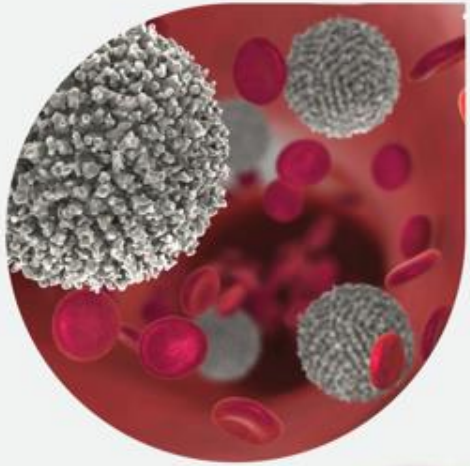
Global Leukemia Academy



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

Webinar

Sponsors: Platinum Silver

AMGEN Adaptive biotechnologies

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Introductions

Hyoung Jin Kang, MD, PhD

Department of Pediatrics, Seoul National University Hospital

South Korea

APTITUDE HEALTH

Agenda Outline

Time	Topic	Presenter
7.00 PM – 7.05 PM (CST) 8.00 PM – 8.05 PM (KST/JST) 5 min	Welcome and introductions	Hyoung Jin Kang, MD
7.05 PM – 7.20 PM (CST) 8.05 PM – 8.20 PM (KST/JST) 15 min	Current Paradigm and Long-Term Toxicities for Pediatric/AYA ALL • Integration of innovative immunotherapies • Role of MRD in treatment • Long-term toxicities	Franco Locatelli, MD
7.20 PM – 7.40 PM (CST) 8.20 PM – 8.40 PM (KST/JST) 20 min	Bispecifics for Pediatric/AYA ALL • Review of trial results in pediatric/AYA ALL • Role of MRD in research and treatment • AYA considerations	Patrick Brown, MD
7.40 PM – 7.55 PM (CST) 8.40 PM – 8.55 PM (KST/JST) 15 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
7.55 PM – 8.20 PM (CST) 8.55 PM – 9.20 PM (KST/JST) 25 min	Questions to Experts	Hyoung Jin Kang, MD

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Current Paradigm and Long-Term Toxicities for Pediatric ALL

Franco Locatelli, MD

University of Rome IRCCS Ospedale Pediatrico Bambino Gesù of Rome

Italy

APTITUDE HEALTH

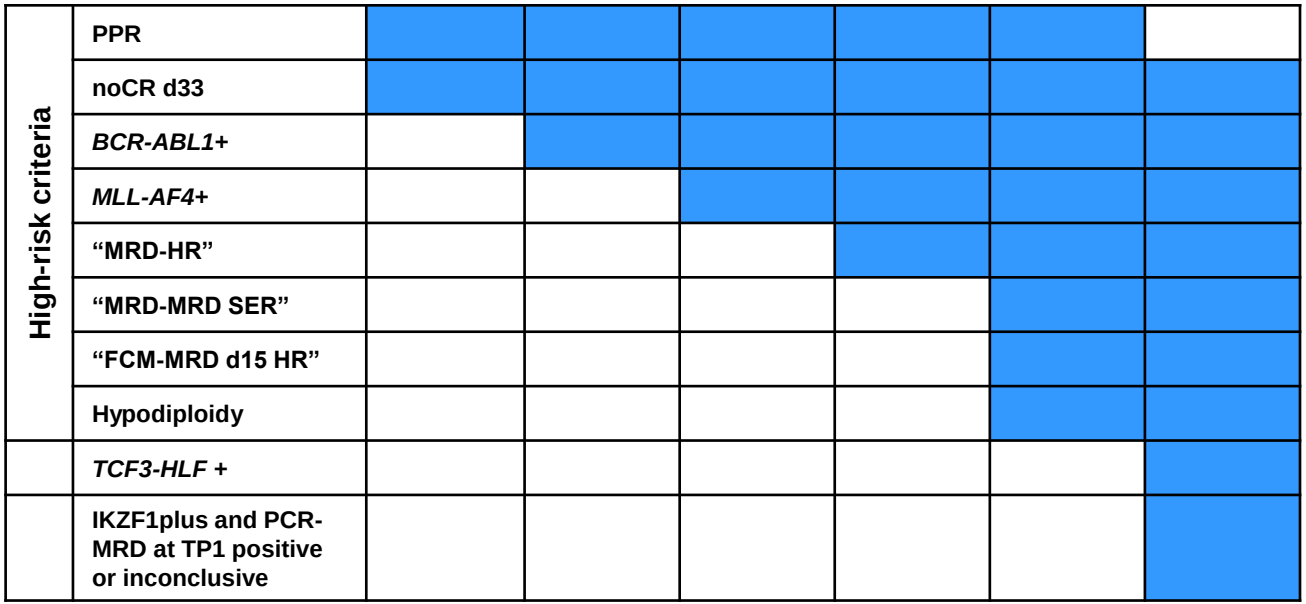
Current Paradigm and Long-Term Toxicities for Pediatric ALL

Franco Locatelli, MD
Università Sapienza, Roma
Dept. Pediatric Hematology/Oncology and Cell/Gene Therapy
IRCCS Ospedale Bambino Gesù, Roma, Italy

The essentials in pediatric ALL: Risk stratification and 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
- New molecular subgroups have been described (eg, Ph-like or *BCR/ABL*-like pB-ALL; MPAL) and their prognostic role defined
- Translation of novel molecular findings into improved treatment outcome is under investigation in various trials
- Reduction of long-term toxicities, especially in adolescents, is a priority
- Novel treatment approaches based on immunotherapy; evidence regarding long-term benefit is yet to be established

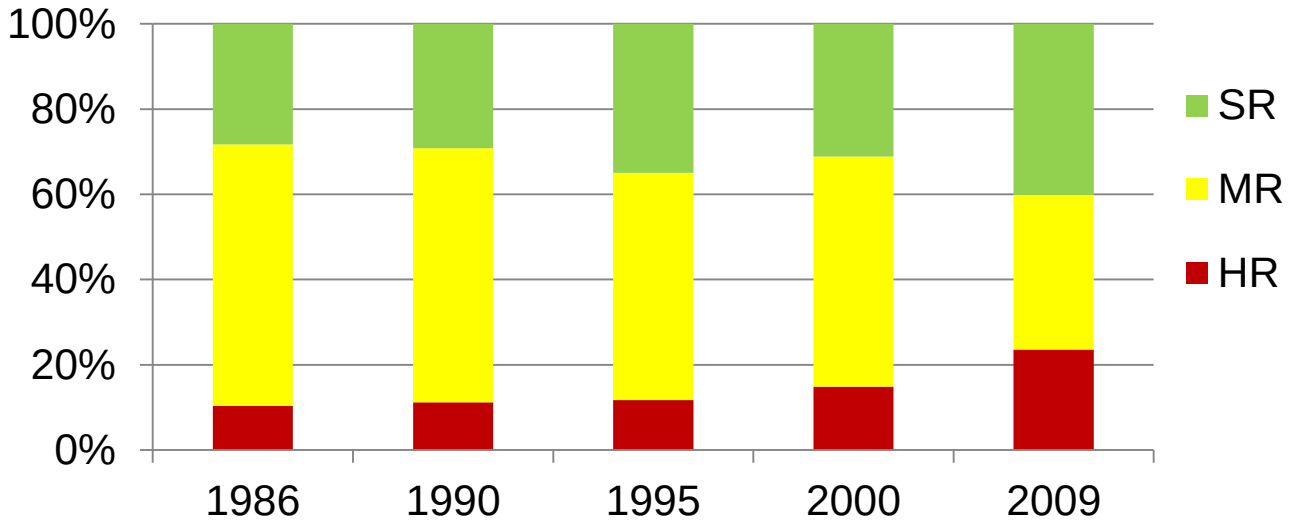
Identification of new high-risk groups and reducing relapses in high-risk patients



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

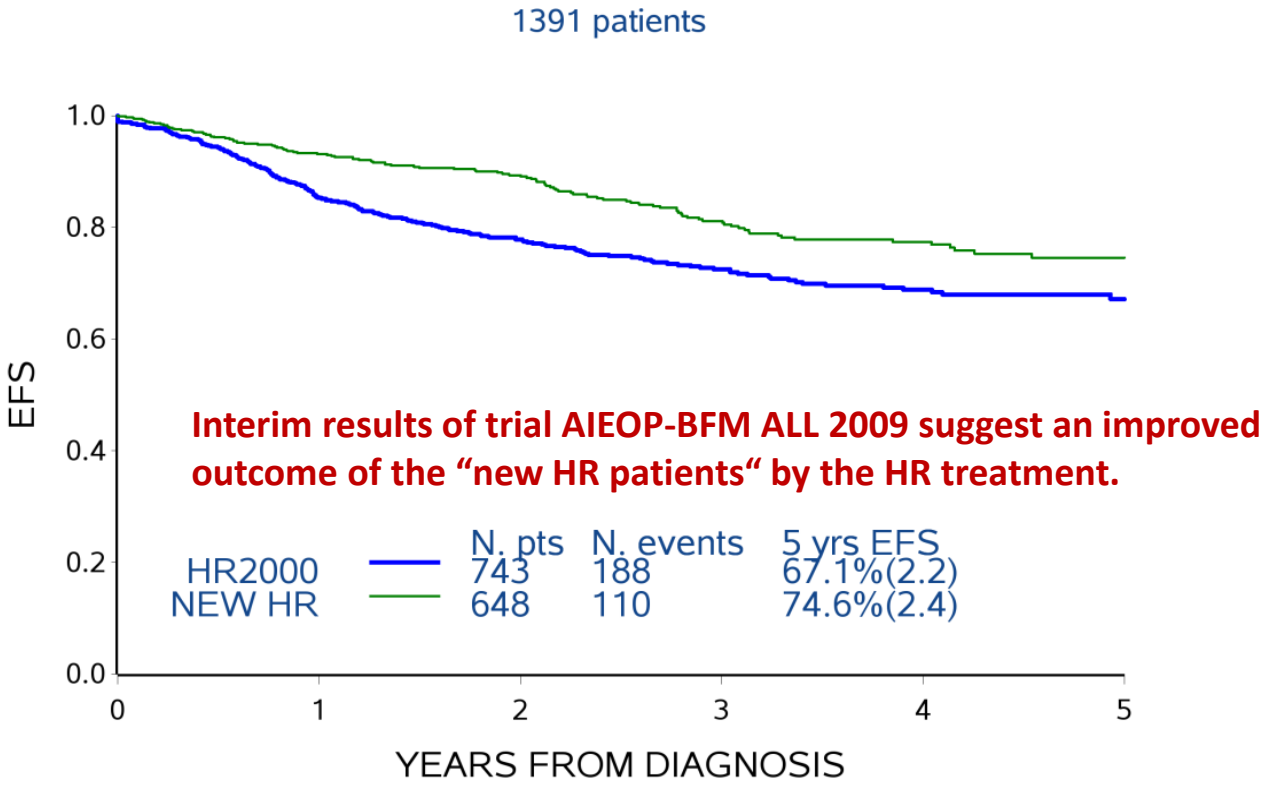
Identification of new high-risk groups and reducing relapses in high-risk patients

→ In AIEOP-BFM ALL 2009, the HR group comprised >20% of the patients



Studies ALL-BFM

AIEOP-BFM ALL 2009 –
Interim analysis of the HR group



Interim results of trial AIEOP-BFM ALL 2009 suggest an improved outcome of the "new HR patients" by the HR treatment.

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

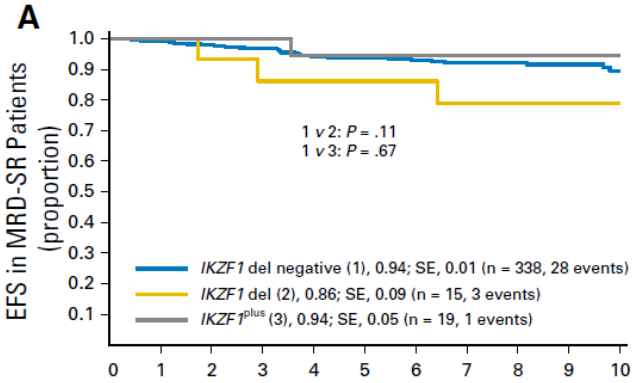
New prognostic pattern: Definition of *IKZF1*^{plus}

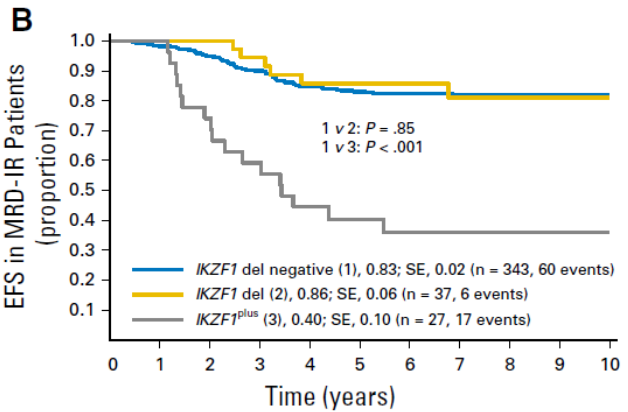
- Deletion of *IKZF1* and
  - *PAX5* and/or
  - *CDKN2A* and/or
  - *CDKN2B* and/or
  - *CRLF2 (PAR)* and

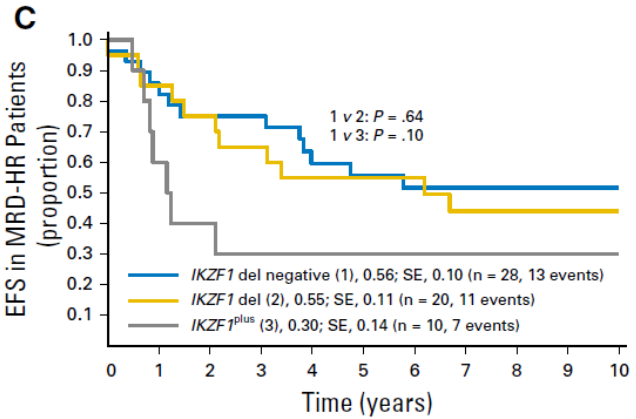
  - Negativity for *ERG* deletion

Stanulla M, et al. *J Clin Oncol.* 2018.

IKZF1^{plus} and MRD: Impact on EFS







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)

Stanulla M, et al. *J Clin Oncol.* 2018.

Perspectives for new trials in ALL

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

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

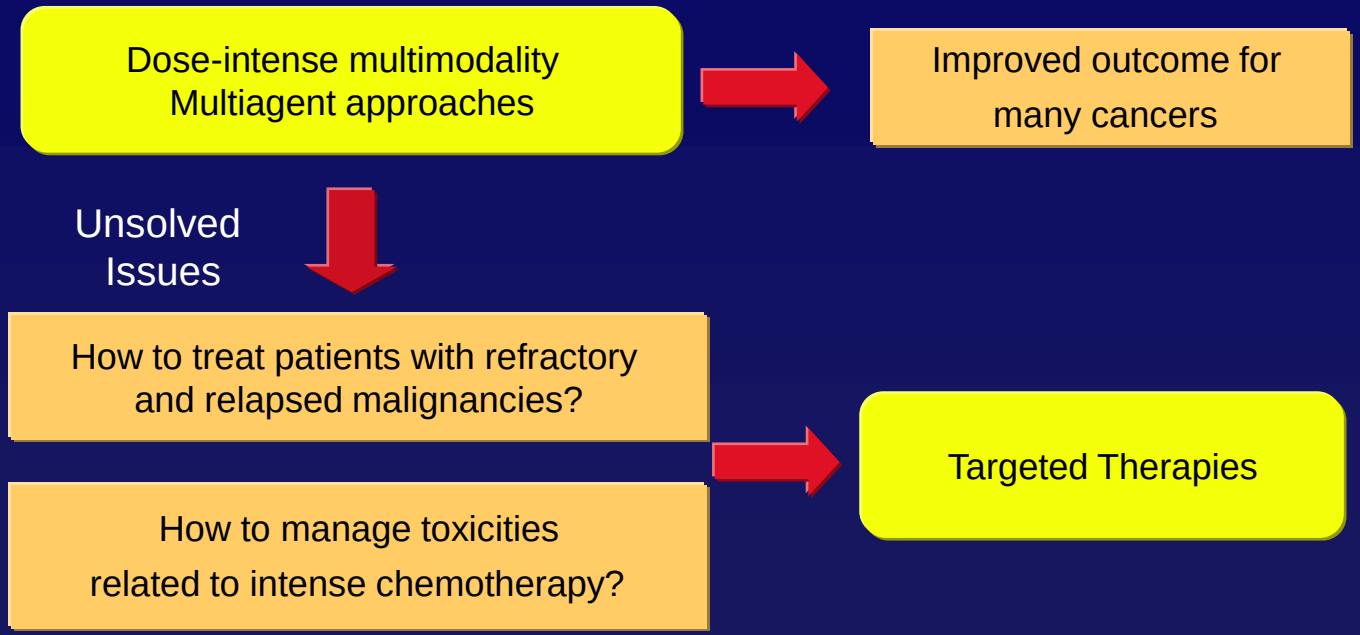
New in trial AIEOP-BFM ALL 2017

- Modified workflow and timing in genetic diagnostics
- Genetic profiles and early MRD response may be combined to characterize previously not identified pts 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 – Risk criteria for pB-ALL MR and HR

High Risk (HR)	• No complete remission on day 33 *or* • Positivity for *KMT2A-AFF1 or* • Positivity for *TCF3-HLF or* • Hypodiploidy <45 chromosomes *or* • FCM-MRD in BM on day 15 ≥10% *and* <u>*not*</u> *ETV6-RUNX1* positive *or* • *IKZF1*^{plus} *and* PCR-MRD at TP1 positive or inconclusive *and* <u>*not*</u> positive for *ETV6-RUNX1*, *TCF3-PBX1* or *KMT2A* rearr. other than *KMT2A-AFF1 or* • PCR-MRD at TP1 ≥5×10^{-4} *and* positive <5×10^{-4} at TP2 (PCR-MRD SER) • PCR-MRD at TP2 ≥5×10^{-4} (PCR-MRD-HR) • Age <1 year and any *KMT2A* rearrangement
Medium Risk (MR)	• No HR criteria *and* • PCR-MRD *either* positive at TP1 and/or TP2 *or* PCR-MRD not evaluable

Why immunotherapy for childhood tumors?



Immunotherapy for de novo pediatric ALL in trial AIEOP-BFM ALL 2017

- **Anti-CD19/anti-CD3 (Blinatumomab/BiTE®)**: prospective evaluation in MR and HR patients

- **Allogeneic hSCT** in predefined subgroups

Blinatumomab activity and toxicity in ALL

- Antileukemic activity demonstrated in both adults and children
- 80% MRD negativity in ALL patients treated in hematological CR but with molecularly-resistant disease
- Toxicity in patients without overt disease limited
- Toxicity profile different from chemotherapy

Stackelberg A, et al. *J Clin Oncol.* 2016;34; Gökbuget N, et al. *Blood.* 2018;131.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

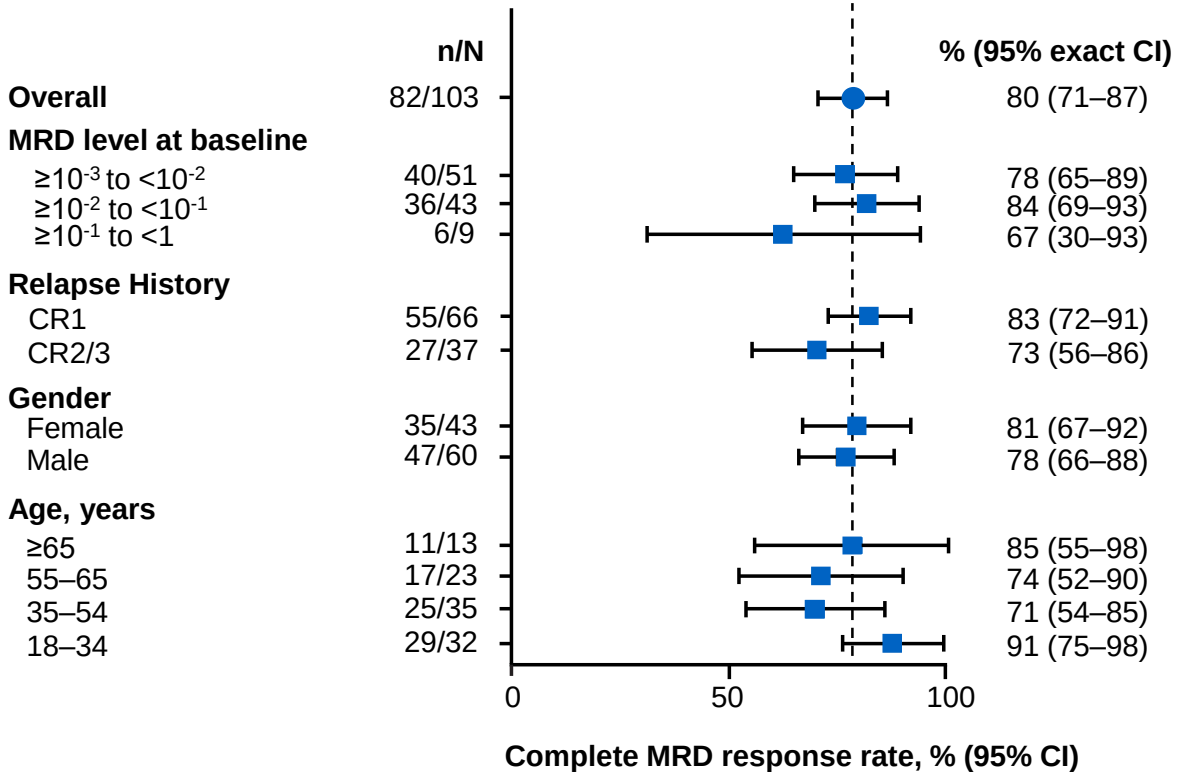
Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

Arend von Stackelberg, Franco Locatelli, Gerhard Zugmaier, Rupert Handgretinger, Tanya M. Trippett, Carmelo Rizzari, Peter Bader, Maureen M. O'Brien, Benoît Brethon, Deepa Bhojwani, Paul Gerhardt Schlegel, Arndt Borkhardt, Susan R. Rheingold, Todd Michael Cooper, Christian M. Zwaan, Phillip Barnette, Chiara Messina, Gérard Michel, Steven G. DuBois, Kuolung Hu, Min Zhu, James A. Whitlock, and Lia Gore

VOLUME 34 · NUMBER 36 · DECEMBER 20, 2016

Complete MRD response after cycle 1 by clinical characteristics

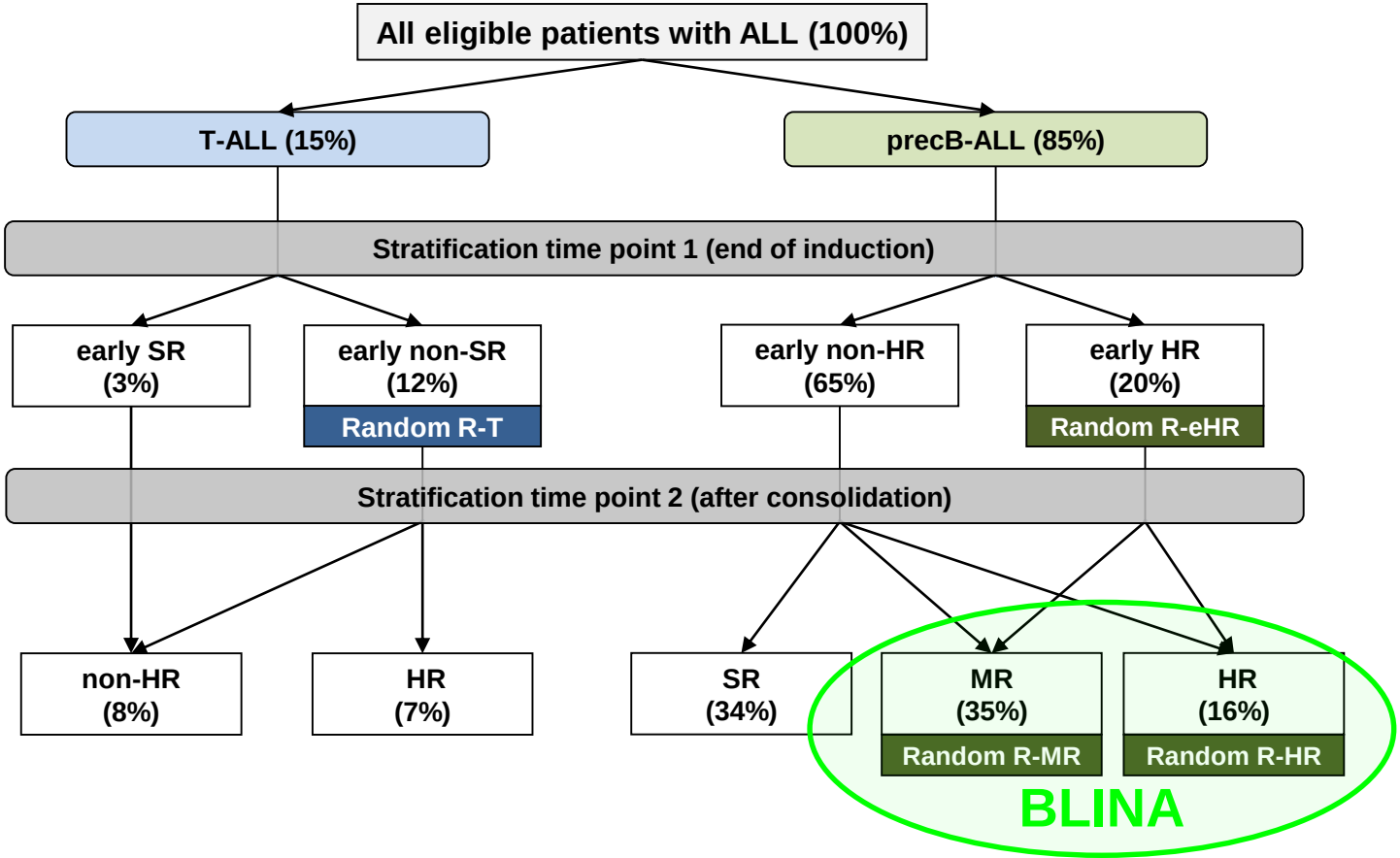
Phase 2 study MT103-203 (BLAST) in adults with MRD-positive B-precursor ALL



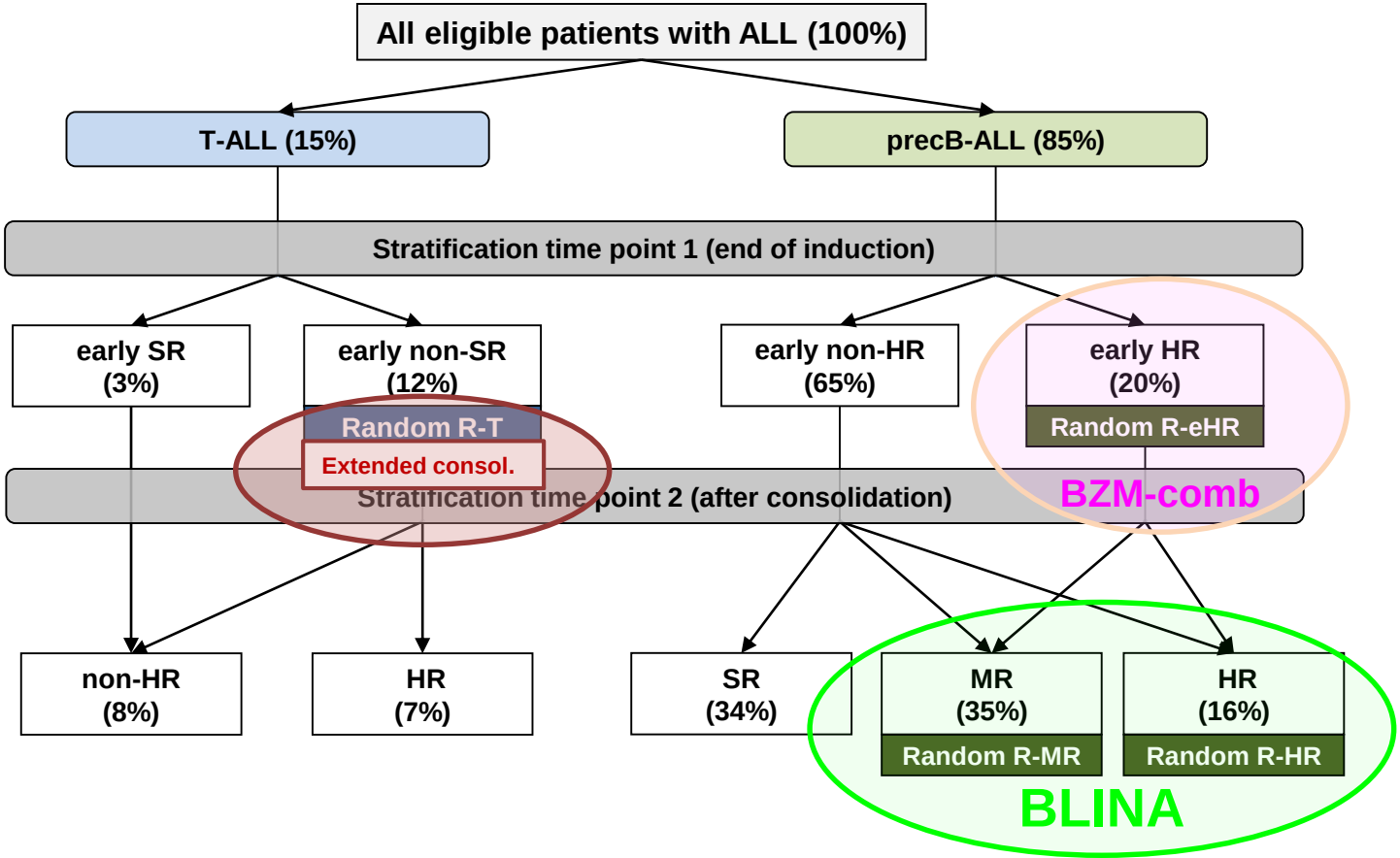
- Complete MRD response (primary endpoint, FAS†): **78%** (88/113)
- Complete MRD response (efficacy set*): **80%** (82/103)

*MRD negative with sensitivity of 10^{-4} (1:10,000).
FAS, full analysis set.
Adapted from Gökbuget N, et al. *Blood.* 2018;131:1522-1531.

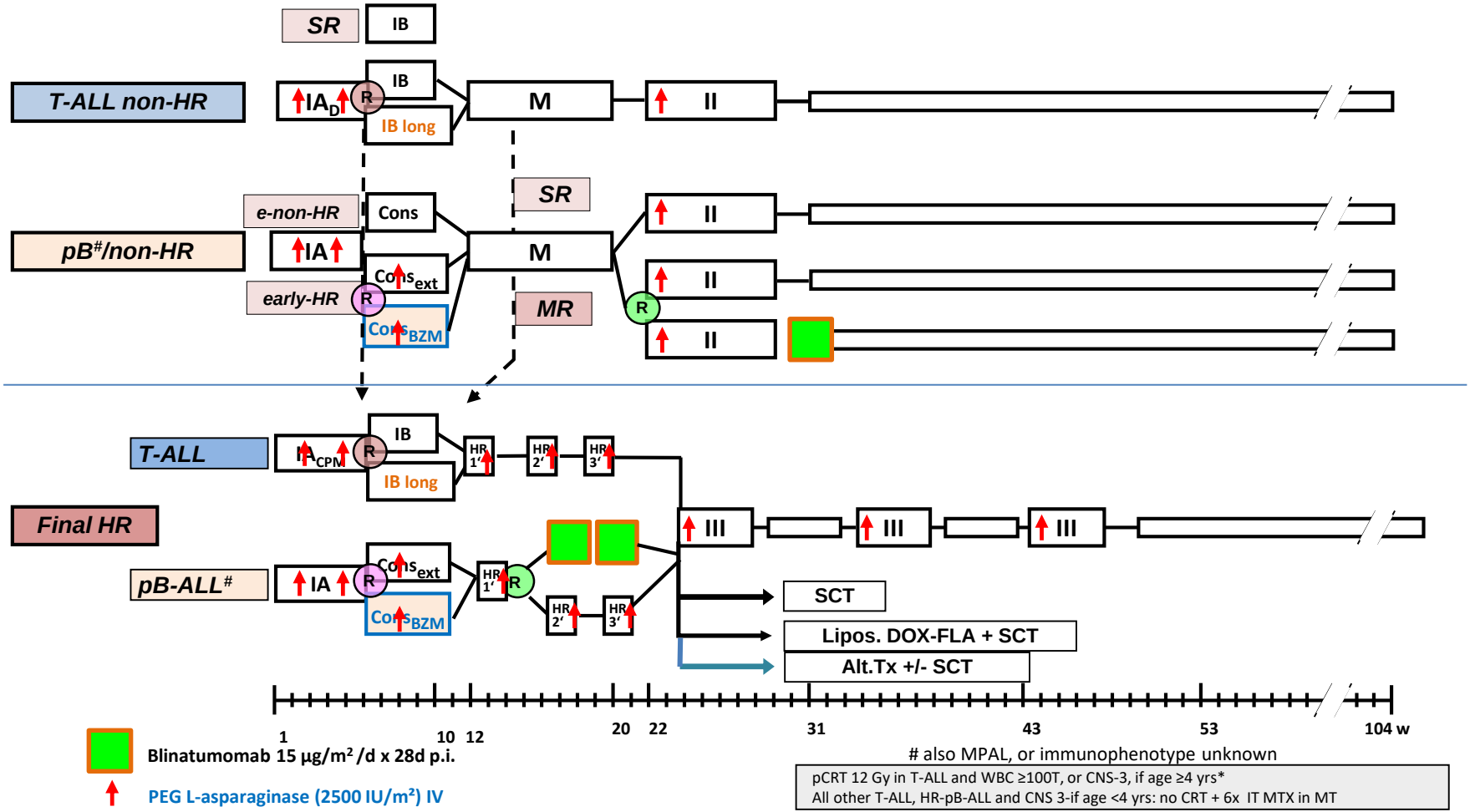
AIEOP-BFM ALL 2017 – Risk stratification and randomizations



AIEOP-BFM ALL 2017 – Risk stratification and randomizations



AIEOP-BFM ALL 2017: Treatment overview

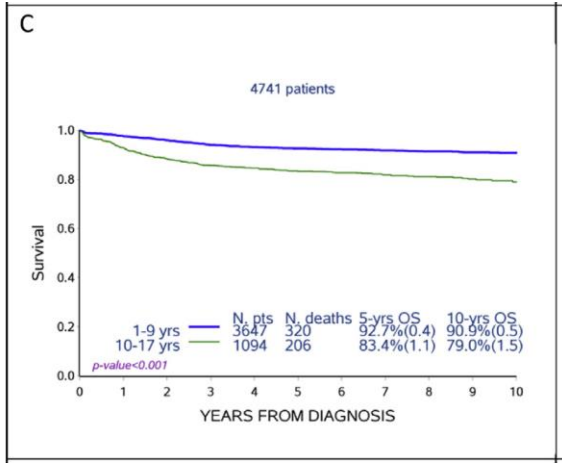


A brief focus on adolescents

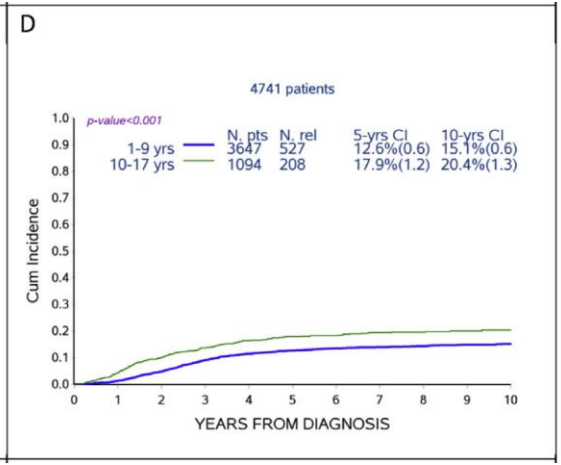
Acute and late toxicities

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

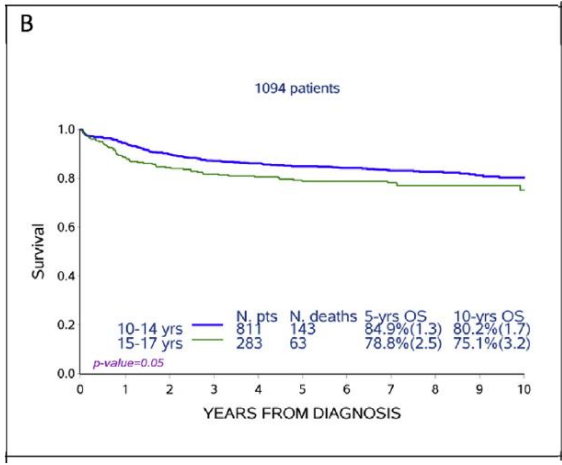
European Journal of Cancer 122 (2019) 61–71



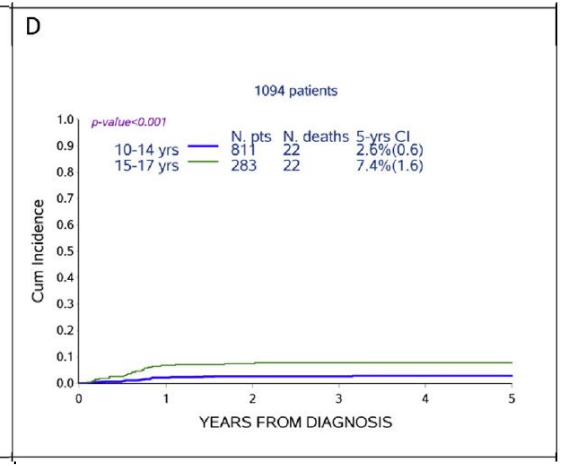
(C) OS by age



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



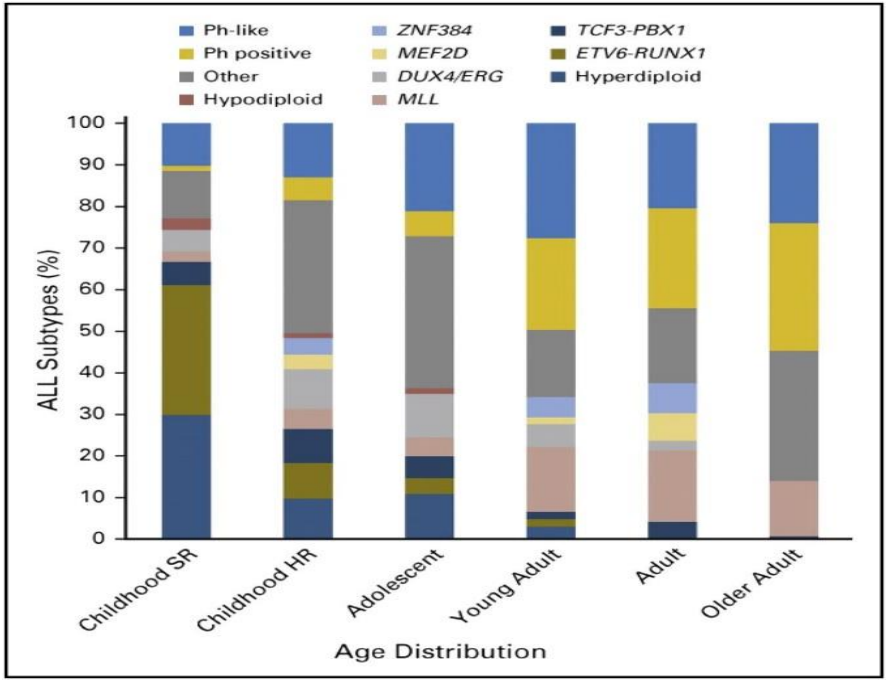
(B) Overall survival (OS) by age



(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]



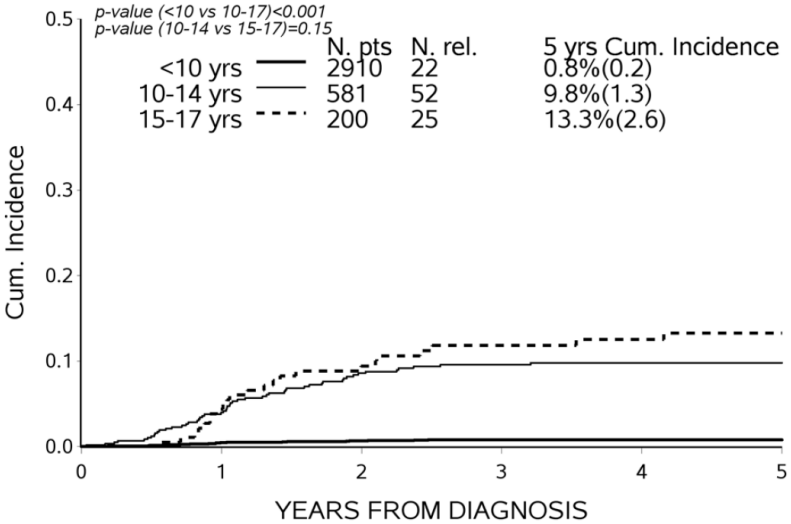
Late effects of treatment in ALL

- 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)

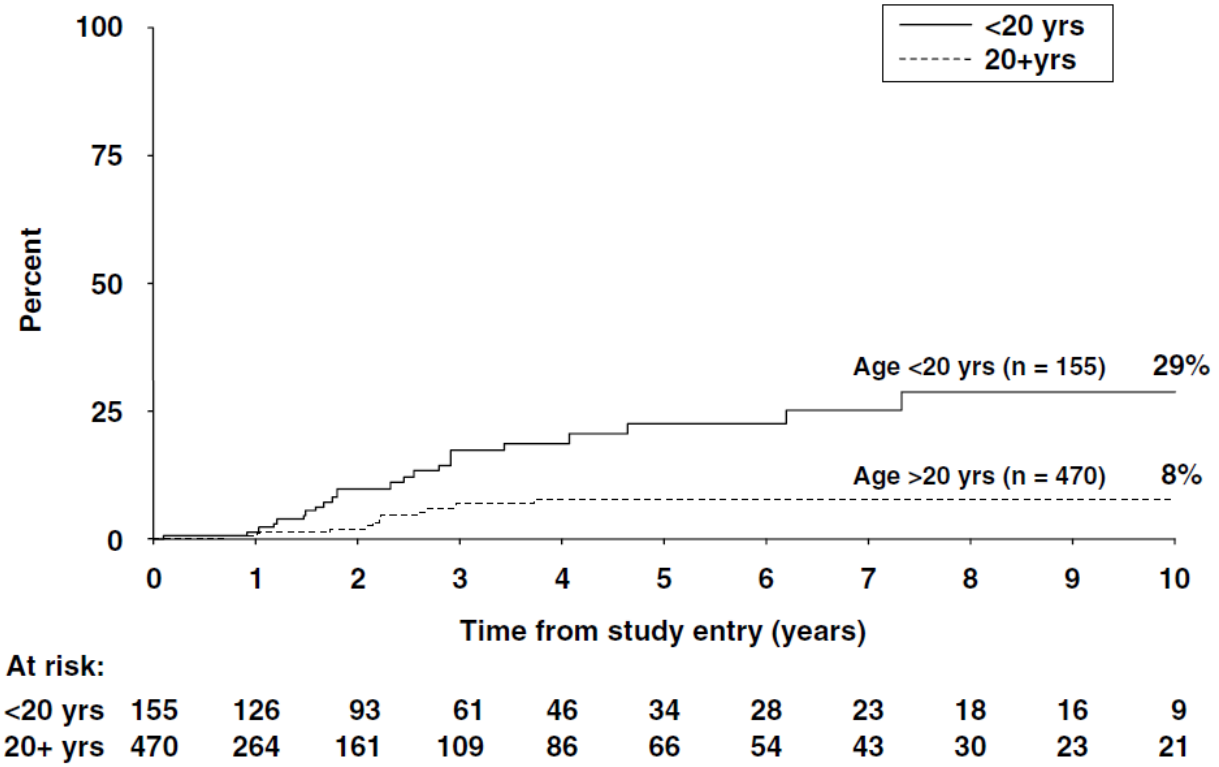
Parasole et al. *Blood Cancer Journal* (2018)8:115

a. Overall incidence in the age groups



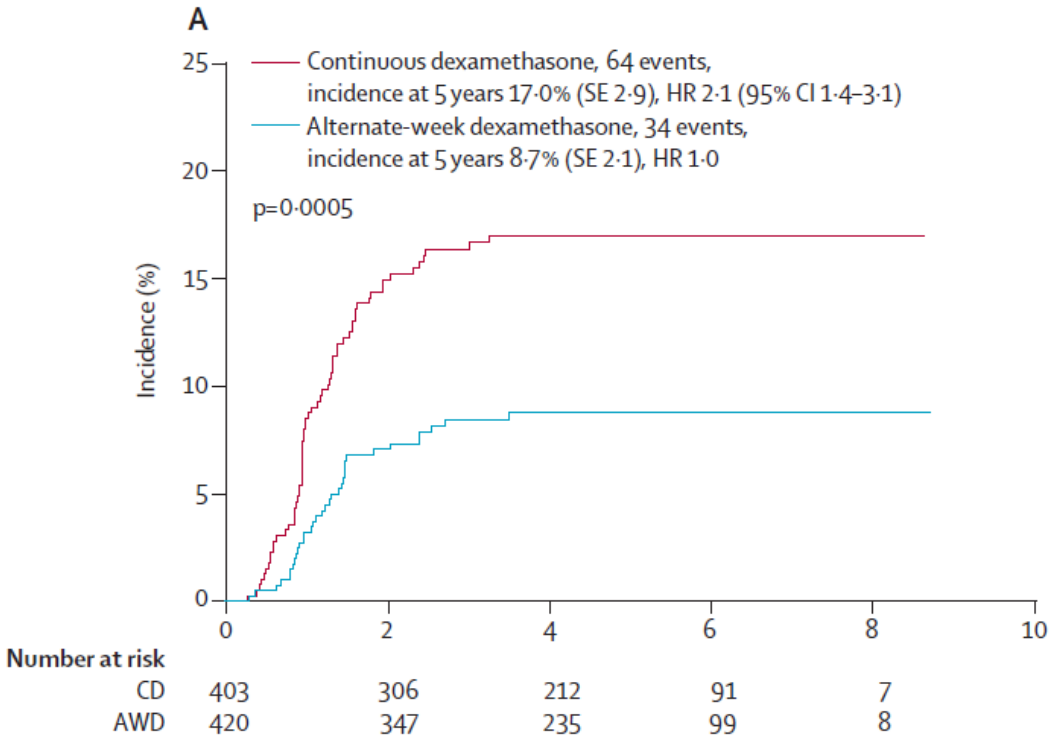
Five-year cumulative incidence of ON according to patient's age at ALL diagnosis

Osteonecrosis by age in ALL: UKALL XII study



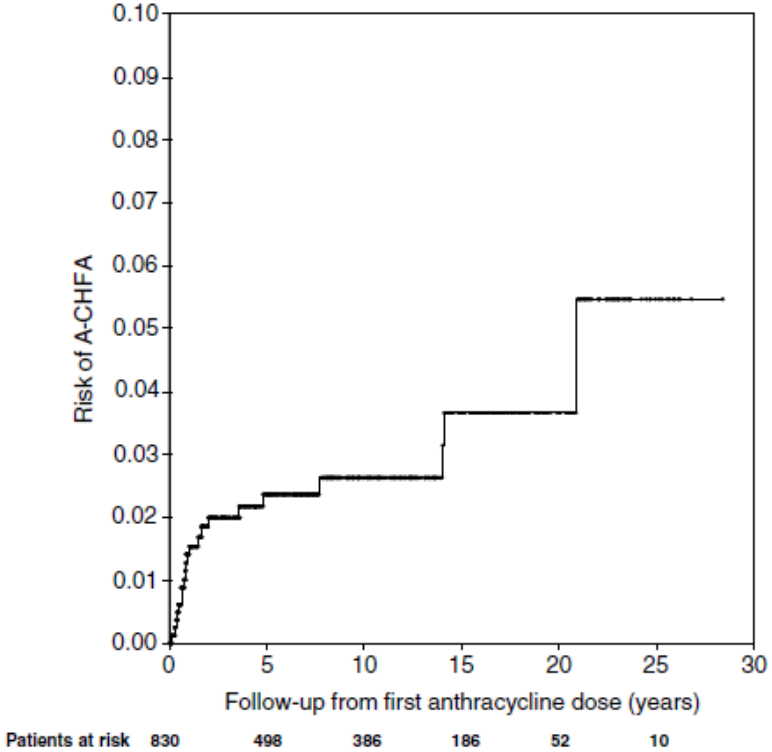
Patel B, et al. *Leukemia*. 2008;22(2):308-312.

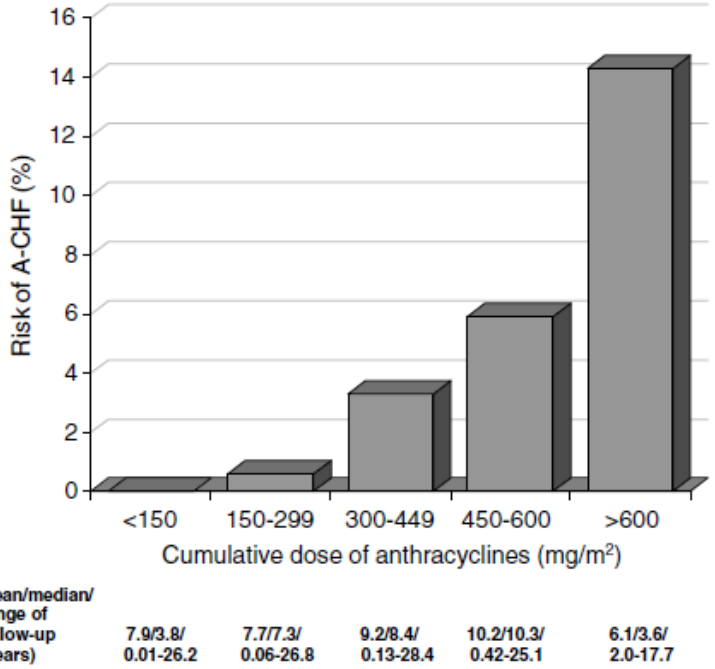
Osteonecrosis: continuous vs alternate-week dexamethasone



Mattano LA, et al. *Lancet Oncol.* 2012;13(9):906-915.

Risk of anthracycline-induced clinical heart failure in childhood cancer





Van Dalen EC, et al. *Eur J Cancer.* 2006;42(18):3191-3198.

Global Leukemia Academy

Bispecifics for Pediatric/AYA ALL

Patrick A. Brown, MD

Johns Hopkins University School of Medicine

USA

APTITUDE HEALTH

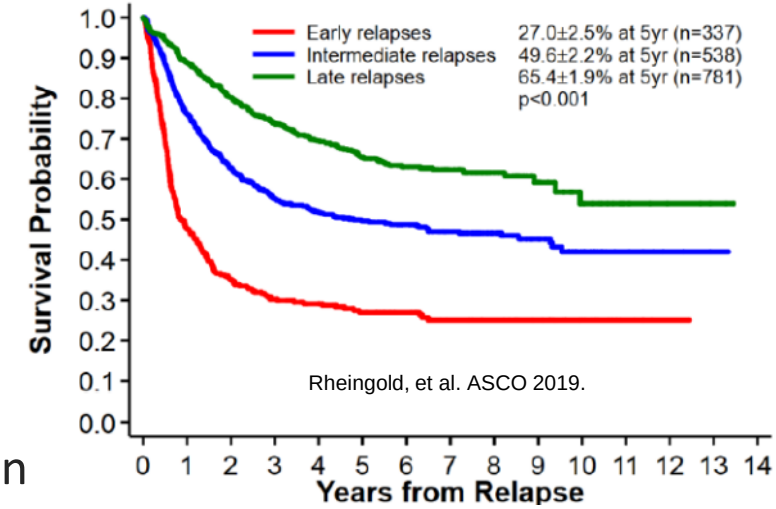
Bispecifics for Pediatric/AYA ALL

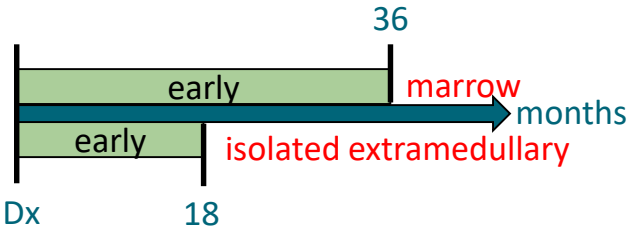
Patrick Brown, MD

Associate Professor of Oncology, Johns Hopkins University
Director, Pediatric Leukemia Program, Sidney Kimmel Comprehensive Cancer Center
Vice Chair for Relapse, COG ALL Committee
Chair, NCCN ALL Guidelines Panel

Background

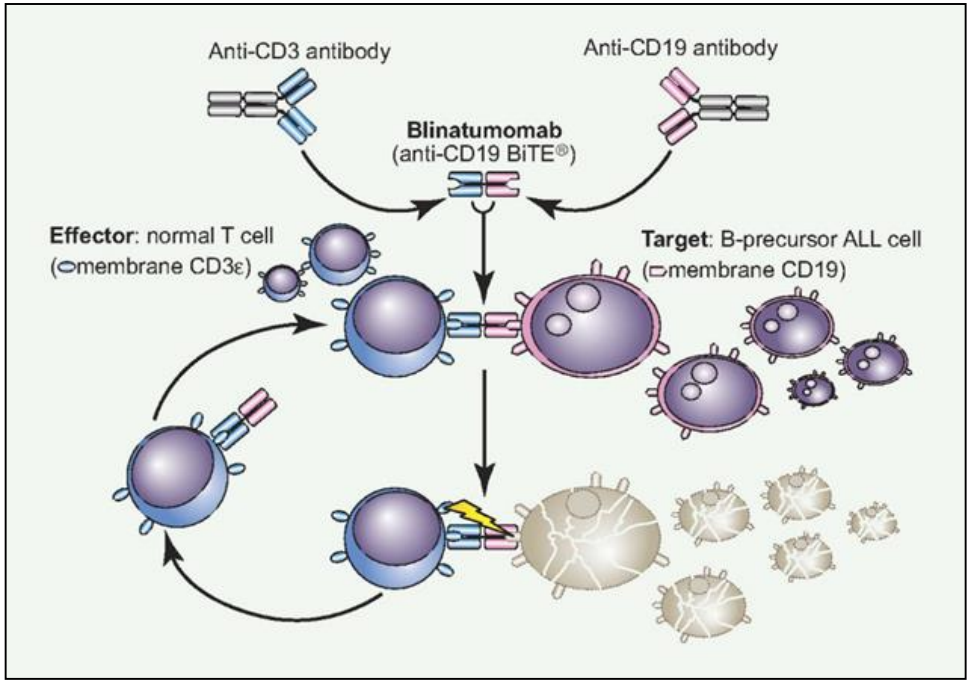
- Poor survival for 1st relapse B-ALL in children, adolescents and young adults (AYA), especially early relapses
- Standard treatment approach
  - Reinduction chemotherapy → 2nd remission
  - Consolidation
    - Early relapse: Intensive chemo → HSCT
      - Goal: MRD-negativity prior to HSCT
    - Late relapse
      - "MRD high": same as early
      - "MRD low": Intensive chemo → maintenance therapy





CHILDREN'S ONCOLOGY GROUP

Blinatumomab (CD19 BiTE)



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

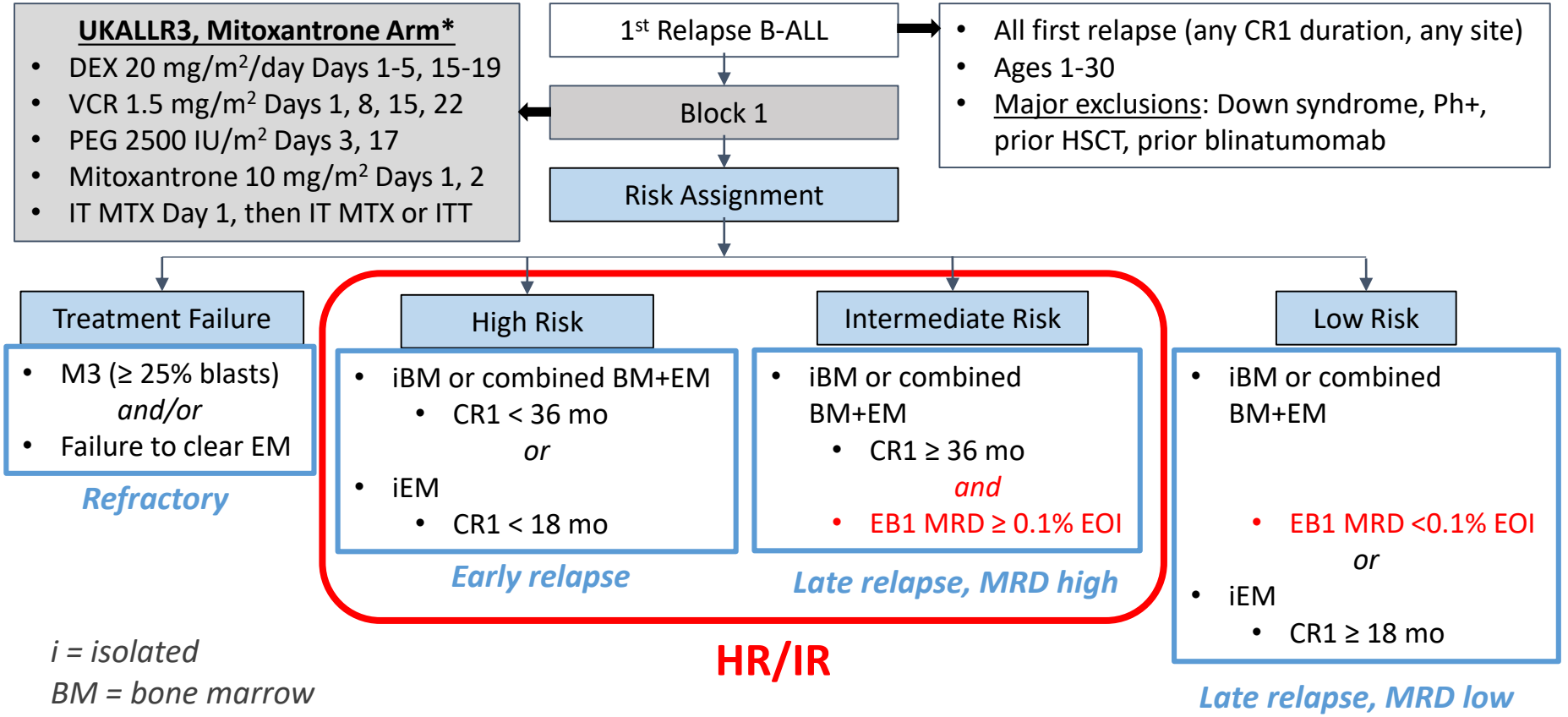
- In multiple relapsed/refractory setting (pediatrics)
  - CR 35%–40%
  - MRD-negative CR 20%–25%

  von Stackelberg et al. *J Clin Oncol.* 2016;34:4381-4389
- In MRD+ setting (adults)
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

  Gokbuget et al. *Blood.* 2018;131:1522-1531

Objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in 1st relapse of childhood/AYA B-ALL

CHILDREN'S ONCOLOGY GROUP



i = isolated
BM = bone marrow
EM = extramedullary (CNS, testes)
CR1 = duration of first remission
EB1 = end-Block 1

*UKALLR3 reference: *Parker, et al. Lancet. 2010; 376: 2009-17*

Stratifications

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

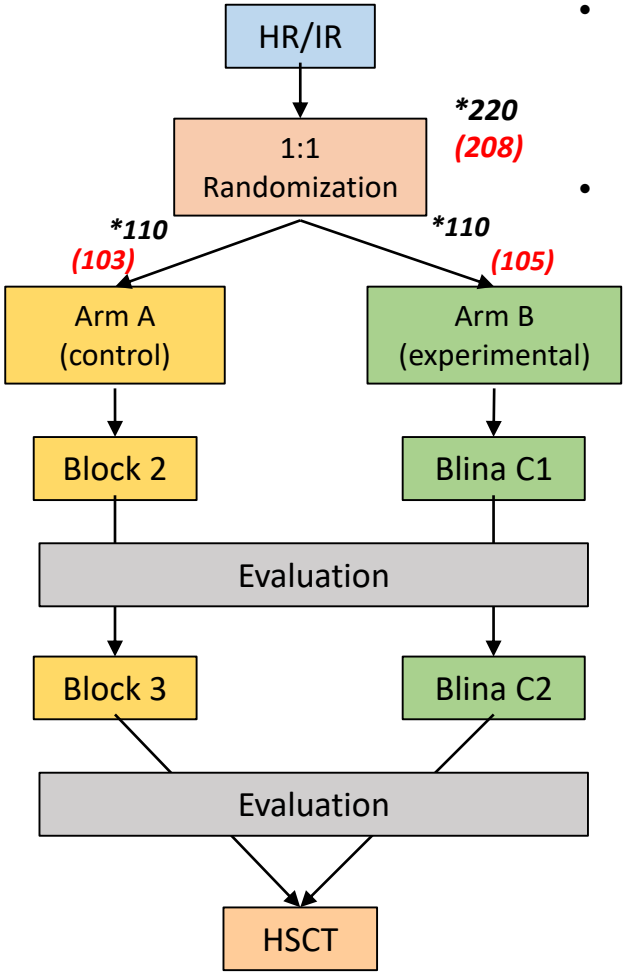
UKALLR3, Block 2*

- 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 ARAC, Erwinia Weeks 1-2
- ID MTX, Erwinia Week 4
- IT MTX or ITT

*UKALLR3 reference: *Parker, et al. Lancet. 2010; 376: 2009-17*



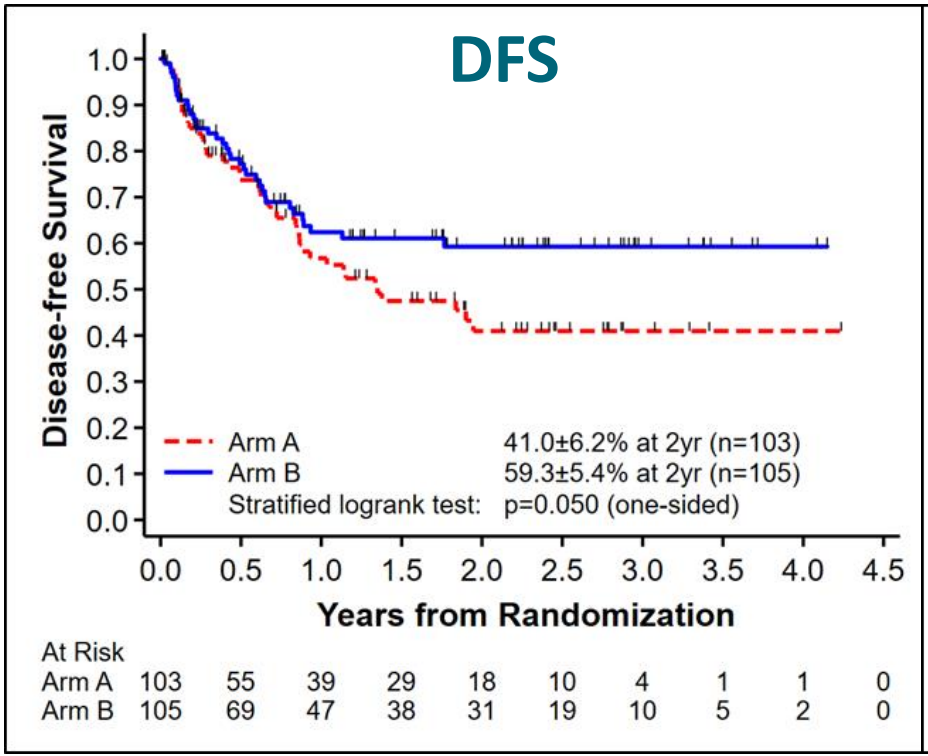
- Endpoints
  - Primary: DFS
  - Other: OS, MRD response, ability to proceed to HSCT
- Sample size n=220 (110 per arm)
  - Power 85% to detect HR 0.58 with 1-sided α=0.025
  - Increase 2 yr DFS from 45% to 63%

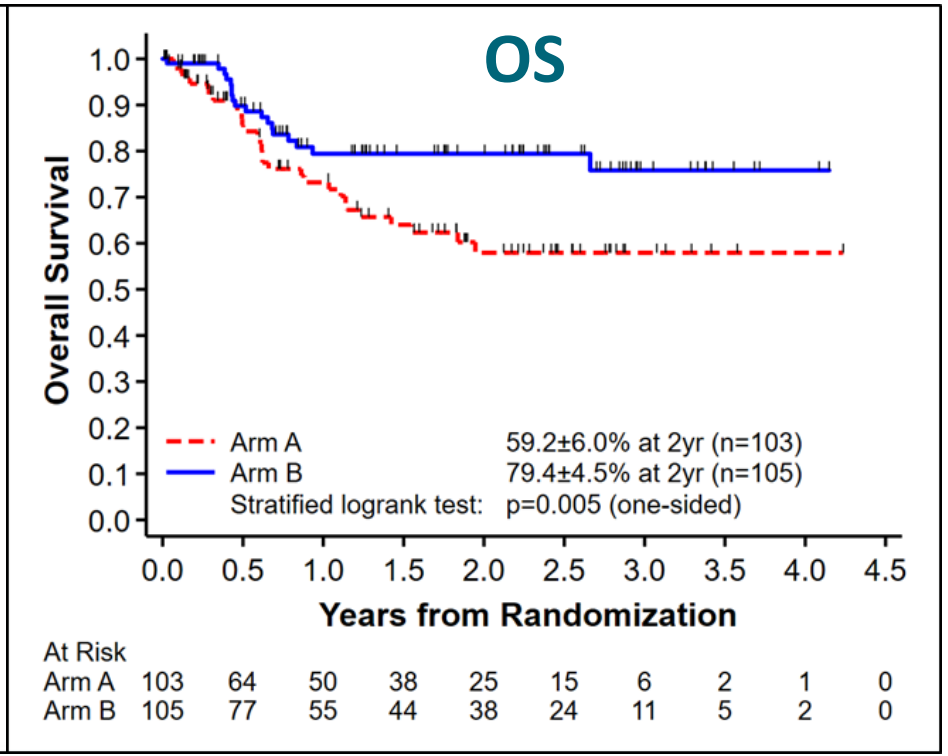
Blina C1 and Blina C2

- Blinatumomab 15 ug/m2/day x 28 days, then 7 days off
- Dex 5 mg/m2/dose x 1 premed (C1 only)

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

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

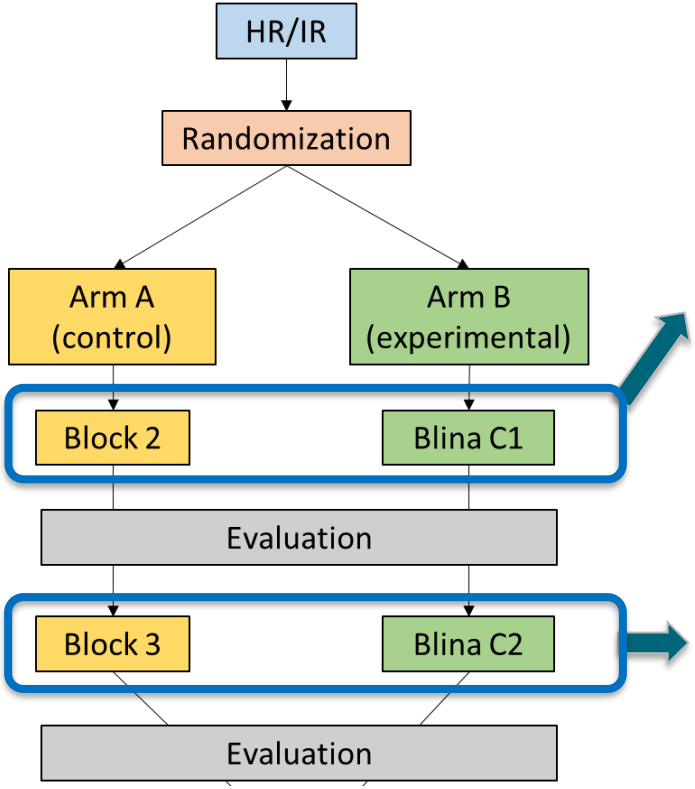


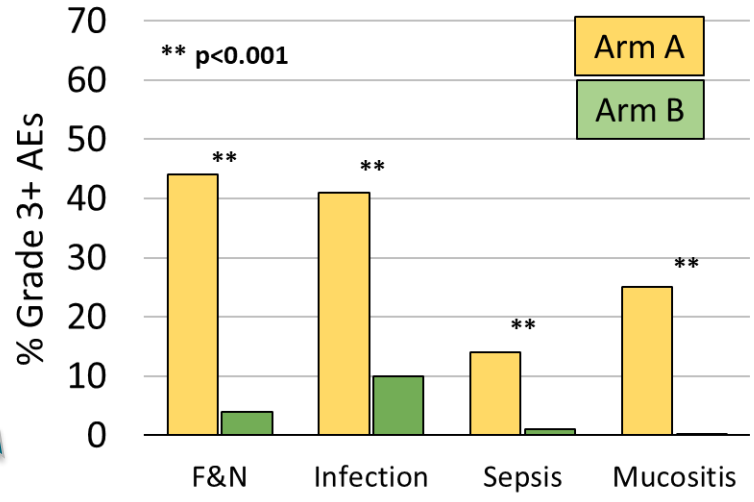


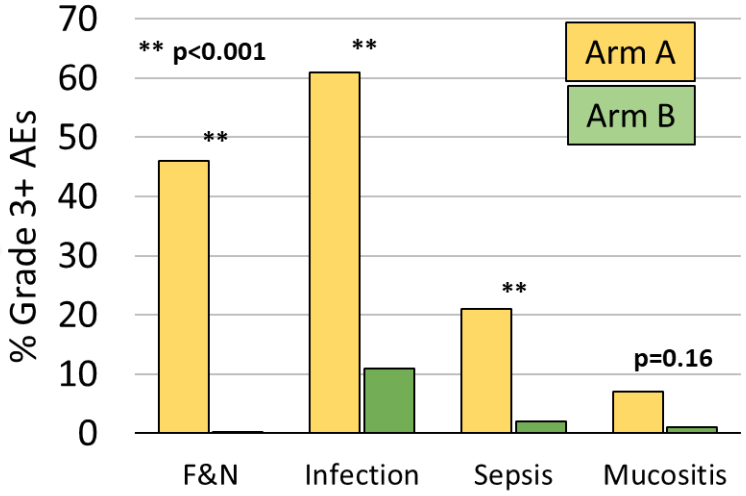
CHILDREN'S ONCOLOGY GROUP

Median follow up 1.4 years

Adverse Events



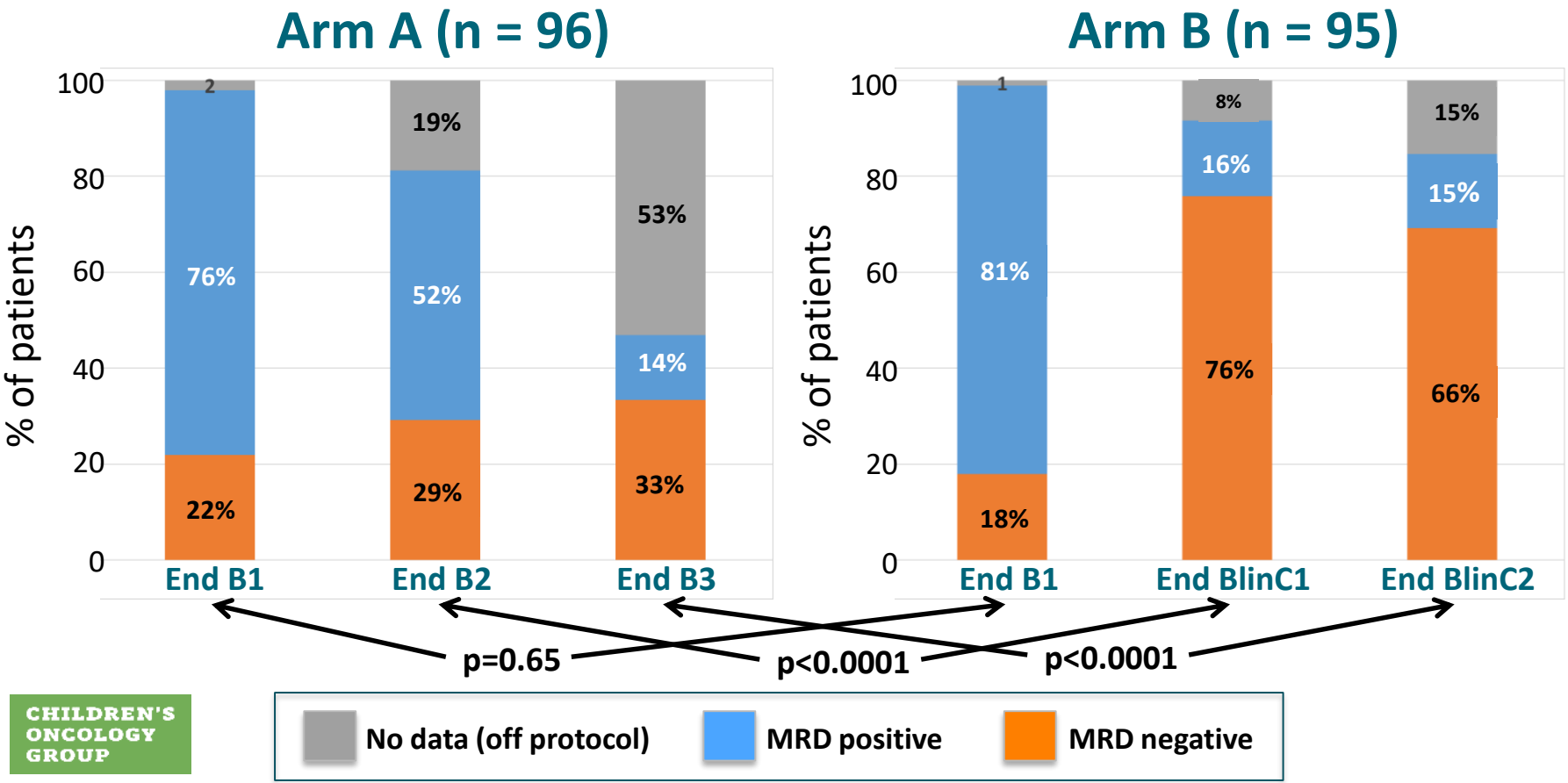




- *N = 4 post-induction Grade 5 AEs on Arm A (all infections)*
- *N = 0 on Arm B*
- *Ages of Arm A deaths: 2, 17, 23, and 26 years old (AYA-skewed)*
- ***NOTE: AE rates significantly higher in AYA (Hogan, et al. ASH Abstract 2018)***

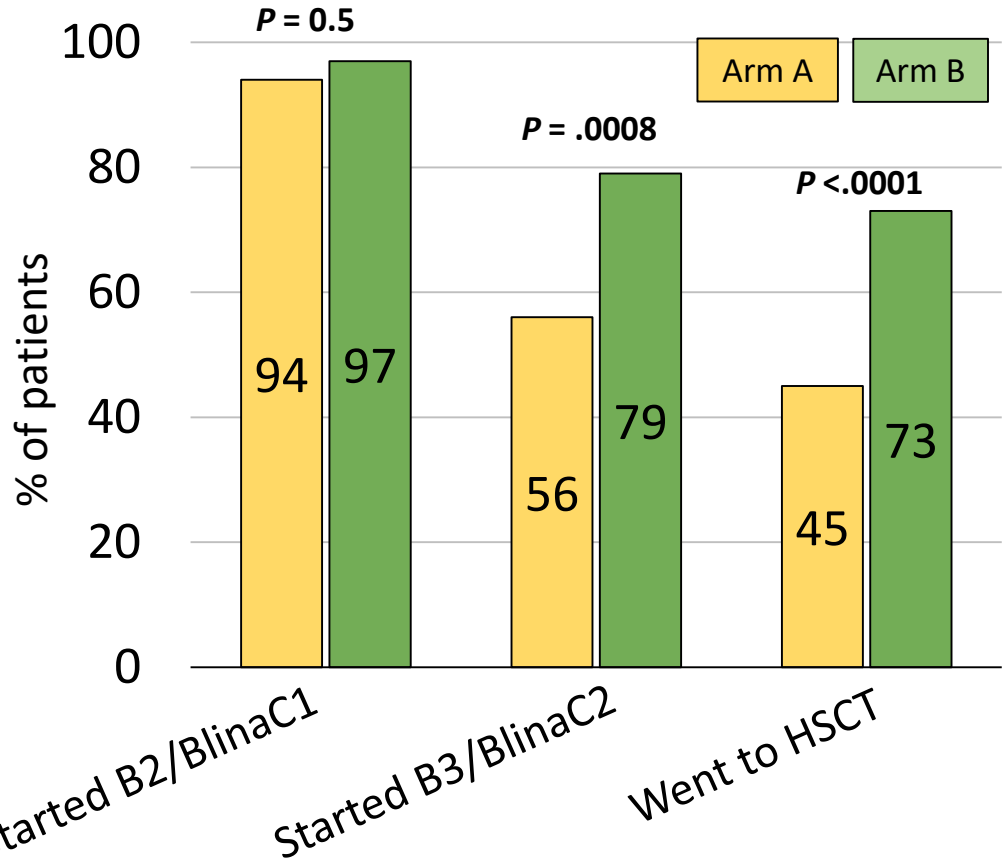
CHILDREN'S ONCOLOGY GROUP

MRD Clearance (for iBM and BM + EM)



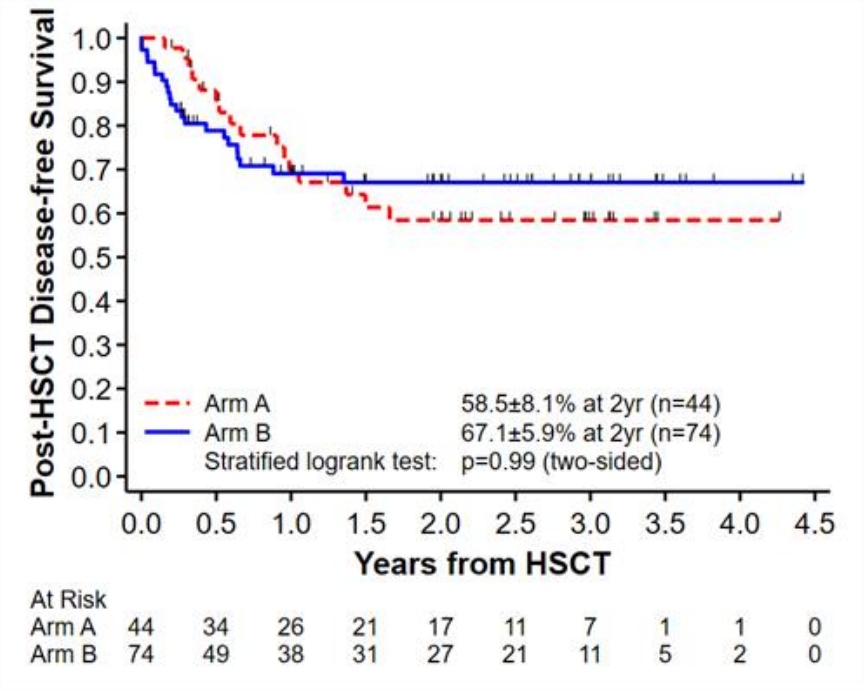
CHILDREN'S ONCOLOGY GROUP

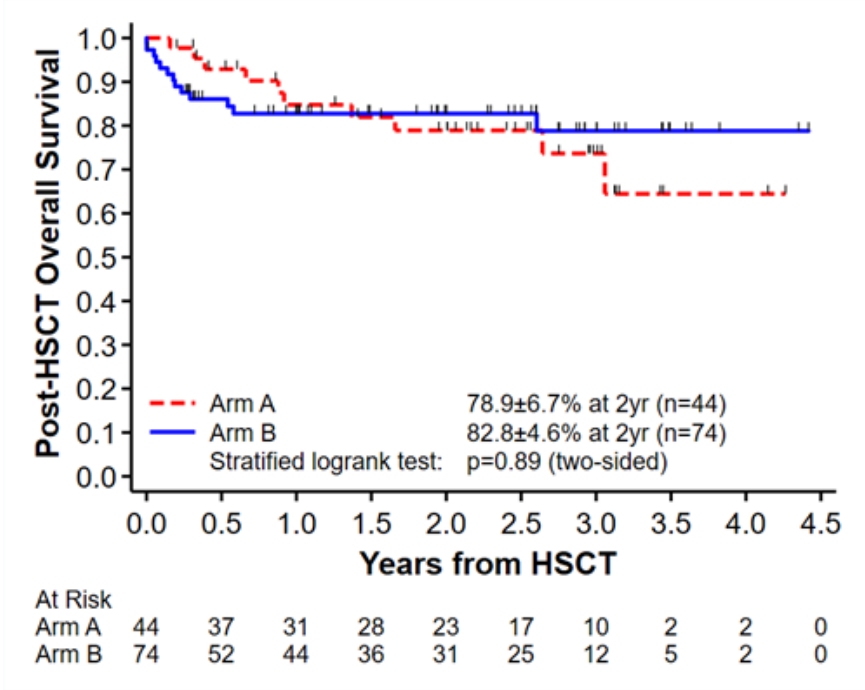
Proceeding to Transplant: Arm A vs Arm B



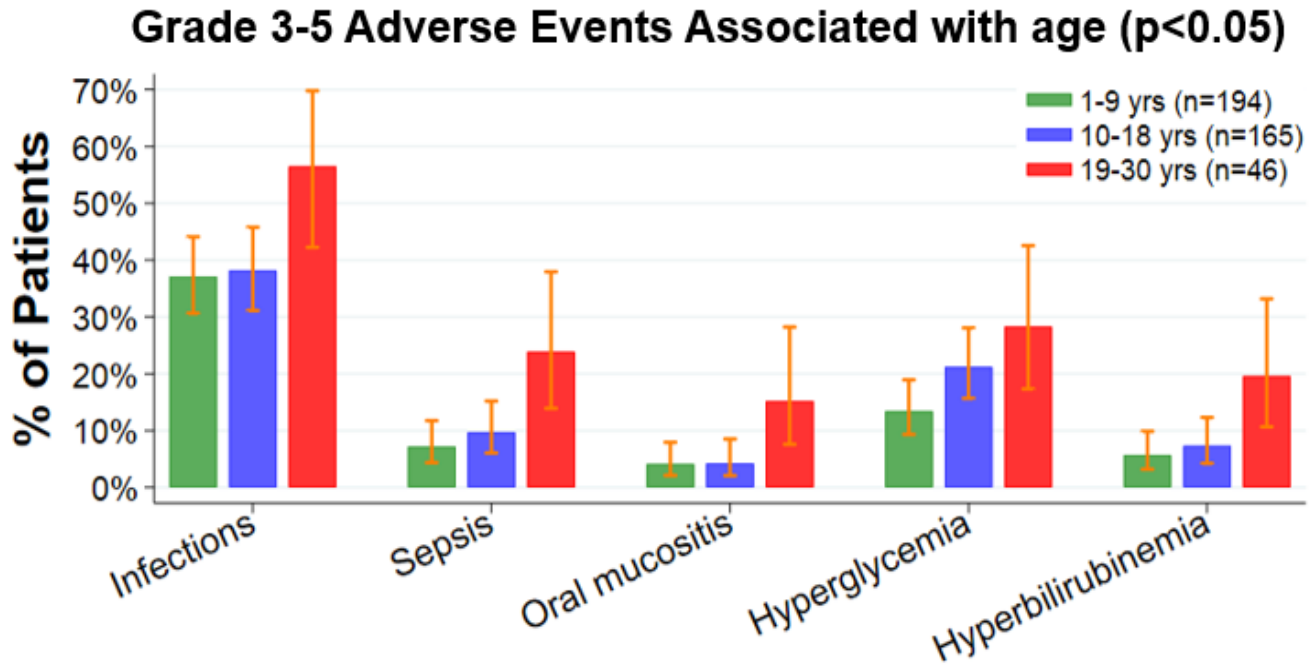
A significant contributor to the improved survival for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may be the **ability of blinatumomab to successfully bridge to HSCT**

Post-HSCT Survival





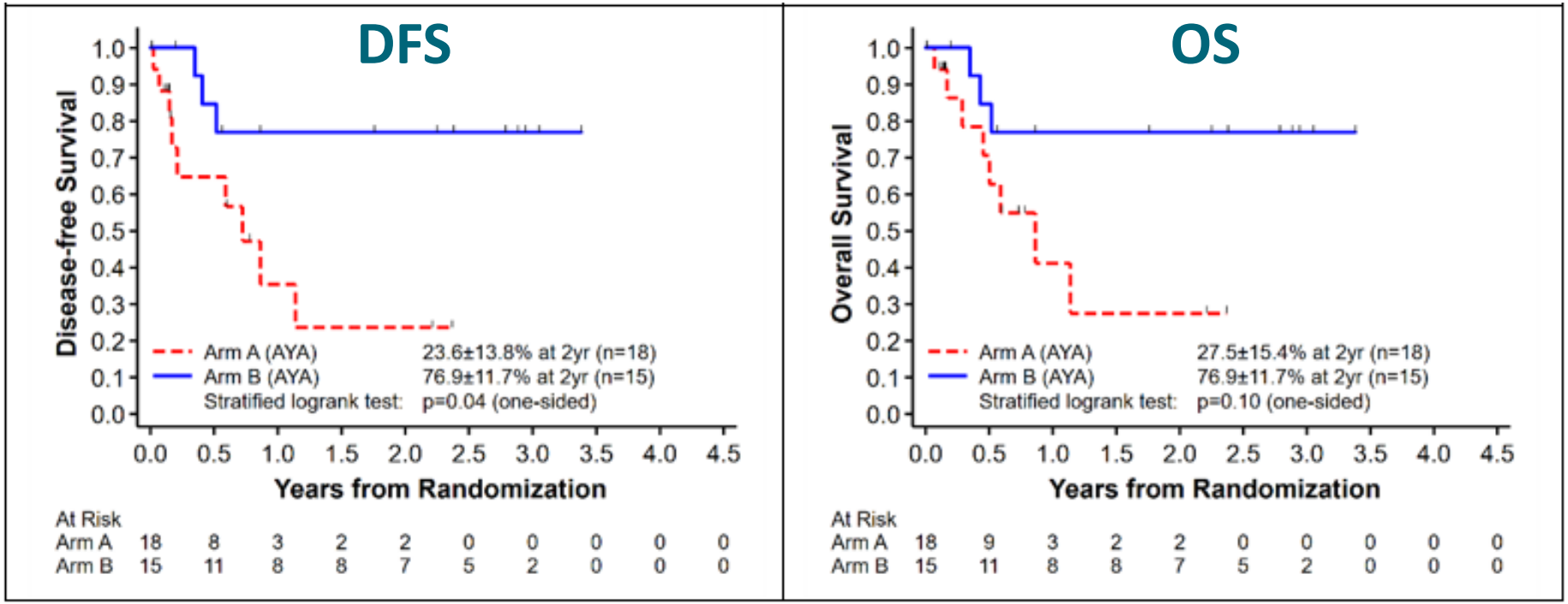
Results AYA Patients (ages 18–30 at relapse)



CHILDREN'S ONCOLOGY GROUP

Hogan, et al. *Blood.* 2018;132(suppl_1):1382.

Results AYA Patients (ages 18–30 at relapse; N = 33/16%)



CHILDREN'S ONCOLOGY GROUP

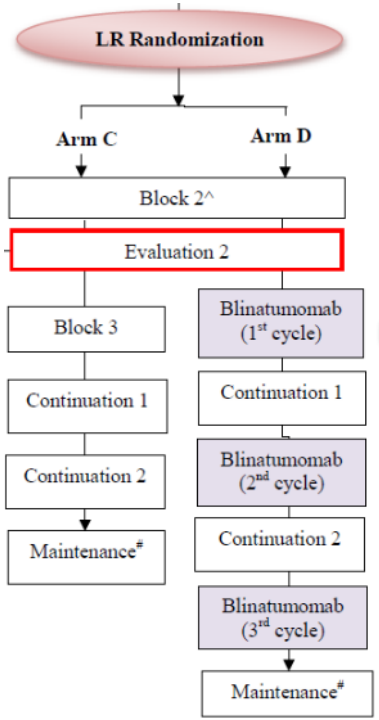
Median follow up 1.4 years

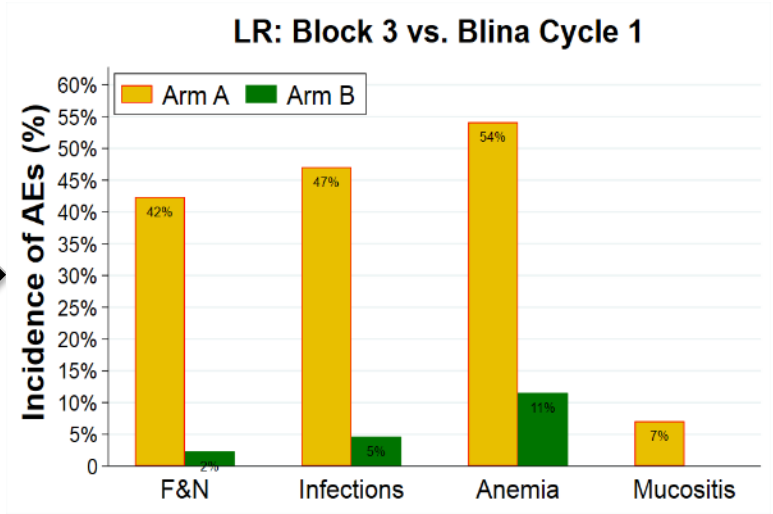
COG AALL1331: LR Randomization

LR

- BM or combined ≥36 mo, MRD <0.01% EOI
- IEM ≥18 mo

- Blinatumomab 15 µg/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed





Other outcomes pending release by DSMC

CHILDREN'S ONCOLOGY GROUP

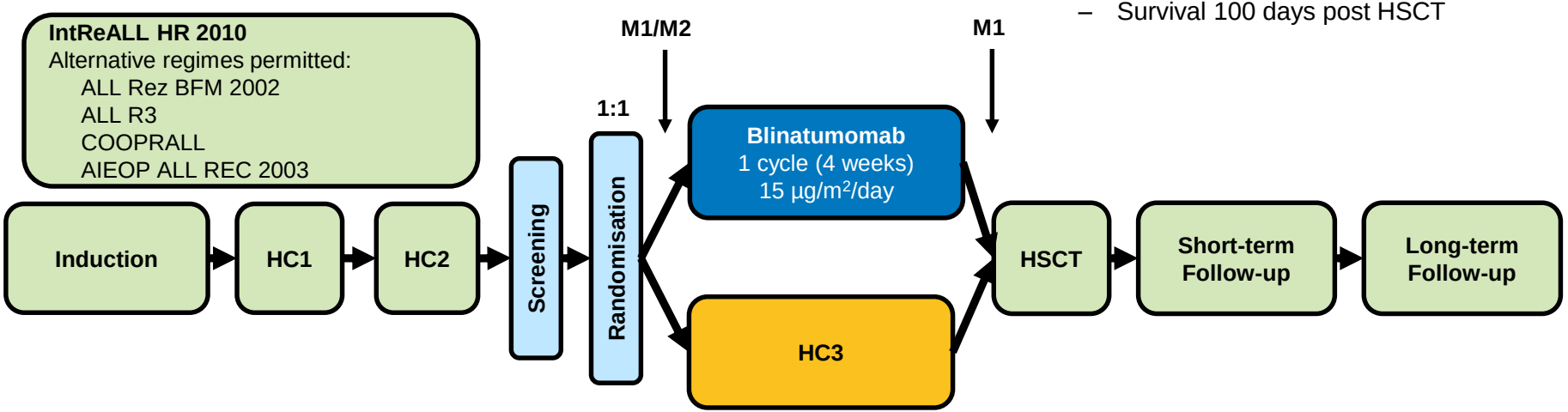
Unpublished data.

Amgen 20120215: Open-label, randomised, Phase 3 trial: 47 centres, 13 countries

Key eligibility criteria
- Age >28 days < 18 years
- HR 1st relapse Ph– BCP-ALL
- M1 or M2 marrow at randomization
- No CNS disease, unless treated before enrollment
- No clinically relevant CNS pathology

Stratification
- Age: <1 year, 1 to 9 years, >9 years
- BM status at end of HC2
  - M1 with MRD >10^{-3}
  - M1 with MRD <10^{-3}
  - M2

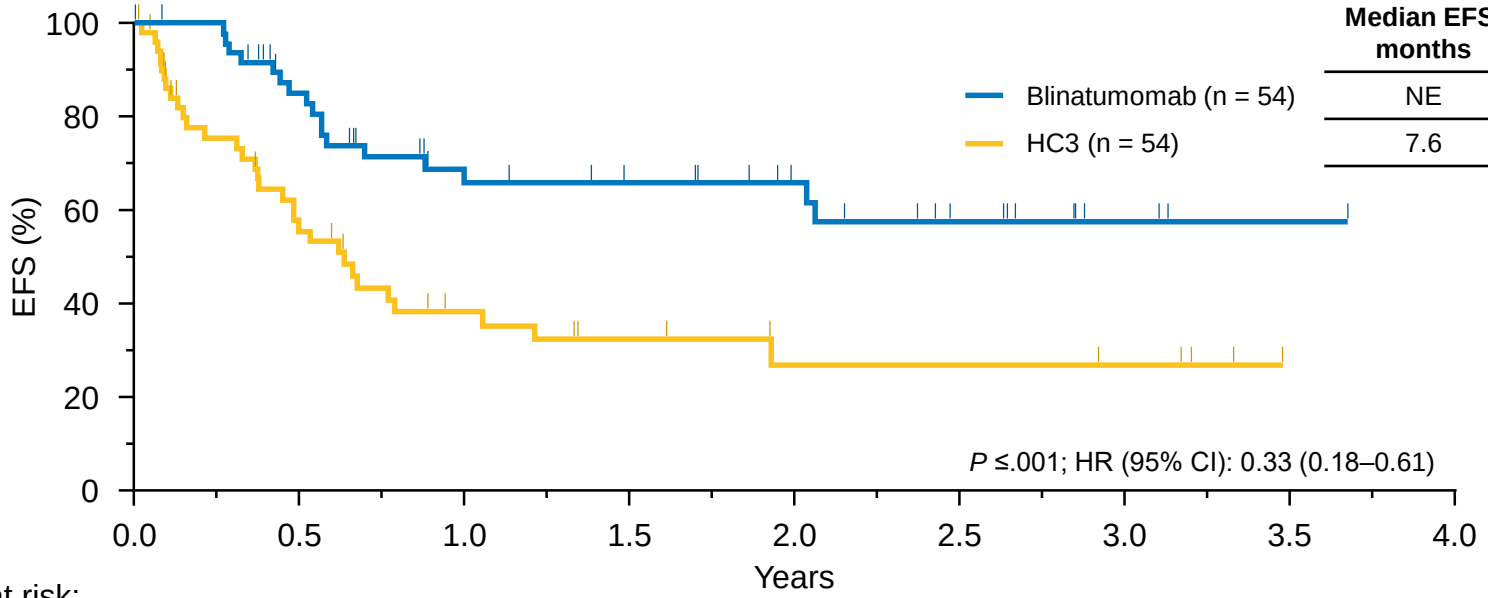
Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post HSCT



Locatelli F, et al. EBMT 2020; Abstract GS2-5.

BCP, B-cell precursor; EFS, event-free survival; HC, high-risk consolidation.

Superior EFS in the Blinatumomab Arm



	Median EFS, months	95% CI
Blinatumomab (n = 54)	NE	24.4–NE
HC3 (n = 54)	7.6	4.5–12.7

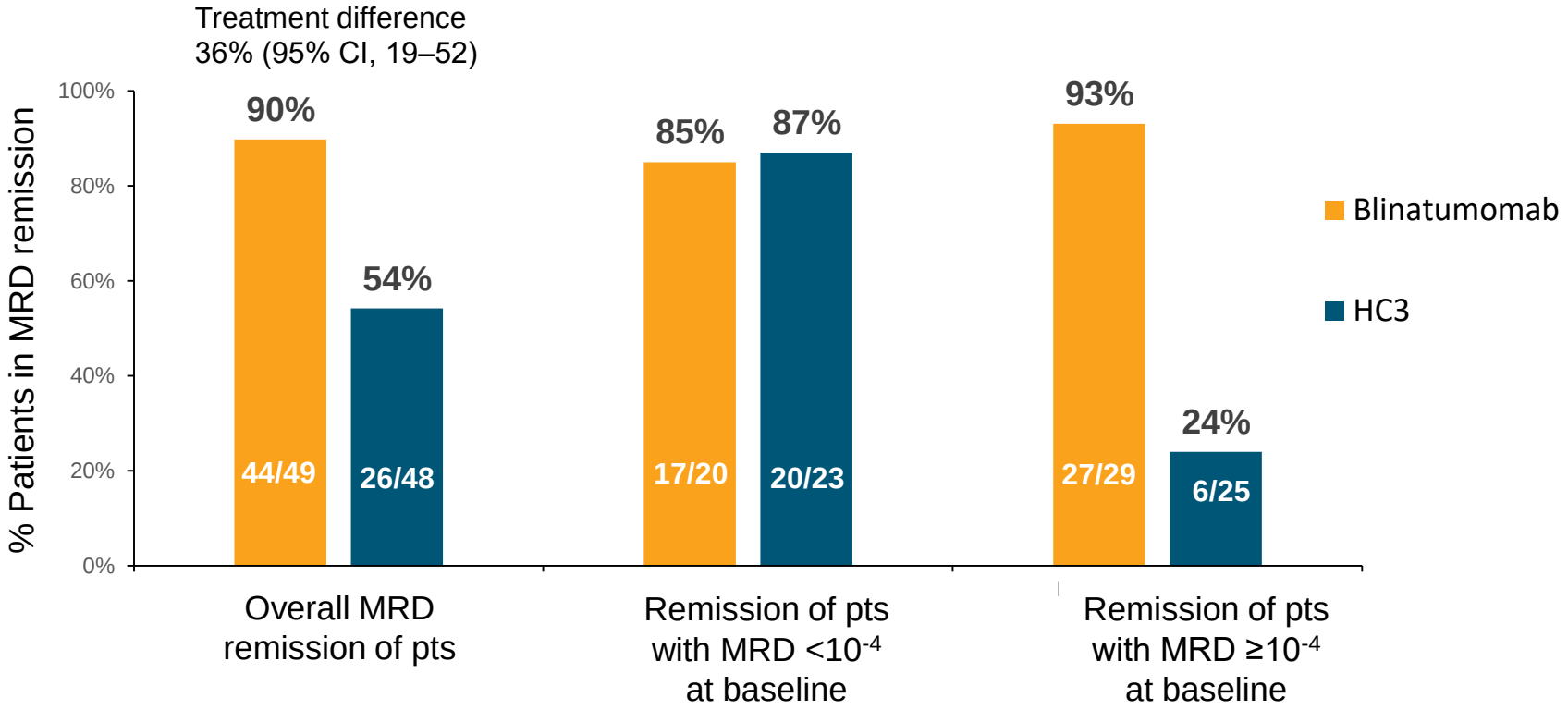
Subjects at risk:

Blinatumomab	54	50	38	29	24	23	21	19	16	13	10	7	4	1	1	0
HC3	54	35	25	17	13	11	9	8	5	5	5	5	4	2	0	

Adapted from Locatelli F, et al. EBMT 2020; Abstract GS2-5 and oral presentation.

P, stratified log rank *P* value; HR, hazard ratio from stratified Cox regression.

Superior MRD Remission by PCR in the Blinatumomab Arm (overall and by baseline* MRD status)



*Baseline: end of HC2 (screening sample before enrollment).
PCR, polymerase chain reaction.

Conclusions for Relapse Trials

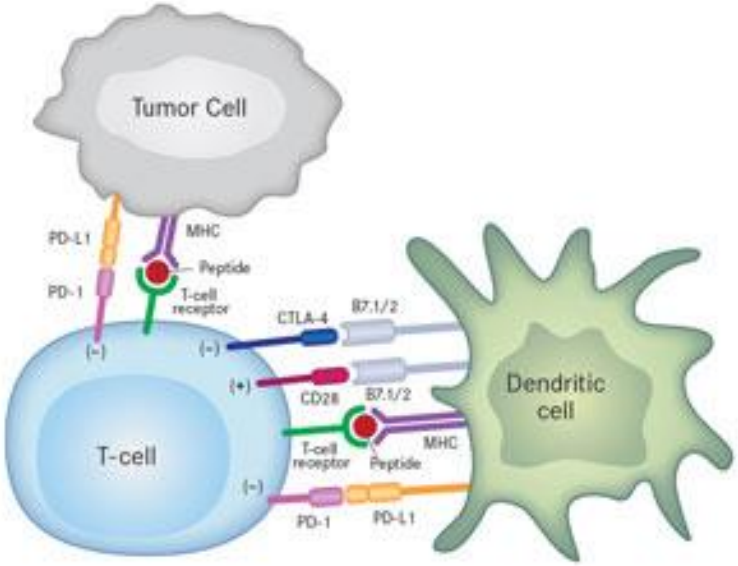
- For children and AYA patients with HR/IR first relapse of B-ALL, blinatumomab is superior to standard chemotherapy as post-reinduction consolidation prior to HSCT, resulting in
  - Fewer and less-severe toxicities (especially AYA)
  - Higher rates of MRD response
  - Greater likelihood of proceeding to HSCT
  - Improved disease-free and overall survival
- Blinatumomab constitutes a new standard of care in this setting
- Future: Optimizing immunotherapy in relapsed ALL
  - Combination of blinatumomab and checkpoint inhibitors
  - Immunotherapy to replace or augment reinduction chemotherapy

CHILDREN'S ONCOLOGY GROUP

What Happens When Blinatumomab Doesn't Work?

- Endogenous T-cell "exhaustion"

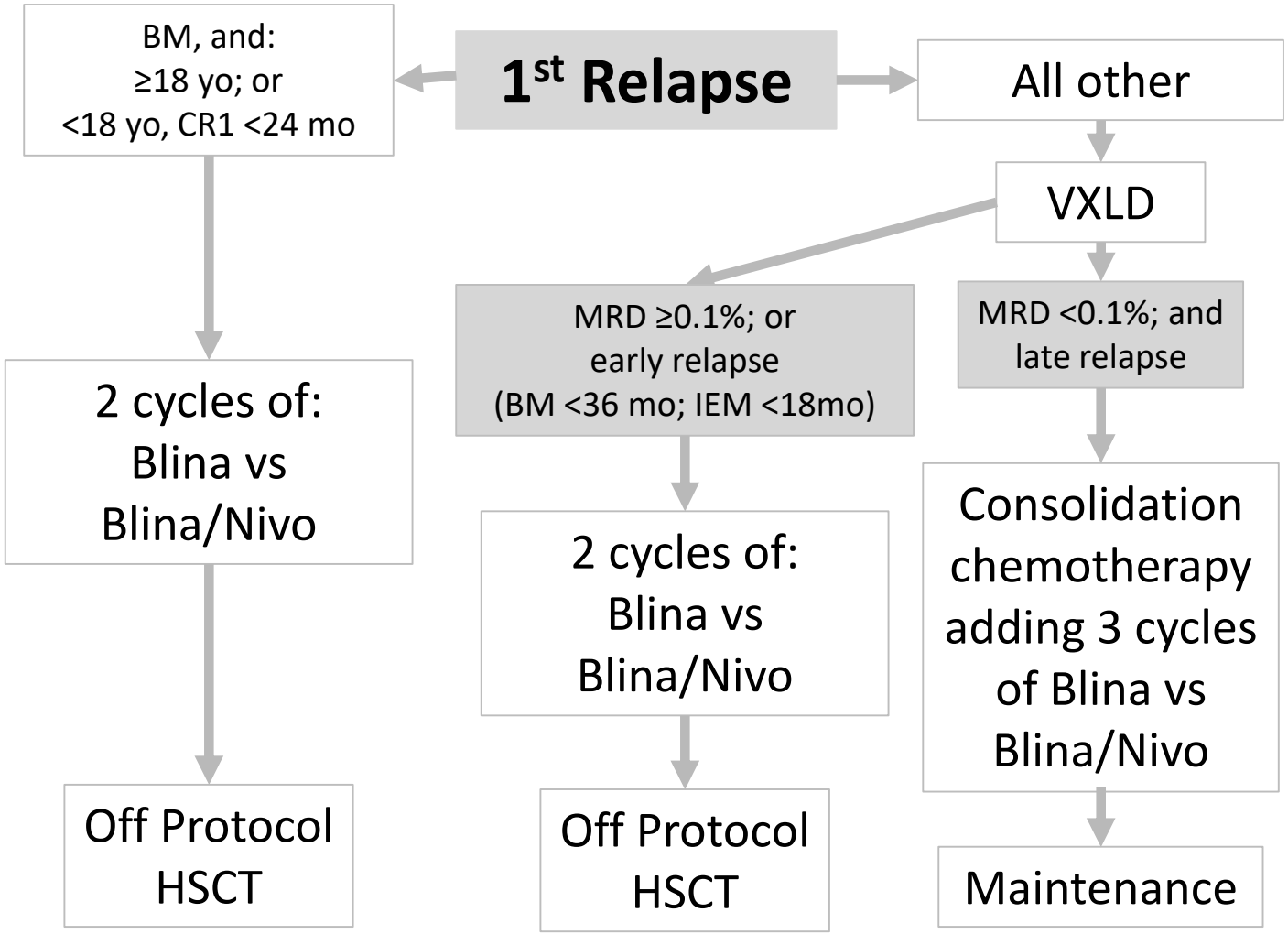
Role for immune checkpoint inhibitors (eg, anti–PD-1)?



PD-1	PD-L1	CTLA-4
Nivolumab	Atezolizumab	Ipilimumab
Pembrolizumab	Avelumab	
	Durvalumab	

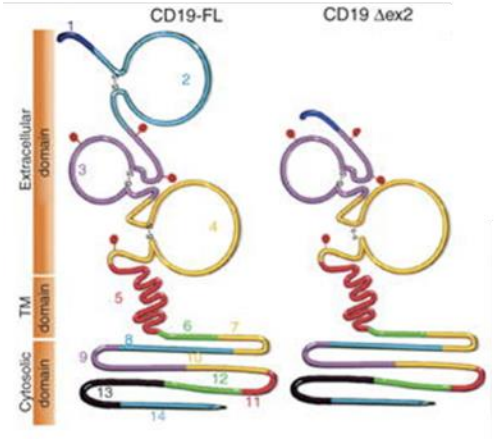
Reports of efficacy in patients relapsing after blina/CAR T cells

- Feucht, et al. *Oncotarget.* 2016;7(47):76902-76919

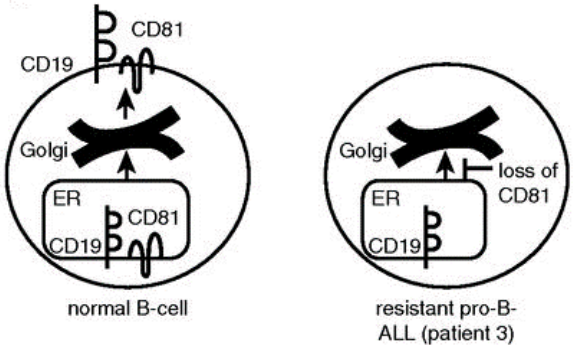

1st Relapse
BM, and:
≥18 yo; or
<18 yo, CR1 <24 mo
All other
VXLD
MRD ≥0.1%; or
early relapse
(BM <36 mo; IEM <18mo)
MRD <0.1%; and
late relapse
2 cycles of:
Blina vs
Blina/Nivo
2 cycles of:
Blina vs
Blina/Nivo
Consolidation
chemotherapy
adding 3 cycles
of Blina vs
Blina/Nivo
Off Protocol
HSCT
Off Protocol
HSCT
Maintenance

What Happens When Blinatumomab Doesn't Work?

- LATE: Antigen escape
  - CD19 splice variants[1]
  - Defective CD19 membrane trafficking[2]
  - Lineage switching (esp. MLL-r)[3]



Multiantigen targeting?

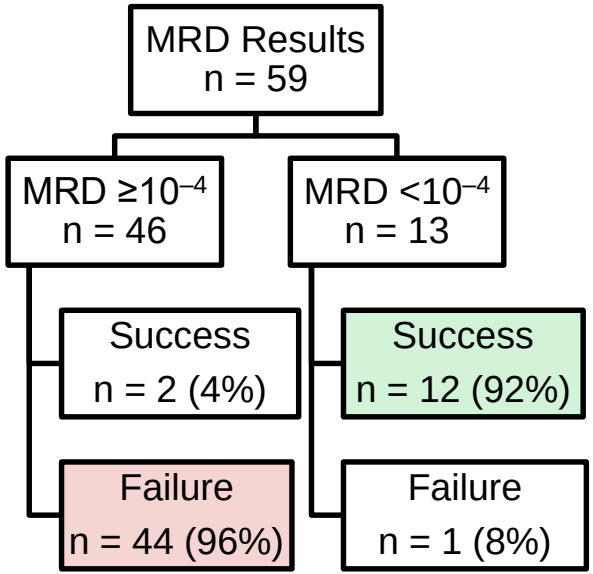


NOTE: Incidence of CD19 escape lower with blina than with CD19 CAR, likely reflecting less-potent CD19 selection pressure

1. Sotillo, et al. *Cancer Discov.* 2015;5(12):1282-1295; 2. Braig, et al. *Blood.* 2017;129(1):100-104; 3. Gardner, et al. *Blood.* 2016;127(20):2406-2410.

Can We Predict When Blinatumomab Won't Work?

- Overall, Day 15 MRD results predicted best response after 2 cycles with 95% accuracy (correctly in 56 of 59 patients)



Parameter	Accuracy (n/N)	Accuracy (%)
Day 8 PB morphology (clearance of blasts)	19/40	49
Day 15 BM morphology (M1)	54/60	90
Day 29 BM morphology (M1)	42/51	84
Day 15 BM MRD (< 10^{-4})	***56/59***	***95***
Day 29 BM MRD (< 10^{-4})	42/49	86

NOTE: Day 8 PB is an especially poor predictor of subsequent response

- Study definitions
  - "**Success**" was defined as complete MRD response in CR (n = 14)
  - "**Failure**" was defined as anything other than success (n = 50)

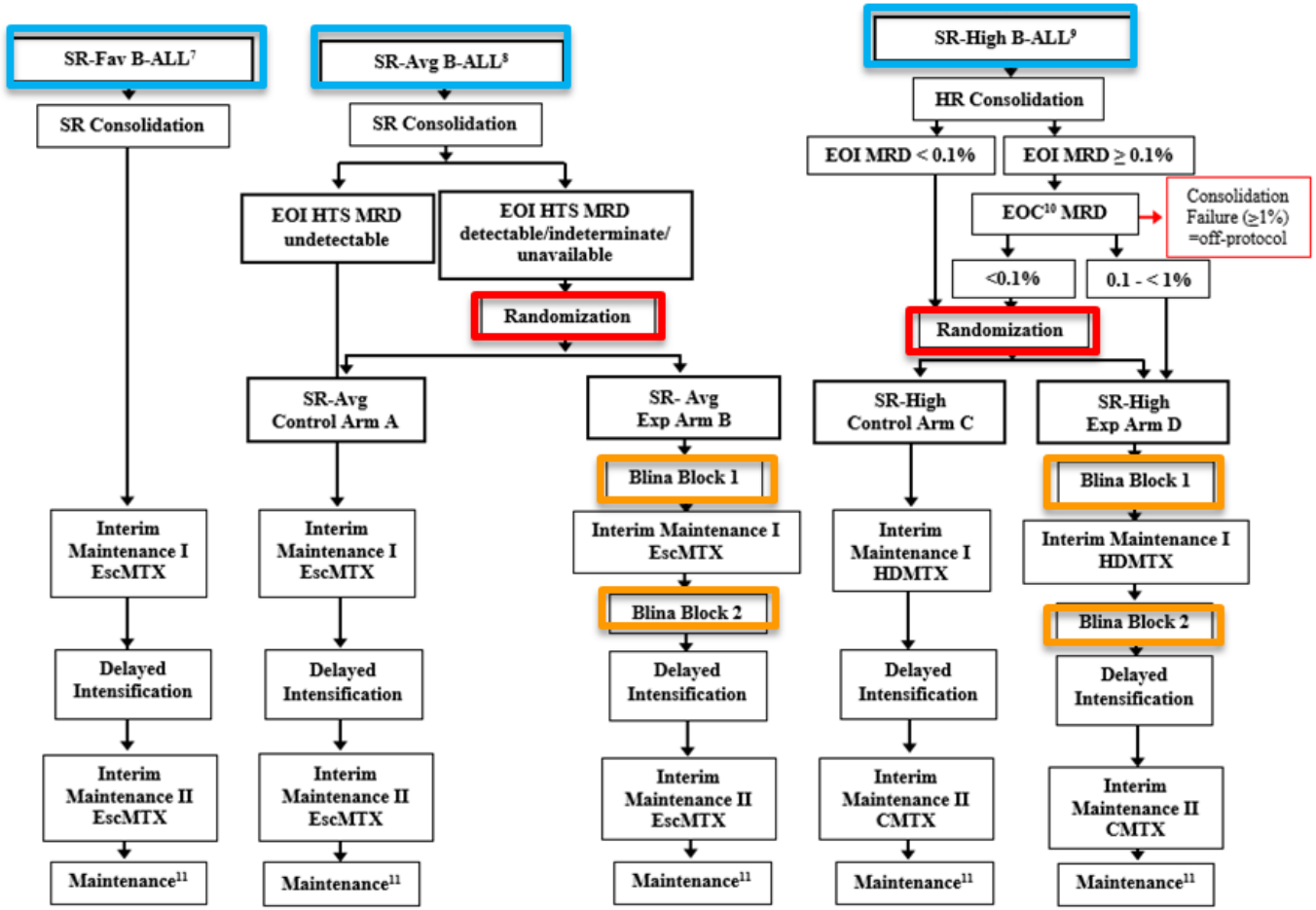
CR, complete remissions; MRD, minimal residual disease

As patients with MRD ≥10^{-4} at Day 15 could potentially pursue alternative therapies, such as dose escalation or combination therapies, ***Day 15 MRD results may allow personalized treatment and improve outcomes in pediatric patients with relapsed/refractory B-ALL***

Brown, P, et al. *Br J Haematol*. 2020;188:e36-e39.

Moving Blinatumomab Into Upfront B-ALL

COG AALL1731: Post-Induction



CHILDREN'S ONCOLOGY GROUP

Blinatumomab: Questions and Discussion

- HSCT after MRD clearance with blinatumomab?
- Role of HTS (ClonoSEQ) MRD?
- Ability of checkpoint inhibition to safely enhance blinatumomab response?
- Earlier (pre-treatment) predictive biomarkers of blinatumomab response?
- Risk of prior blinatumomab exposure and CD19 escape after subsequent CD19 CAR T therapy?

Global Leukemia Academy

CAR T Cells for Pediatric/AYA ALL

Franco Locatelli, MD

University of Rome IRCCS Ospedale Pediatrico Bambino Gesù of Rome

Italy

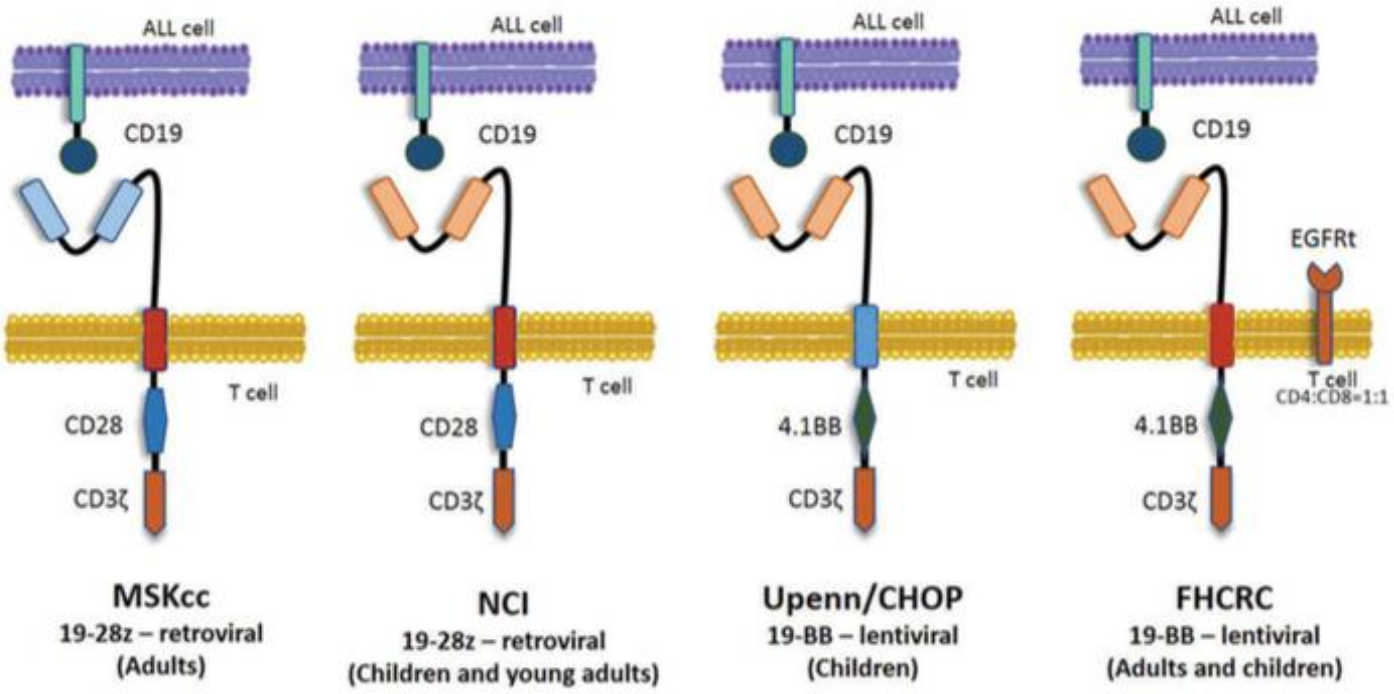
APTITUDE HEALTH

CAR T Cells for Pediatric/AYA ALL

Franco Locatelli, MD
Università Sapienza, Roma
Dept. Pediatric Hematology/Oncology and Cell/Gene Therapy
IRCCS Ospedale Bambino Gesù, Roma, Italy

Published constructs of second-generation CD19 CARs for ALL

CAR design important for persistence and sustained efficacy



Del Bufalo F, Locatelli F. *Exp Rev Clin Immunol.* 2019.

Published studies of second-generation CD19 CAR-T cells for R/R ALL

Reference	Treated Patients (n)	CAR Vector	Response + Consolidation
Maude SL, et al. *N Engl J Med.* 2014;371:1507-1517	30 (18 post-HSCT)	FMC63-41BB-ζ lentivirus	**27** CR; **22** MRD-negative **3** ➔ allogeneic HSCT
Lee DW, et al. *Lancet.* 2015;385:517-528	20 (7 post-HSCT)	FMC63-CD28-ζ retrovirus	**13** CR + **1** CRi; **12** MRD-negative **10** ➔ allogeneic HSCT
Gardner RA, et al. *Blood.* 2017;129:3322-3331	43 (28 post-HSCT)	FMC63-41BB-ζ lentivirus	**41** CR; **41** MRD-negative **11** ➔ allogeneic HSCT
Maude SL, et al. *N Engl J Med.* 2018;378:439-448	75 (46 post-HSCT)	FMC63-41BB-ζ lentivirus	**61** CR/CRi; **61** MRD-negative **8** ➔ allogeneic HSCT
Turtle CJ, et al. *J Clin Invest.* 2016;126:2123-2138	30 (11 post-HSCT)	FMC63-41BB-ζ lentivirus	**29** CR; **25** MRD-negative **13** ➔ allogeneic HSCT
Park JH, et al. *N Engl J Med.* 2018;378:449-459	53 (19 post-HSCT)	SJC25C1-CD28-ζ retrovirus	**44** CR; **32** MRD-negative **17** ➔ allogeneic HSCT

- **251 patients treated: 85% CR, 76% MRD-negative**

ELIANA study design

Key Eligibility Criteria

- **Inclusion**
  - R/R B-cell ALL, aged 3-21 years[a]
  - Bone marrow with ≥5% lymphoblasts
- **Exclusion**
  - Isolated extra-medullary disease relapse
  - Prior CD19-directed or gene therapy

Endpoints

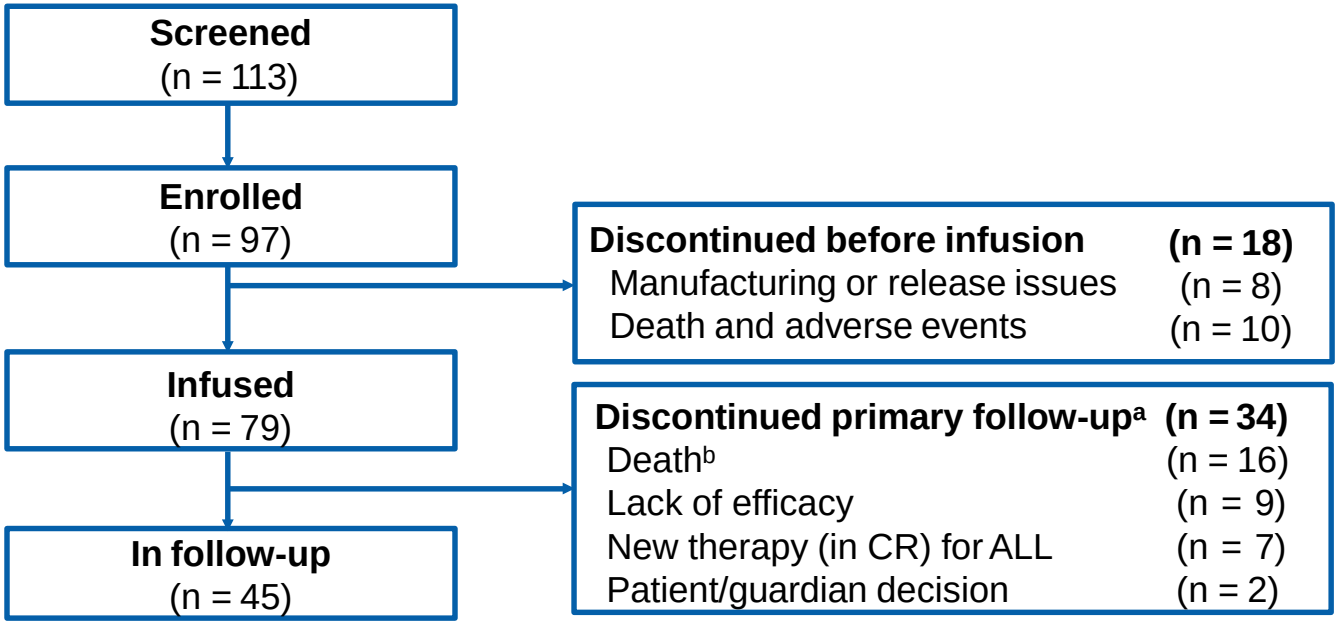
- Primary endpoint: Overall remission rate (CR + CRi) within 3 months
  - 4-week maintenance of remission
  - IRC assessment
- Secondary endpoints
  - MRD status, DOR, OS, EFS, cellular kinetics, safety

Study Treatment

- **Lymphodepleting chemotherapy prior to infusion**
  - Fludarabine 30 mg/m^2 IV daily for 4 doses
  - Cyclophosphamide 500 mg/m^2 IV daily for 2 doses
- **Tisagenlecleucel dose range (single infusion)**
  - 0.2 to 5.0 × 10^6 cells/kg for patients ≤50 kg
  - 0.1 to 2.5 × 10^8 cells for patients >50 kg

[a] Age of 3 years at the time of screening to age of 21 years at time of initial diagnosis.
CR, complete response; CRi, CR with incomplete blood count recovery; DOR, duration of response; IRC, Independent Review Committee; MRD, minimal residual disease; OS, overall survival; R/R B-ALL, relapsed or refractory B-cell acute lymphoblastic leukemia.

ELIANA patient disposition



Median time from infusion to data cut-off (13 April 2018) was 24.2 months (range, 4.5-35.1 months)

[a] Patients followed for survival.

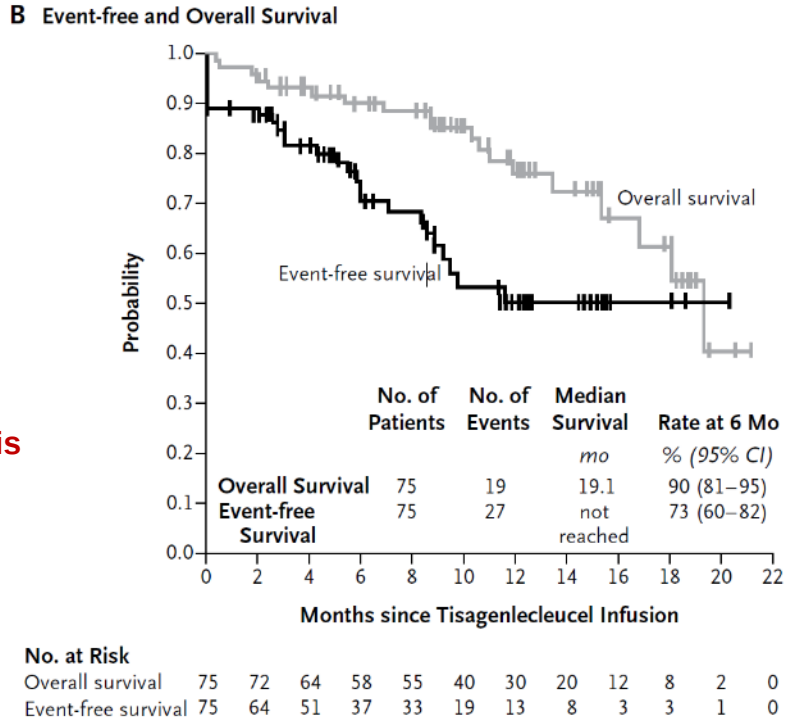
[b] One death occurred while the patient was in remission; other deaths occurred after treatment failure or relapse.

Summary of ELIANA study

ORIGINAL ARTICLE

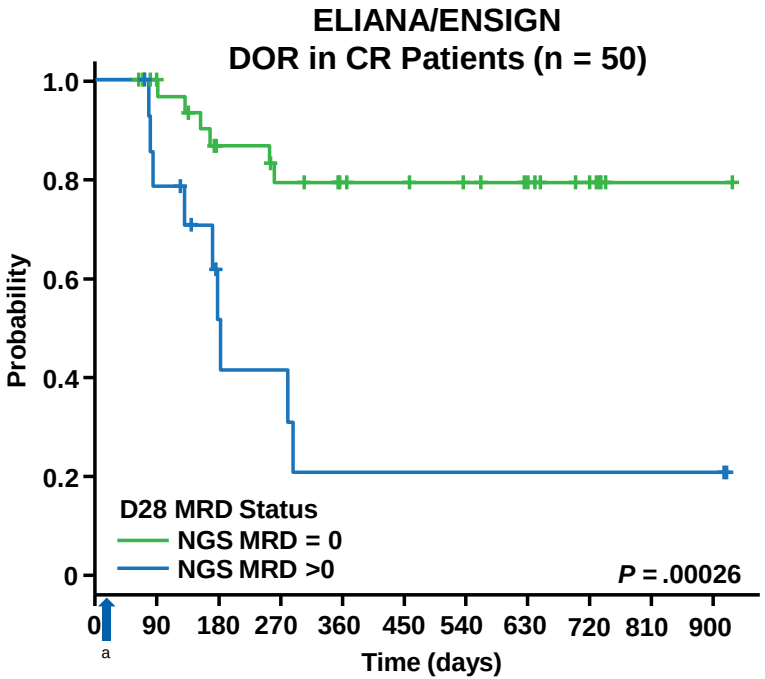
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

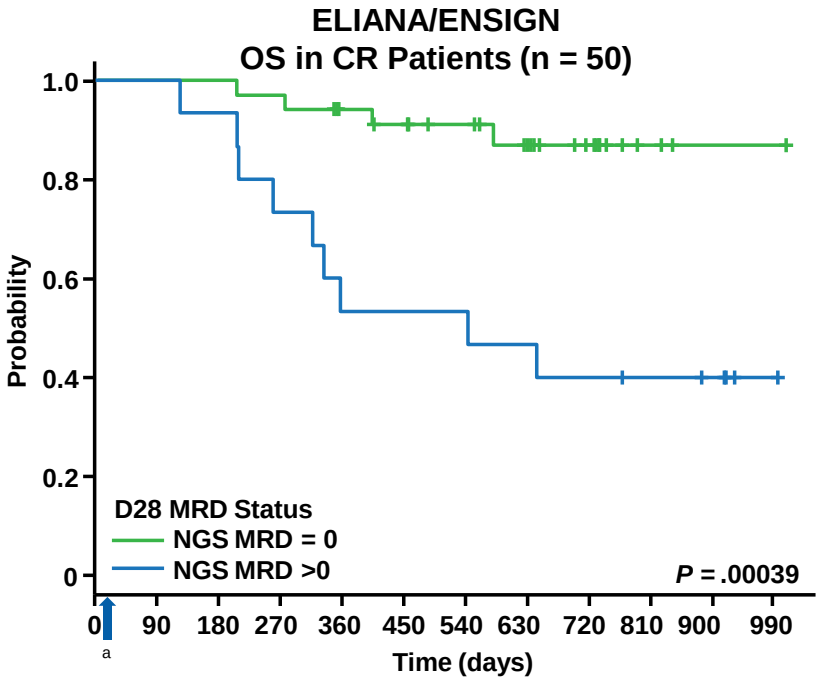
- 92 patients enrolled, 75 treated
- 73% Grade 3–4 AEs related to CAR T
- **81% → CR/CRi, all MRD negative; 66% in intention-to-treat analysis**
- 1-year EFS at 50%, no relapses after this
- **Demonstrates feasibility of delivery in multiple centers**
- **FDA approval for R/R pediatric ALL: August 2017**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



Maude SL, et al. *N Engl J Med*. 2018;378:439-448; KYMRIAH™ (tisagenlecleucel) Prescribing Information. Novartis Pharmaceuticals Corporation.

Patients with no MRD detected in D28 bone marrow by NGS had superior outcomes





Pulsipher MA, et al. *Molecular Detection of Minimal Residual Disease Precedes Morphological Relapse and Could be Used to Identify Relapse in Pediatric and Young Adult B-Cell Acute Lymphoblastic Leukemia Patients Treated with Tisagenlecleucel.* ASH 2018 Abstract 1551

[a] Tisagenlecleucel infusion at Day = 1.

CR, complete remission; DOR, duration of response; MRD, minimal residual disease; NGS, next-generation sequencing.

Frequency of high-risk cytogenetic abnormalities in ELIANA and ENSIGN

- 29 of 137 infused patients had high-risk cytogenetic abnormalities

High-Risk Cytogenetic Abnormality	n
Hypodiploidy[a]	3
t(9;22)(q34;q11.2)/*BCR-ABL1*	5
KMT2A (MLL) rearrangement	4
Intrachromosomal amplification of chromosome 21 (iAMP21)	7
t(17;19)(q23;p13), encoding *TCF3-HLF* fusion	1
BCR-ABL1-like	6
CRLF2 rearrangement	2
TP53 mutation/deletion	1

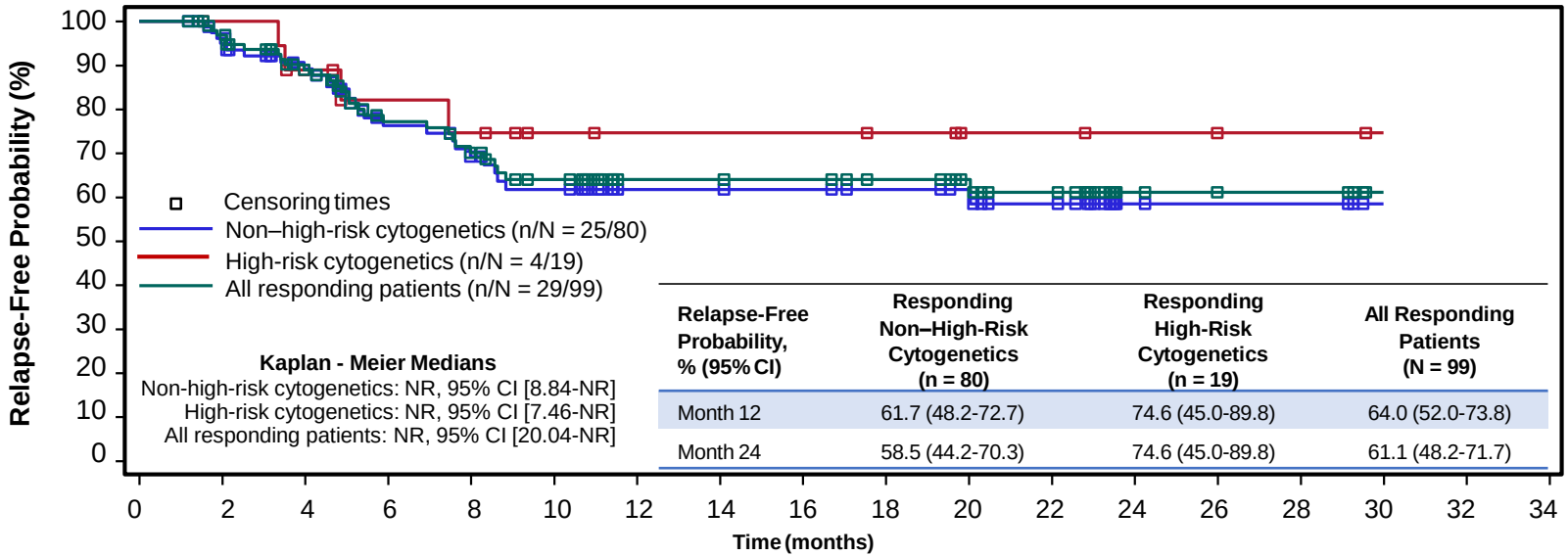
[a]<46 chromosomes.

High response rate in evaluable patients

	High-Risk Cytogenetics (n = 25)	Non–High-Risk Cytogenetics (n = 104)	All Patients (N = 129)
ORR, n (%)	19 (76.0)	80 (76.9)	99 (76.7)
CR	17 (68.0)	72 (69.2)	89 (69.0)
CRi	2 (8.0)	8 (7.7)	10 (7.8)
Responding patients with MRD-negative disease,[a] n/N (%)	18/19 (94.7)[b]	78/80 (97.5)[c]	96/99 (97.0)
HSCT post-infusion while in remission, n (%)	1 (4.0)	9 (8.6)	10 (7.8)

[a]Achieved BOR (CR+ CRi) within 3 months; [b]For one patient the MRD status was not available; [c]Two patients had 0.01% ≤ MRD <5.0%.
BOR, best overall remission; MRD, minimal residual disease.

Median RFS was not reached in responding high-risk and non–high-risk cytogenetics subgroups



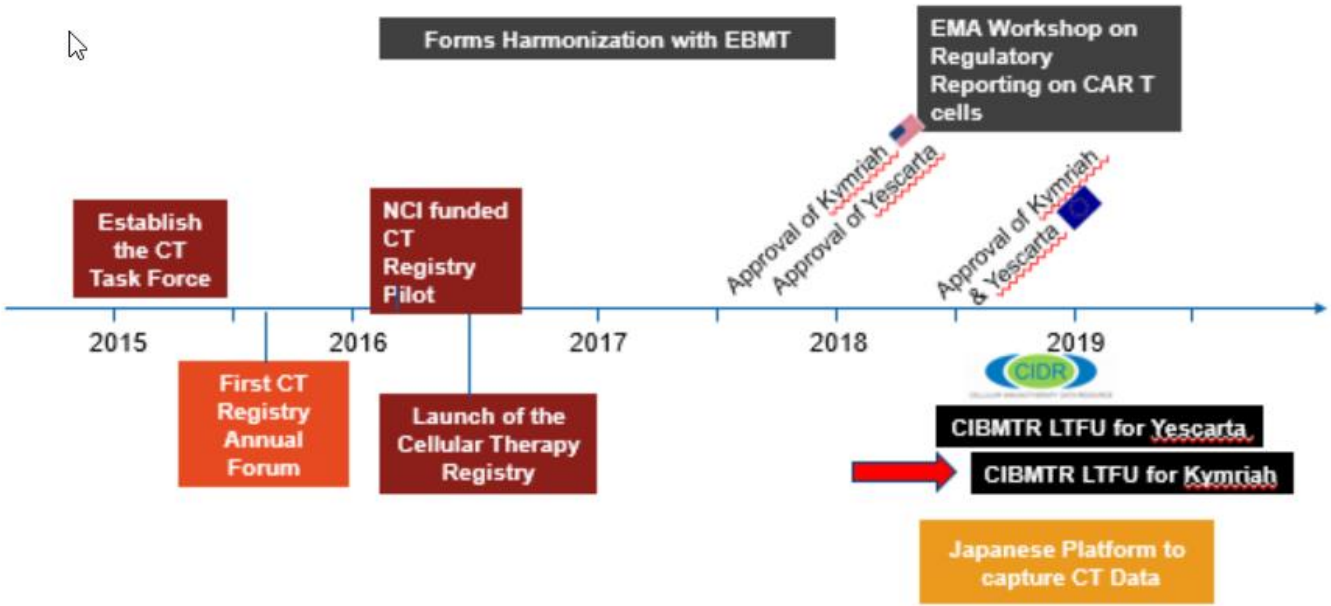
Relapse-Free Probability, % (95% CI)	Responding Non–High-Risk Cytogenetics (n = 80)	Responding High-Risk Cytogenetics (n = 19)	All Responding Patients (N = 99)
Month 12	61.7 (48.2-72.7)	74.6 (45.0-89.8)	64.0 (52.0-73.8)
Month 24	58.5 (44.2-70.3)	74.6 (45.0-89.8)	61.1 (48.2-71.7)

Number of patients still at risk

Non–high-risk cytogenetics	80	74	60	44	38	33	24	24	23	21	19	15	4	3	3	0
High-risk cytogenetics	19	18	14	11	10	7	6	6	6	5	3	3	2	1	1	0
All responding patients	99	92	74	55	48	40	30	30	29	26	22	18	6	4	4	0

Note: Only patients who achieved CR or CRi were included. Time is relative to onset of remission. NR, not reached.

Development of the Cellular Therapy Registry



Pasquini M, et al. *Clin Lymphoma Myeloma Leuk.* 2019;19(suppl 1):S1-S396.

Acute lymphoblastic leukemia

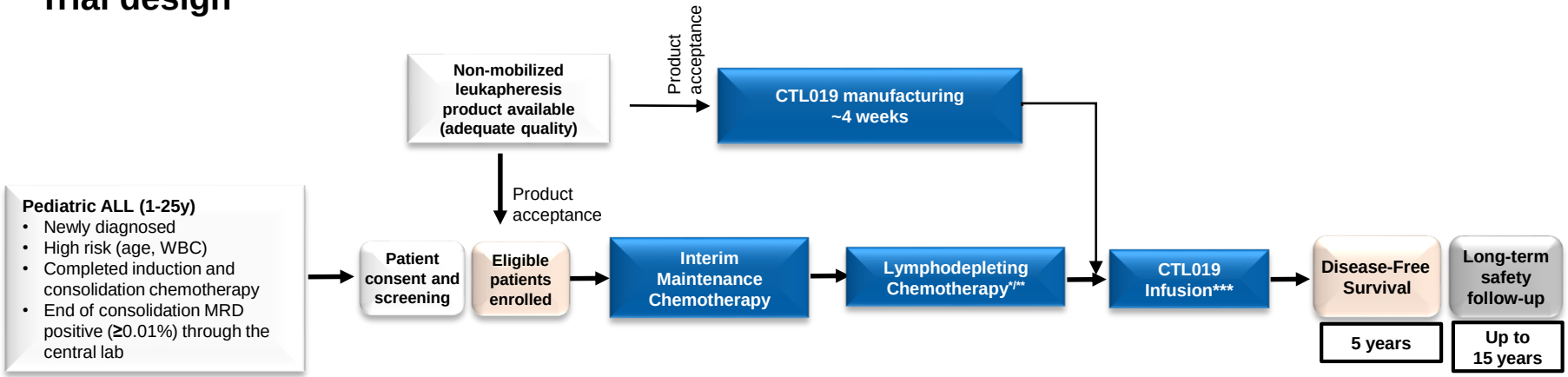
ALL Characteristic	N (%)
No. of patients	144
Disease status at CT	
Primary induction failure	18 (12)
Morphologic CR	50 (35)
Disease relapse	76 (53)
≥5% blast in marrow prior to CT	45 (31)
Extramedullary disease prior to CT	20 (14)
Ph+ ALL	11 (8)
≥3 of lines of prior therapies	70 (49)
Prior allogeneic HCT	48 (33)

- Median time from diagnosis to CT – 33 months
- CR rate was 87% and among patients with MRD assessment (N = 58), 98% were negative
- DOR at 6m – 71%
- EFS at 6m – 66%
- OS at 6m – 91%

Pasquini M, et al. *Clin Lymphoma Myeloma Leuk.* 2019;19(suppl 1):S1-S396.

Study of efficacy and safety of tisagenlecleucel in HR B-ALL EOC MRD-positive patients (CASSIOPEIA)

Trial design



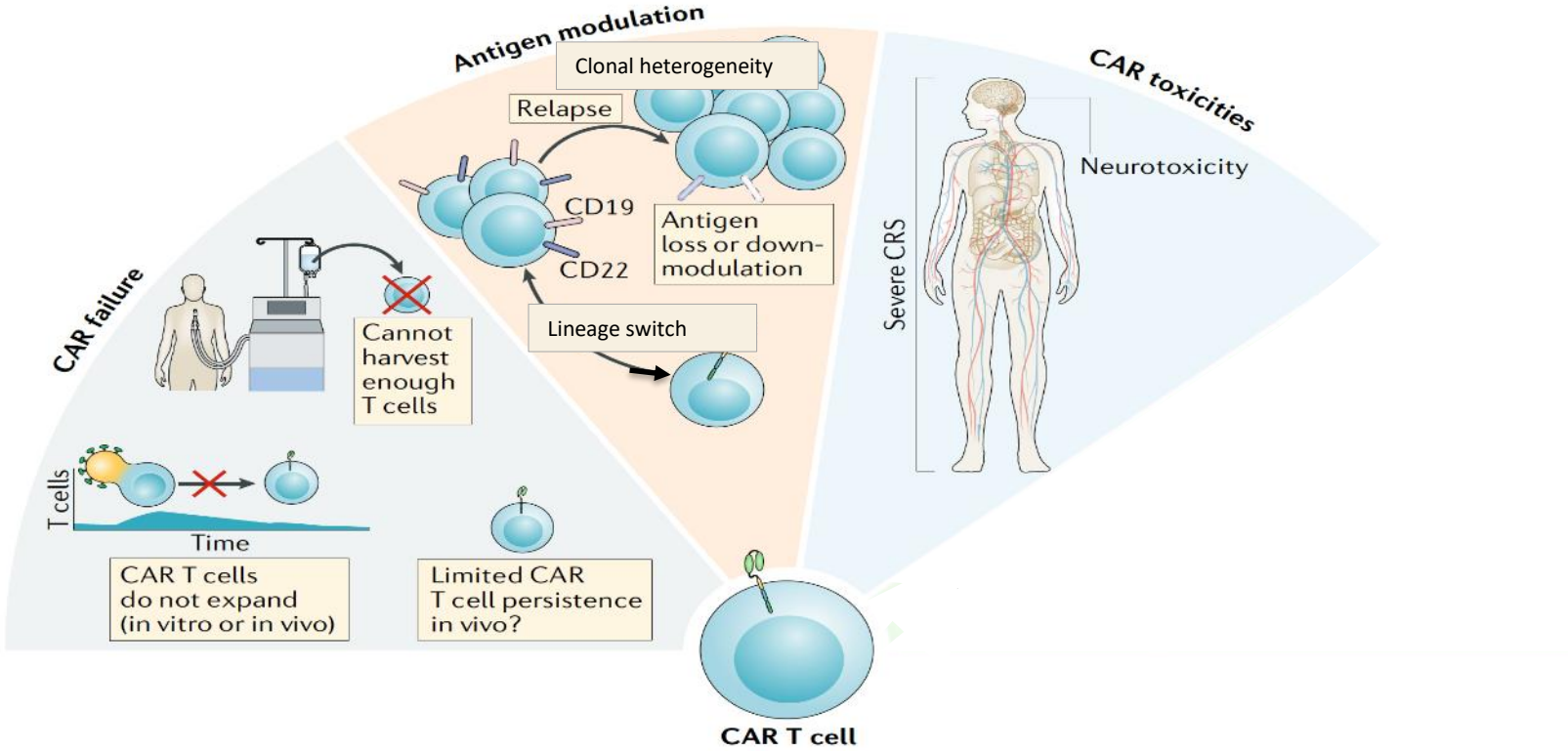
*Lymphodepleting chemotherapy
- Fludarabine (25 mg/m^2 IV daily for 4 days)
- Cyclophosphamide (500 mg/m^2 IV daily for 2 days starting with the first dose of fludarabine)

**Second Infusion: If the patient satisfies certain criteria, a second infusion may be possible. The patient would then restart all visits starting from the LD chemo visit

***Single IV infusion
- ≤50 kg body weight: 0.2 to 5 × 10^6 tisagenlecleucel transduced cells/kg
- >50 kg body weight: 0.1 to 2.5 × 10^8 tisagenlecleucel transduced cells

NCT03876769; https://clinicaltrials.gov/ct2/show/NCT03876769, protocol version 0.0 Feb 2018.

Current limitations of CAR T cells



Wayne A, adapted from Shah and Fry. *Nat Rev Clin Oncol.* 2019.

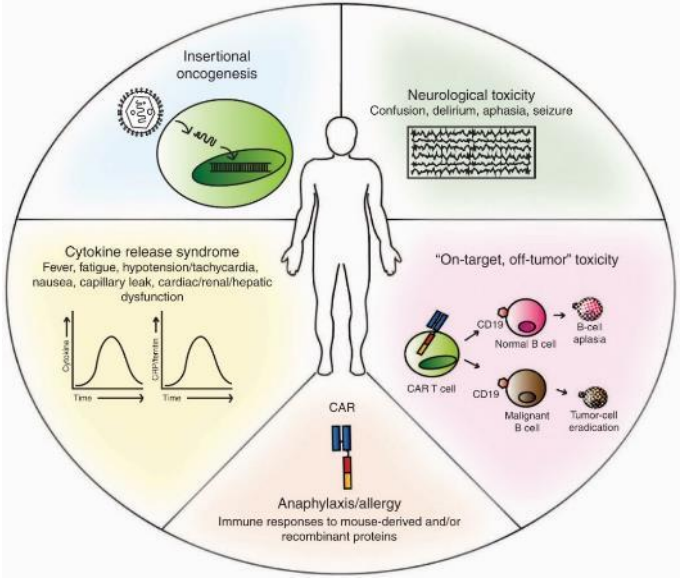
Peculiar toxicities associated with CD19 CAR T cells

“On-target, off-tumor” toxicities

- B cell-aplasia

Non–antigen-specific toxicities

- Cytokine release syndrome (CRS)
- Neurotoxicity
- HLH



Overall safety and AEs of special interest within 8 weeks after infusion

AESI[a]	Patients (N = 79)		
	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome	77	22	27
Infections	43	20	4
Cytopenias not resolved by day 28	42	18	18
Neurological events	39	13	0
Tumor lysis syndrome	5	5	0

- Majority of AEs occurred in the first 8 weeks after tisagenlecleucel infusion
- No cases of cerebral edema reported

[a] Occurring within 8 weeks of tisagenlecleucel infusion.
[b] Cytokine release syndrome was graded using the Penn scale.
AESI, adverse events of special interest.

Cytokine release syndrome

	Patients Infused (N = 79)
Patients developed CRS, n (%)	**61 (77)**
Time to onset, median (range), days	3.0 (1-22)
Duration of CRS, median (range), days	8.0 (1-36)
ICU admission, n (%)	38 (48)
Anticytokine therapy, n (%)	31 (39)
Tocilizumab, n (%)	31 (39)
1 dose	18 (23)
2 doses	10 (13)
3 doses	3 (4)
Corticosteroids, n (%)	16 (20)
Hypotension that required intervention, n (%)	42 (53)
High-dose vasopressors, n (%)	19 (24)
Intubation, n (%)	12 (15)
Dialysis, n (%)	8 (10)

CRS was graded using the Penn scale and managed by a protocol-specific algorithm[1]

CRS, cytokine release syndrome; ICU, intensive care unit.

1. Porter DL, et al. *Sci Transl Med.* 2015;7(303):303ra139.

Positive association of CRS grade and neurological event grade

CRS	N	Any-Grade Neurological Events, n (%)	Grade 3 Neurological Events, n (%)
None	18	4 (22)	1 (6)
Grade 1/2	23	7 (30)	1 (4)
Grade 3	17	7 (41)	2 (12)
Grade 4	21	13 (62)	6 (29)

- Grade 3 neurological events were more frequent with grade 4 CRS compared with grade 0-3 CRS (95% CI, –2% to 45%)
- Median onset of any-grade CRS (day 3) preceded median onset of neurological events (day 7)
- Grade 3 or 4 CRS and neurological events occur earlier than grade 1 or 2

CRS, cytokine release syndrome.

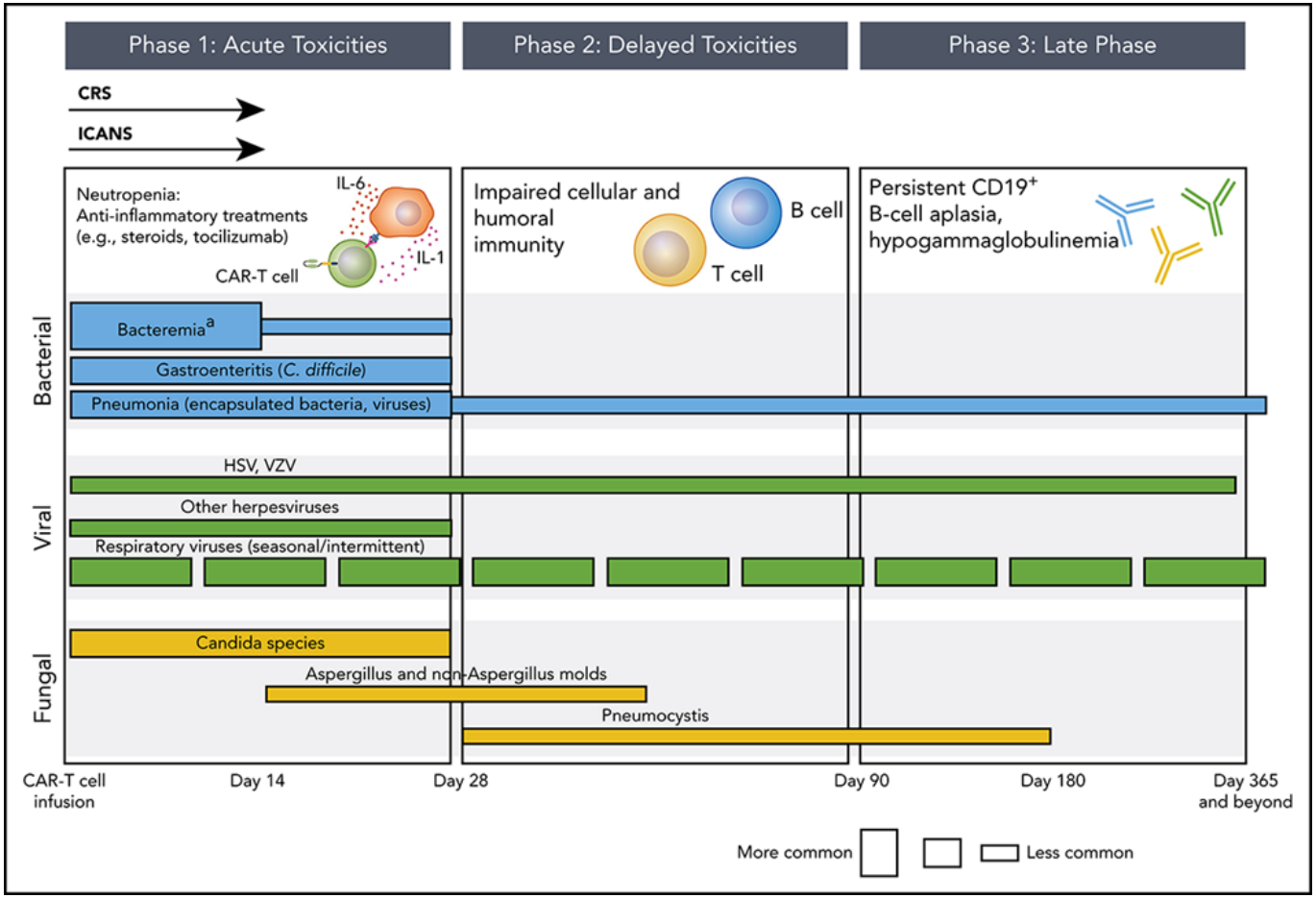


Table 1. Infectious diseases screening prior to CD19-targeted CAR–T-cell therapy

Screening for infectious diseases
Required
HIV using the fourth-generation antigen/antibody combination HIV-1/2 immunoassay*
HBsAg, anti-HBs, and anti-HBc*
HCV IgG*
Consider†
HSV-1 and HSV-2 IgG‡
VZV IgG
CMV IgG
HTLV-1 IgG
Toxoplasma gondii IgG
Treponema pallidum (syphilis) treponemal or nontreponemal test
M tuberculosis skin test and/or blood interferon-γ release assay§
S stercoralis IgG or empiric treatment§

Table 2. Antimicrobial management and infection monitoring in patients with CRS and/or ICANS

Management and monitoring
• Empiric broad-spectrum antibiotics according to fever and neutropenia guidelines*
• ID consultation should be obtained to guide escalation and de-escalation of antimicrobial therapy, particularly in high-risk patients†
High-risk patients are those who meet any of the below criteria
o Receiving >1 dose of tocilizumab
o Requiring >3 days of ≥10 mg dexamethasone per day within a 7-day period
o Receiving 1 or more doses of methylprednisolone ≥1 g per day
o Receiving second-line agents for management of CRS or ICANS (eg, anakinra, siltuximab)
• Antibiotic de-escalation should be addressed on a daily basis with consideration for the type of immunosuppressive therapies that have been administered.
• Consider weekly CMV monitoring with serum polymerase chain reaction testing in high-risk patients who are CMV seropositive‡
• Consider using mold-active azole prophylaxis with posaconazole in high-risk patients§

Hill et al. *Blood*. 2020.

Mechanisms of leukemia escape after CAR T-cell therapy

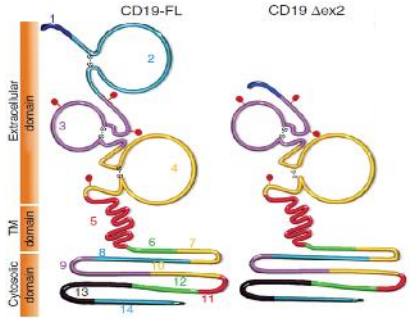
Tumor evasion systems in BCP-ALL: CD19-negative relapses

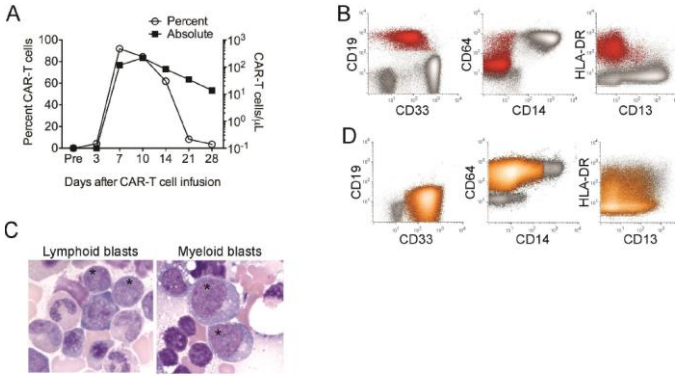
➢ Loss of CAR-recognized epitope as a result of alternative exon splicing forms of the CD19 gene where exon 2 was lost **(Sotillo et al. *Cancer Discov.* 2015)**

➢ Altered trafficking of CD19 protein to the cell membrane of blast cells **(Braig et al. *Blood.* 2016)**

➢Myeloid switch and loss of CD19 in patients with mixed-phenotype leukemia and MLL rearrangement **(Gardner et al. *Blood.* 2016)**

➢Induction of resistance to CAR T-cell therapy by transduction of a single leukemic B cell **(Ruella et al. *Nat Med.* 2018)**





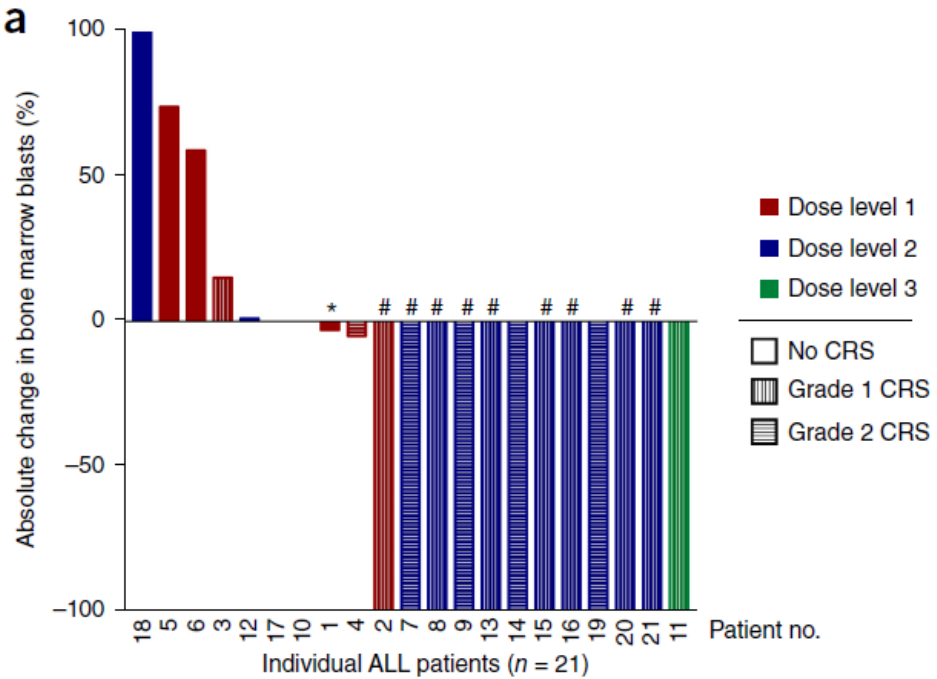
Characteristics of remission and relapse

- Relapses tended to occur early (within the first year)
- Most relapses were CD19-negative:

CD19-Negative	CD19-Positive	Unknown CD19 Status
14/19 (73.7% of relapses)	3/19 (15.8% of relapses)	2/19 (10.5% of relapses)

- All CD19-negative relapses occurred in the context of persistent B-cell aplasia
- One CR patient with B-cell recovery at 12 months is still in ongoing CR for 27 months at the time of data cut-off

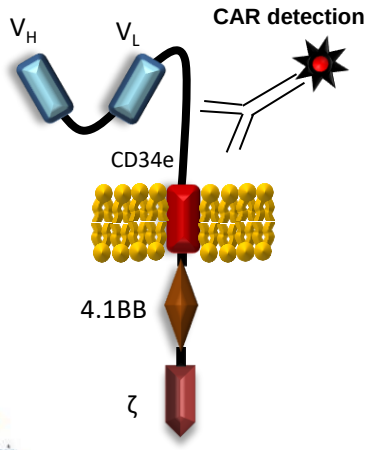
CD22.CAR

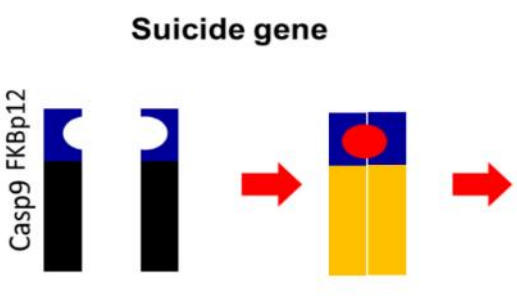


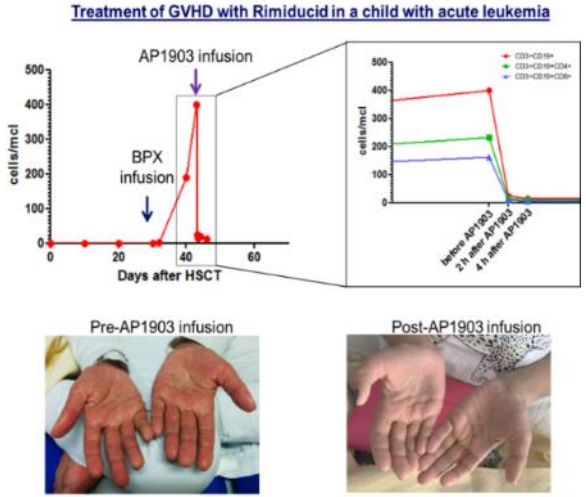
- **Twenty-one children/young adults treated with CD22.4-1BB CAR T cells**
- **Antileukemia activity is dose-dependent**
- **CR obtained in 73% (11/15) of patients receiving ≥1×10^6 CD22-CAR T cells/kg, including 5 of 5 patients with CD19dim or CD19− B-ALL**
- **Eight patients relapsed (reduced CD22 surface site density in 7 of them)**

CAR.CD19 strategy at OPBG: Second-generation CAR targeting CD19

CAR.CD19-4.1BB-ζ







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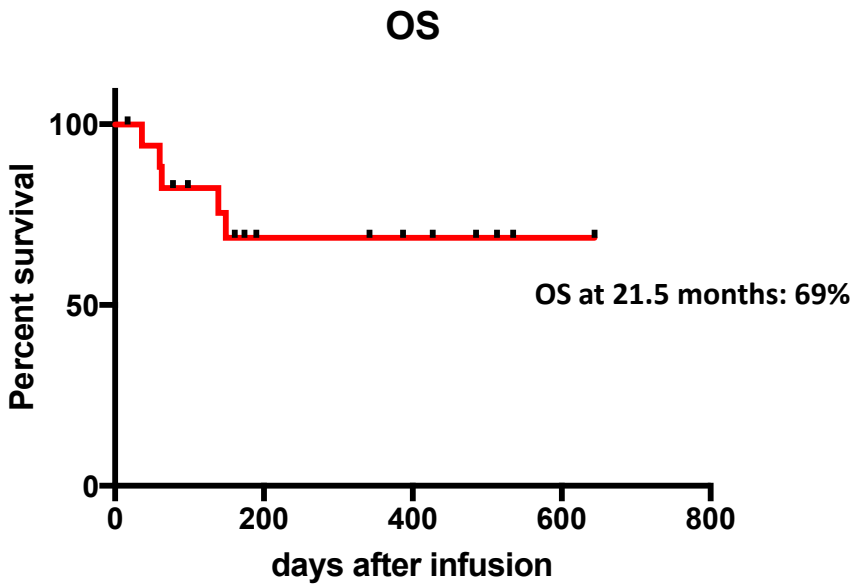
Quintarelli C, et al. *Mol Ther.* 2016.

Outcome of ALL patients treated with CD19-CAR T cells at OPBG

➢**Fourteen out of the 17 (82%) patients with Bcp-ALL infused obtained CR with MRD negativity after DP infusion**



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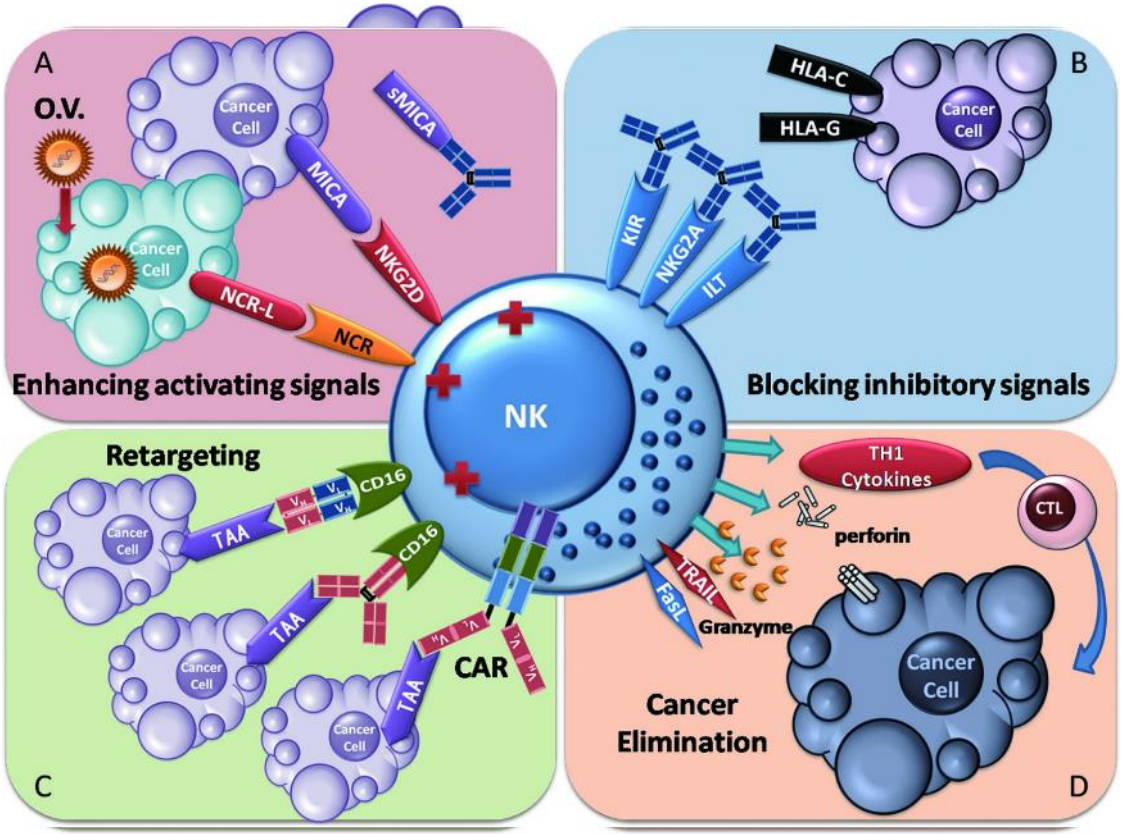
Role of CAR T cells in AYA

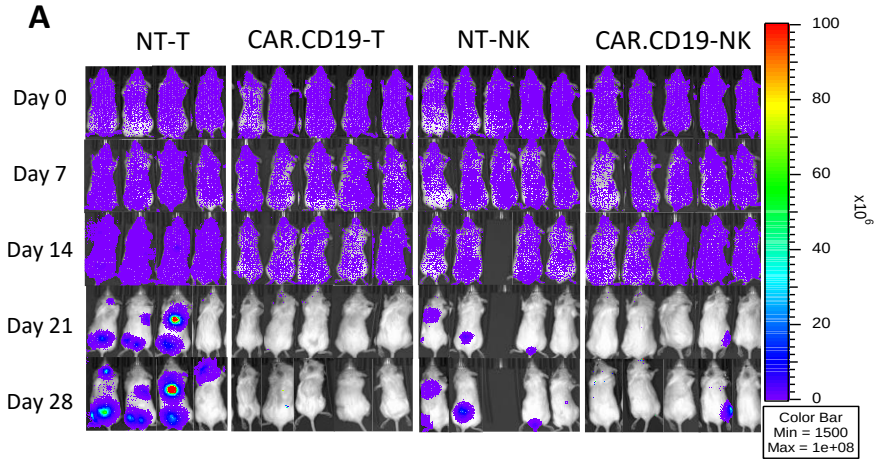
- **Commercially available CAR T-cell products are approved for patients until 25 years of age**
- **No data are available on safety and efficacy outcome of CAR T cells in AYA as compared with children below the age of 13 years**
- **Considering the relevant toxicities and the risk of treatment-related fatality observed in AYA with intensive chemotherapy protocols and HSCT, CAR T cells could represent an attractive option to be considered for relapsed/refractory patients**

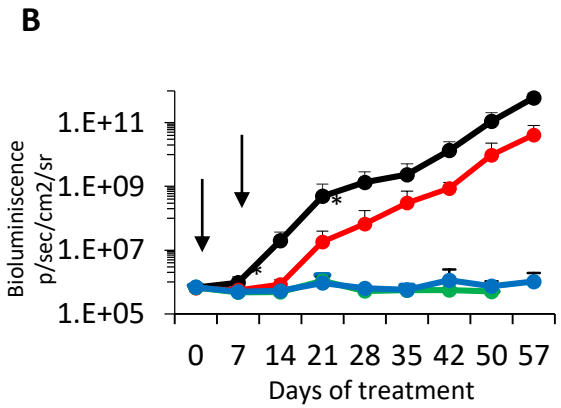
The role of NK cells in the cancer

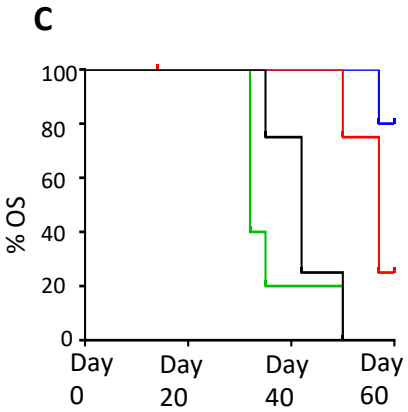


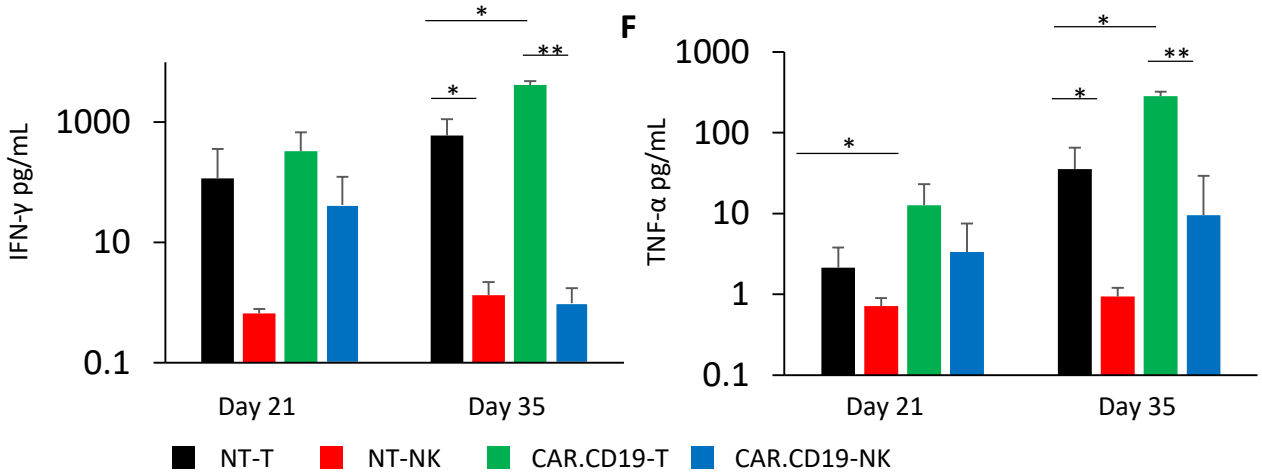
Yangxi L, et al. *Front Immunol.* 2018.

CAR NK cells









D

	P Value
NT-T vs NT-NK	.018
NT-T vs CAR.CD19-T	n.s.
NT-NK vs CAR.CD19-NK	n.s.
CAR.CD19-T vs CAR.CD19-NK	.001
NT-T vs CAR.CD19-NK	.003
NT-NK vs CAR.CD19-T	.01

Quintarelli C, et al. *Leukemia*. 2020.

Global Leukemia Academy

Questions to the Experts

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Thank you to all participants!

And thank you to Amgen and Adaptive Biotechnologies for their sponsorship

- Please complete the evaluation form using the provided link
- To obtain a copy of the meeting slides and access other educational materials, please visit the GLA website at: www.globalleukemiaacademy.com
  - Meeting materials will be available in approximately 1 week
- If you have a question for any of our experts that was not answered today, you can submit it through the GLA website at: https://globalleukemiaacademy.com/ask-the-expert/