?

CASE 2: PATIENT HISTORY AND FRONTLINE THERAPY

- White Brazilian girl
- In October 2020, 1 year and 6 months old
  - Fever; diagnosed with urinary tract infection
  - Complete blood count with low hemoglobin, platelets, and 150,000 leukocytes/mm^3
  - Acute lymphoblastic leukemia: CD34++, CD45+-, CD19++, CD10++, CD79++, CD20+, CD22+, HLA DR+, TdT+, CD81+, CD66+, CD123+, CD73+, CD304++, CD58+++
  - Risk assessment: high risk
  - SNC1; karyotype 46,XX; negative BCR/ABL, *KTM2A*, and *ETV6-RUNX1*
- Frontline therapy
  - BFM 2009 protocol – high risk
  - Refractory to first induction – M3 marrow
  - Refractory to second phase of induction (Cy, AraC, 6-MP) – M3 marrow

RELAPSED/REFRACTORY SETTING

- Second-line therapy
  - Blinatumomab
  - MRD 0.8% after first cycle

- Further therapies
  - T-cell replete haploidentical transplant from her father in January 2021
  - Conditioning: Flu/TBI 1200 cGy + post-transplant Cy and CSA, MMF
  - Post-transplant monthly blinatumomab cycles with prophylactic donor leukocyte infusions

DISCUSSION

- Is it possible to overcome resistance to blinatumomab by increasing the dose above 15 µg/m^2, as demonstrated in lymphoma?
- What is the role of blinatumomab maintenance after BMT in patients with high-risk disease?

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Session Close

Franco Locatelli

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Interactive Q&A

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Educational ARS Questions

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Q

Educational Questions Pediatric ALL

Question 1: Which of the following subsets of 1st relapse ALL patients can be considered at very high risk?

a) All patients with B-ALL relapsing within 18 months from diagnosis
b) All patients with MLL-rearranged leukemia
c) All patients with hypodiploidy
d) Each of the 3 previous subsets

Q

Educational Questions Pediatric ALL

Question 2: Which assertion is correct for children with B-ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment
b) Inotuzumab dosage is 3 mg/m^2
c) TBI-based conditioning regimen should be preferentially used in children above the age of 4 years
d) None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

Global Leukemia Academy

Closing Remarks

Franco Locatelli

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Thank You!

- Thank you to our sponsors, 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

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24 April 2021

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