Global Leukemia Academy

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

Webinar

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Global Leukemia Academy

Welcome and Introductions

Franco Locatelli, MD
University of Rome IRCCS Ospedale Pediatrico Bambino Gesù of Rome
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Patrick A. Brown, MD
Johns Hopkins University School of Medicine
USA

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Agenda

14 September 2021

Time (BRT)	Topic	Presenter
5.00 PM – 5.05 PM	Welcome and Introductions	Franco Locatelli, MD, PhD and Patrick Brown, MD
5.05 PM – 5.15 PM	Current Paradigm and Long-term Toxicities for Pediatric ALL • Integration of innovative immunotherapies • Role of MRD in treatment • Long-term toxicities	Franco Locatelli, MD, PhD
5.15 PM – 5.25 PM	CAR T Cells for Pediatric/AYA ALL • Benefits and risks of CAR Ts and bispecifics • Role of MRD in research and treatment • AYA considerations	Franco Locatelli, MD, PhD
5.25 PM – 5.40 PM	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
5.40 PM – 6.00 PM	Questions to Experts	Franco Locatelli, MD, PhD and Patrick Brown, MD

Global Leukemia Academy

Current Paradigm and Long-Term Toxicities for Pediatric ALL

Franco Locatelli, MD

University of Rome IRCCS Ospedale Pediatrico Bambino Gesù of Rome

Italy

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Current Paradigm for Treatment of Pediatric ALL

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

DISCLOSURES

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

Outcome of contemporary trials involving children and adolescents with ALL

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

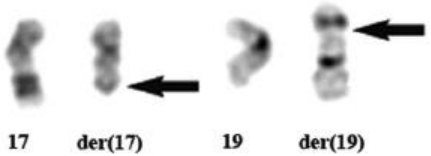
* Infants younger than 1 year of age were excluded from these studies when possible. AIEOP denotes Italian Association of Pediatric Hematology and Oncology, BFM Berlin–Frankfurt–Münster, DCOG Dutch Childhood Oncology Group, DFCI Dana–Farber Cancer Institute, EORTC CLG European Organization for Research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

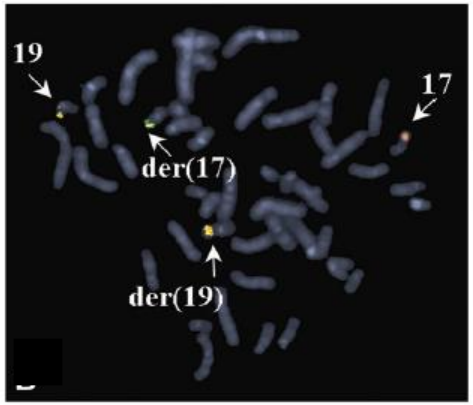
Hunger SP and Mullighan CG N Engl J Med 2015;373: 1541-52
Teachey DT and Pui CH Lancet Oncolo.2019: 20(30):142-154

Perspectives for new trials in ALL

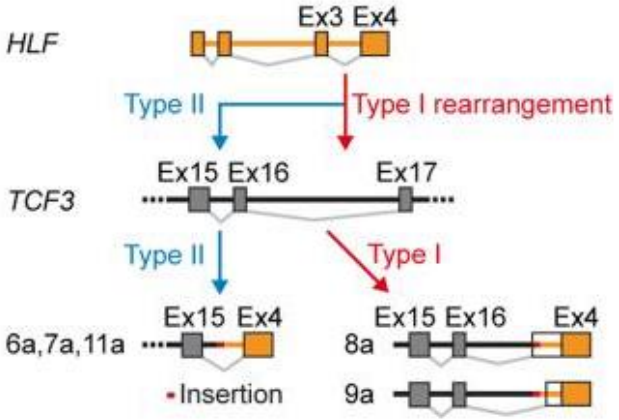
- Utilize novel genetic approaches
- Improve risk stratification by wider combination of genetic factors and response (MRD)
- Avoid additional toxic agents in most patients
- Introduce novel agents under controlled conditions

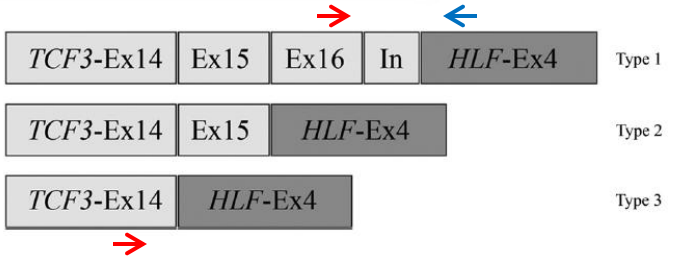
A novel TCF3-HLF fusion in ALL with a t(17;19)(q22;p13)





Panagopoulos I. et al., Cancer Genet. 2012;205:669-72





RT-PCR

Multiplex RT-PCR (x6)

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

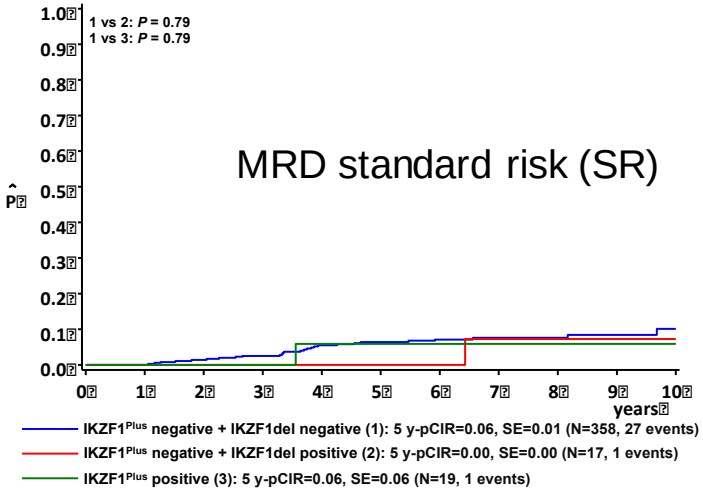
New prognostic pattern: Definition of *IKZF1*^{plus}

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

  - Negativity for *ERG* deletion

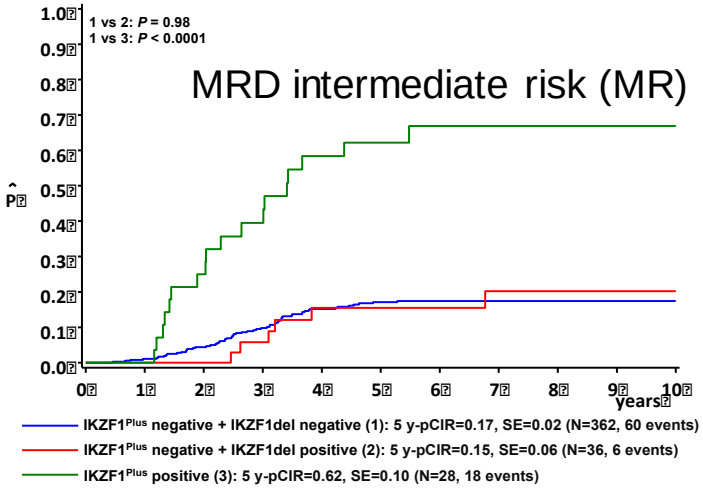
Stanulla M, et al. *J Clin Oncol.* 2018.

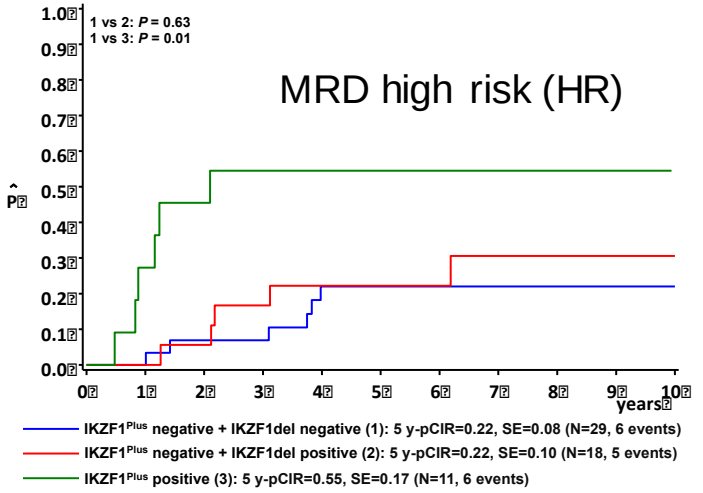
IKZF1^{plus} – cumulative relapse incidence in MRD-based risk groups



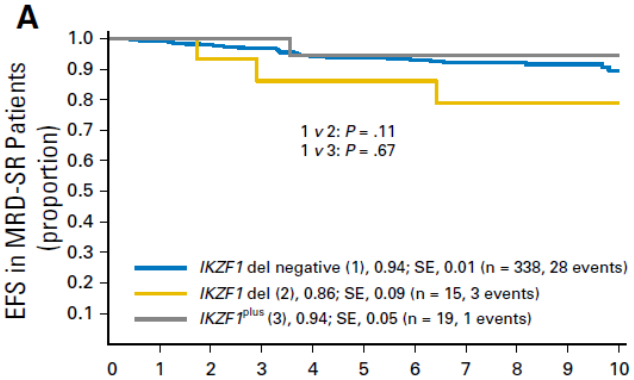
SR = 6%
MR = 62%
HR = 55%

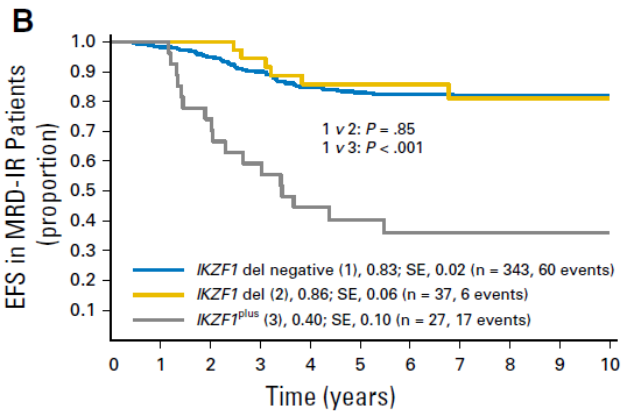
A: MRD – Standard risk (MRD neg at 5w and 12w)
B: MRD – Intermediate risk (MRD non SR/HR)
C: MRD – High risk (MRD pos ≥10^{-4} at 12w)

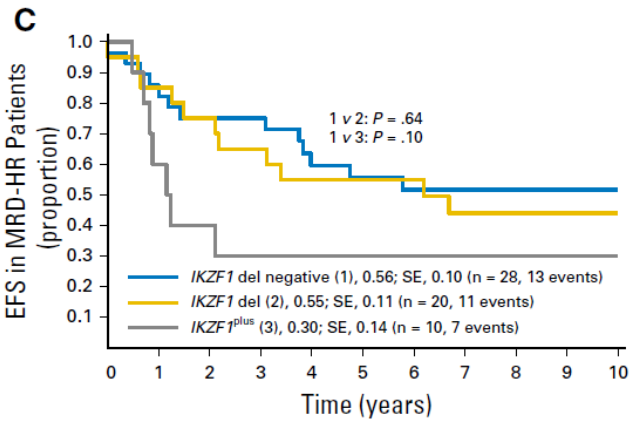




IKZF1^{plus} and MRD: Impact on EFS







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

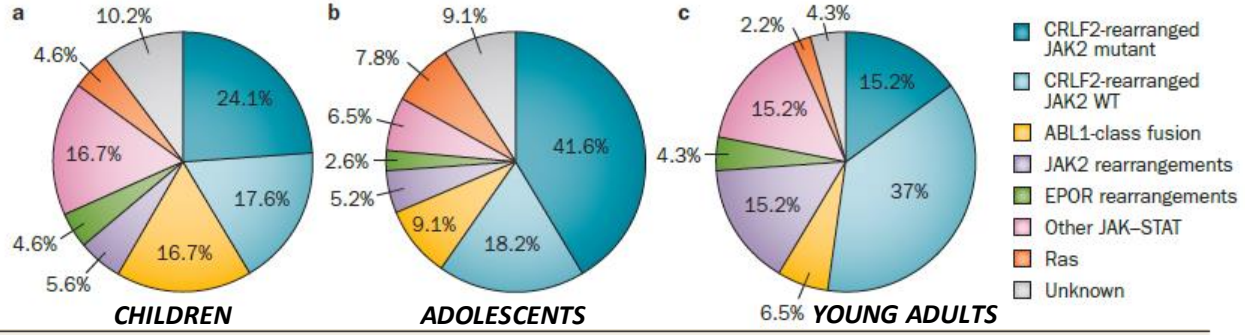
Stanulla M, et al. *J Clin Oncol*. 2018.

AlloHSCT indications in HR pB-ALL in AIEOP-BFM ALL 2017

2017		PCR-MRD results			
		MRD-SR	MRD-MR	MRD-HR	
				MRD TP2 = level 10^{-3}	MRD TP2 ≥ level 10^{-2}
criteria hierarchical	*TCF3-HLF*	MMD	MMD	MMD	MMD
	no CR d33	no	MD	MMD	MMD
	t(4;11)	no	MD	MD	MMD
	hypodiploidy < 44 chr.	no	MD	MD	MMD
	IKZF1^{plus} and FCM d15 ≥10%	no	MD	MD	MMD
	IKZF1^{plus} and FCM d15 <10%	n.a.*	no	MD	MMD
	FCM d15 ≥10% only	no	no	MD	MMD
none of the above features		n.a.*	n.a.*	MD	MMD

*treated in non-HR

Class of Kinase rearrangements and therapeutic targets in Ph-like ALL

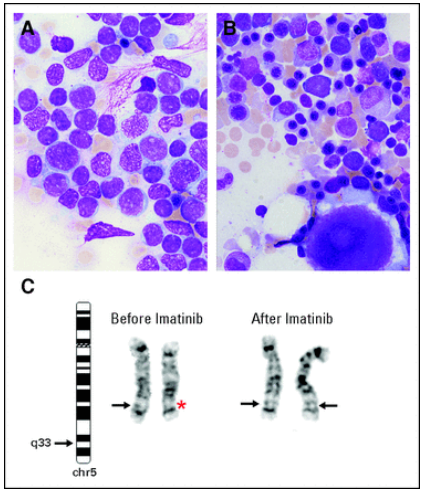


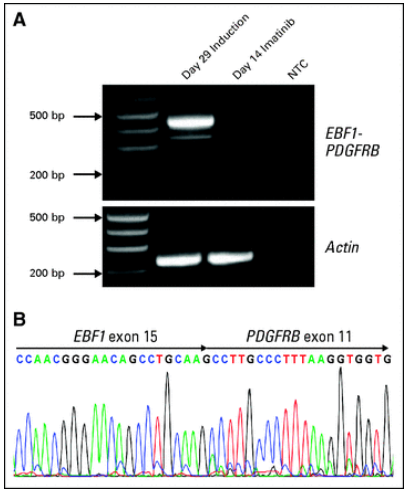
Kinase	Tyrosine kinase inhibitor	Number of gene partners	Number of patients	Fusion partner genes
ABL1	Dasatinib	6	14	*ETV6, NUP214, RCSD1, RANBP2, SNX2, ZMIZ1*
ABL2	Dasatinib	3	7	*PAG1, RCSD1, ZC3HAV1*
CSF1R	Dasatinib	1	4	*SSBP2*
PDGFRB	Dasatinib	4	11	*EBF1, SSBP2, TNIP1, ZEB2*
CRLF2	JAK2 inhibitor	2	30	*IGH, P2RY8*
JAK2	JAK2 inhibitor	10	19	*ATF7IP, BCR, EBF1, ETV6, PAX5, PPFIBP1, SSBP2, STRN3, TERF2, TPR*
EPOR	JAK2 inhibitor	2	9	*IGH, IGK*
DGKH	Unknown	1	1	*ZFAND3*
IL2RB	JAK1/JAK3 inhibitor	1	1	*MYH9*
NTRK3	Crizotinib	1	1	*ETV6*
PTK2B	FAK inhibitor	2	1	*KDM6A, STAG2*
TSLP	JAK2 inhibitor	1	1	*IQGAP2*
TYK2	TYK2 inhibitor	1	1	*MYB*

*Several ABL1-class and JAK kinases are rearranged to multiple fusion partners. Abbreviations: ALL, acute lymphoblastic leukaemia; Ph-like, Philadelphia chromosome-like. From the *New England Journal of Medicine*, Roberts, K. G. *et al.* Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. **371**, 1010. Copyright © (2014) Massachusetts Medical Society. Reprinted with permission.

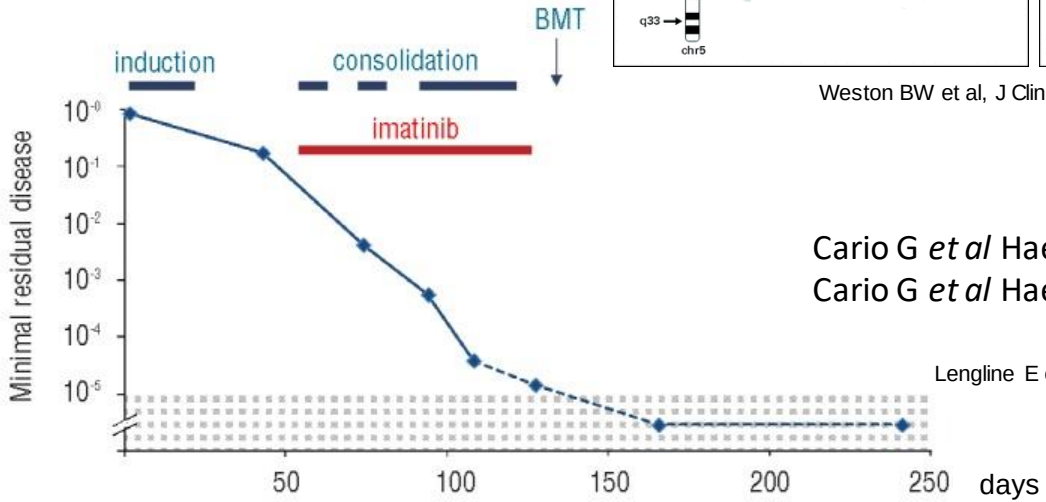
Roberts KG & Mullighan CG, Nat Rev Clin Onc 201

EBF1-PDGFRB (Ph-like) responds to TKI





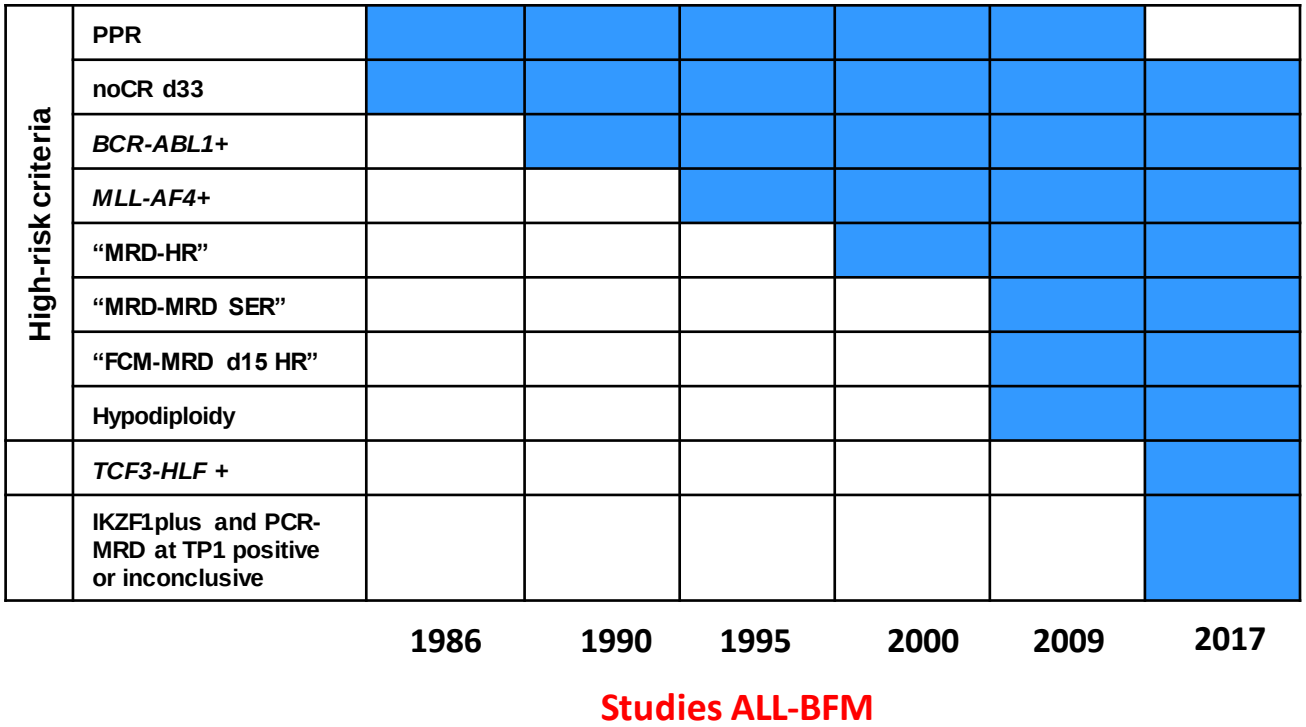
Weston BW et al, J Clin Oncol. 2013;31:e413-6



Cario G *et al* Haematologica, 2020
Cario G *et al* Haematologica, *2019*

Lengline E et al, Haematologica. 2013;98:e146-8

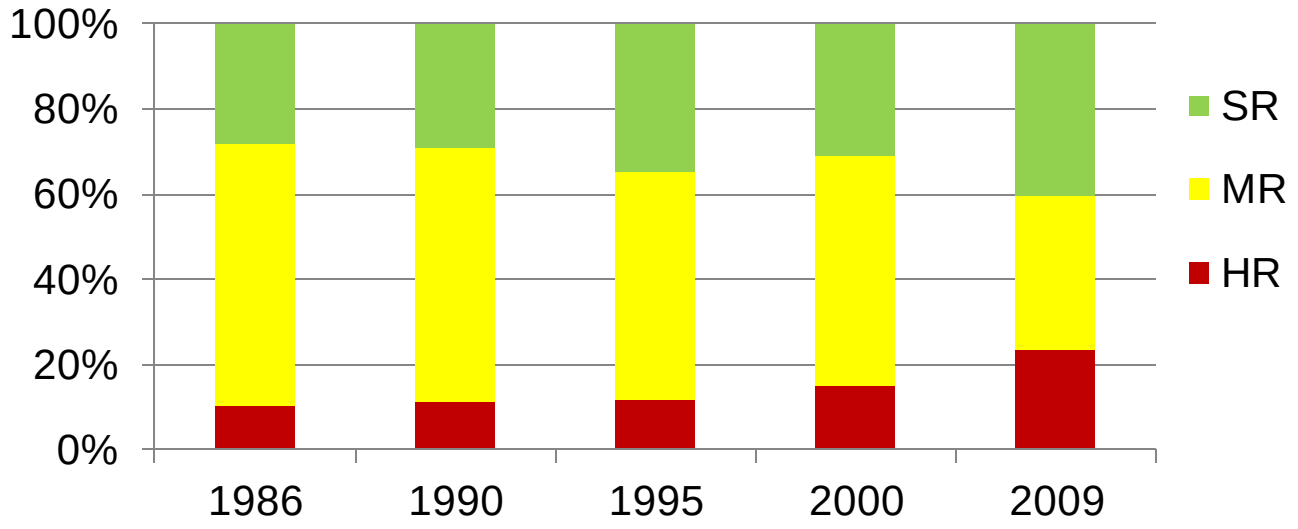
Identification of new high-risk groups and reducing relapses in high-risk patients



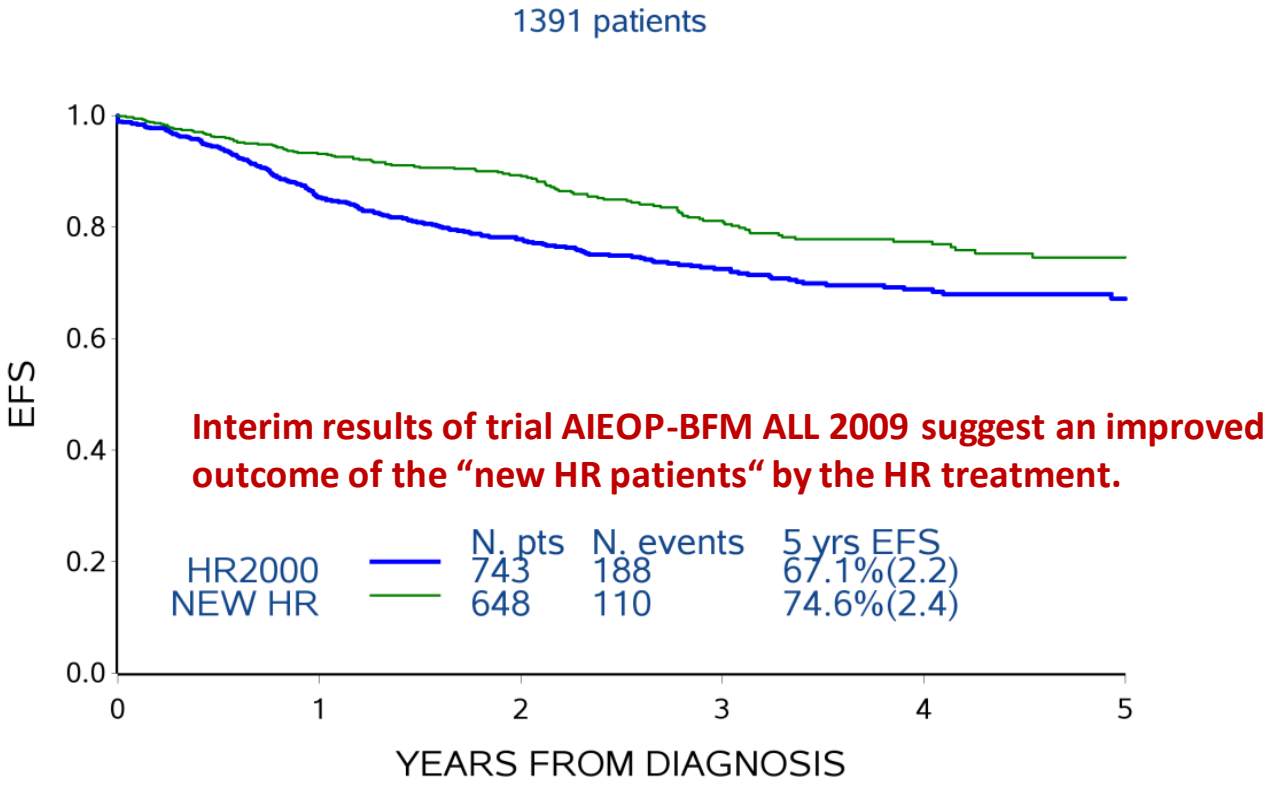
More and more patients with "intermediately unfavorable" outcome have been identified and shifted to the high-risk arm

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



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

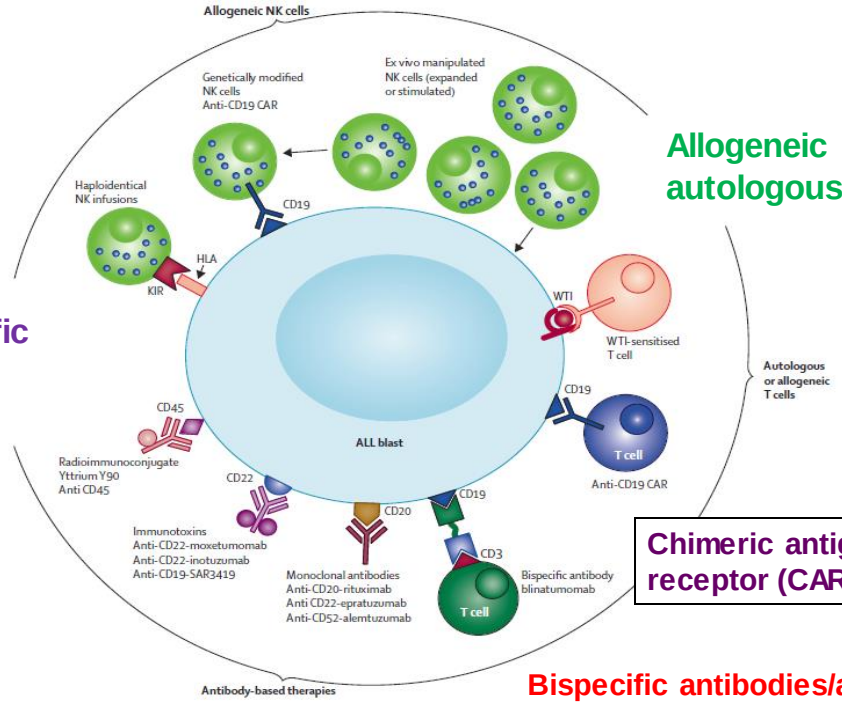


Interim results of trial AIEOP-BFM ALL 2009 suggest an improved outcome of the "new HR patients" by the HR treatment.

The essentials in pediatric ALL: Risk stratification and frontline therapy

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

New immunological approaches under investigation in childhood ALL



Allogeneic and autologous NK cells

Immunotoxin-specific antibodies

Chimeric antigen receptor (CAR) T cells

Bispecific antibodies/antibody constructs

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

AIEOP-BFM ALL 2017

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

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

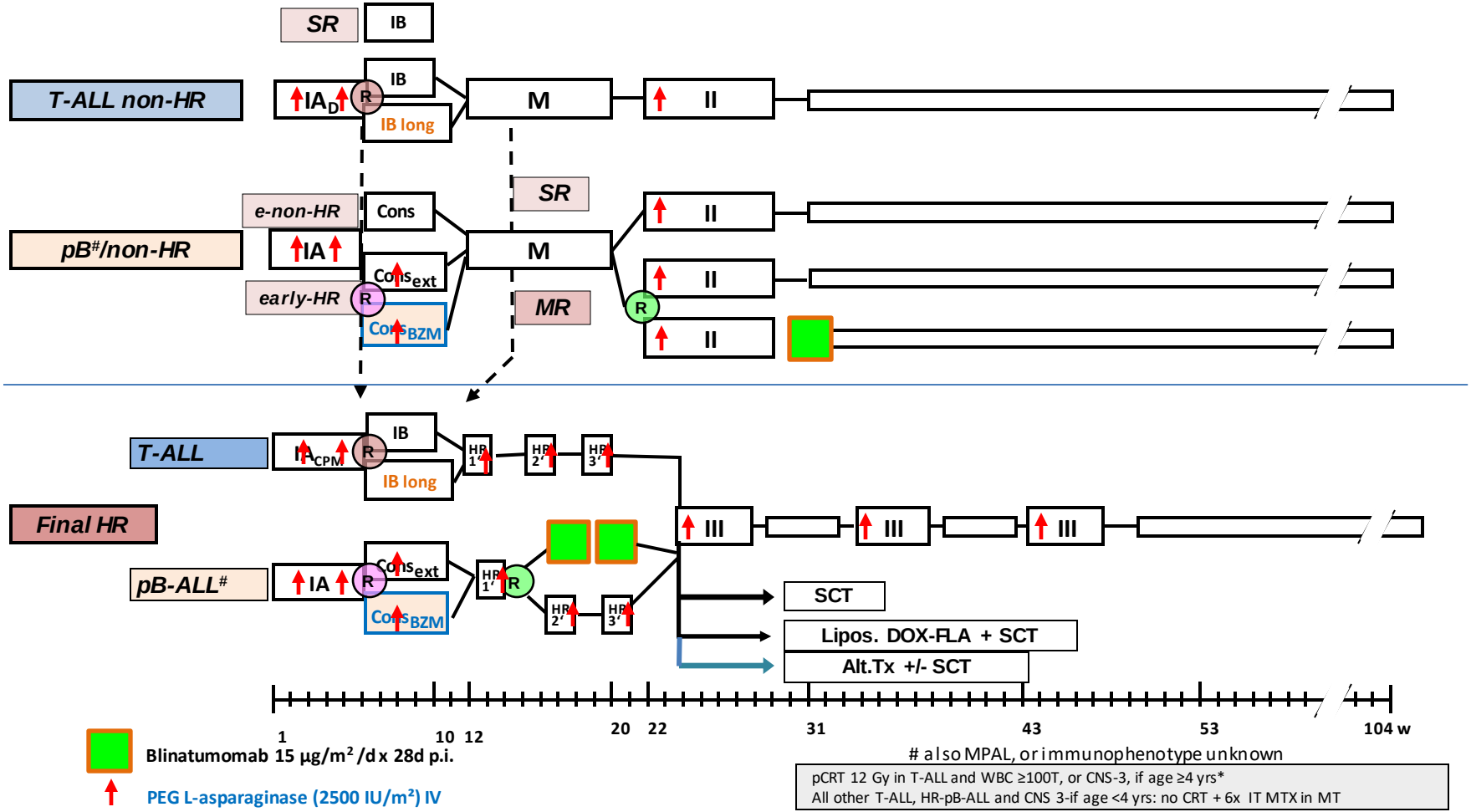
EudraCT Number: 2016-001935-12

Sponsor: Universitätsklinikum Schleswig-Holstein, Campus Kiel

New in trial AIEOP-BFM ALL 2017

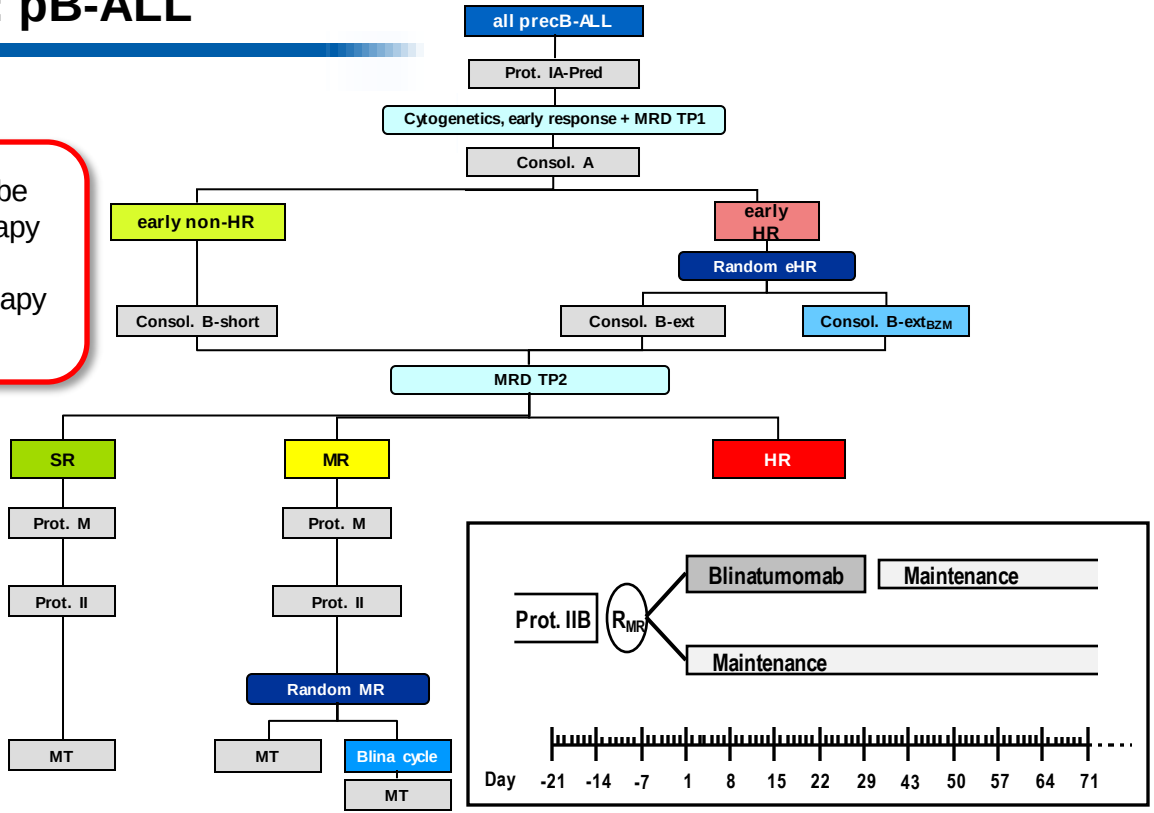
- Modified workflow and timing in genetic diagnostics
- Genetic profiles and early MRD response may be combined to characterize previously not identified pts at high risk to relapse, eg, ***IKZF1*^{plus}**
- **Randomized evaluation of blinatumomab in *de novo* ALL in all non-SR patients**
- Selective 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: Treatment overview



AIEOP-BFM ALL 2017: pB-ALL

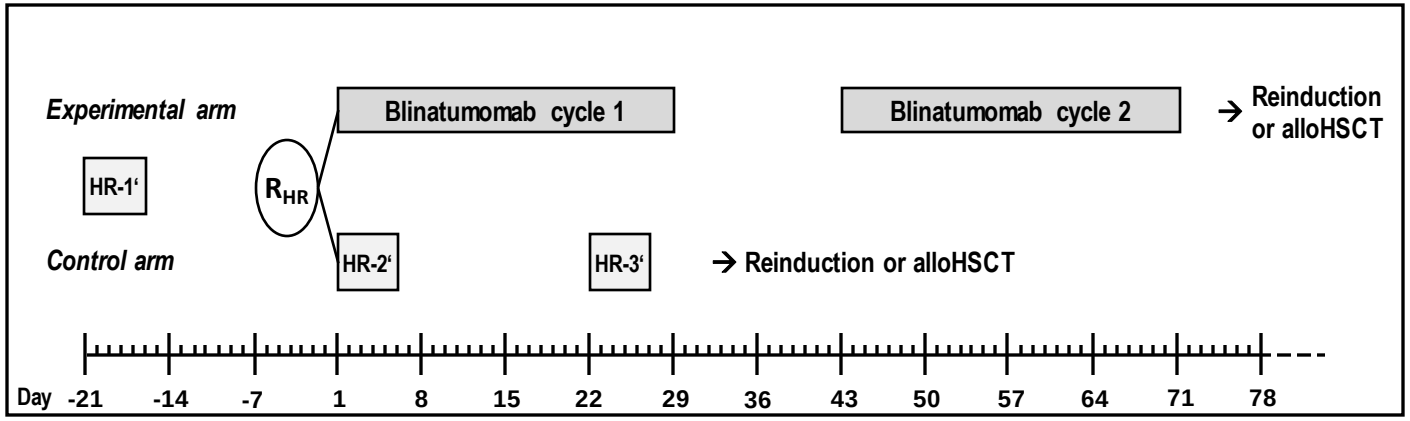
Can pDFS of MR patients be improved by additional therapy with one cycle of post-reintensification immunotherapy with blinatumomab?



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

AIEOP-BFM ALL 2017: pB-ALL
Approach for HR patients: Randomization HR

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

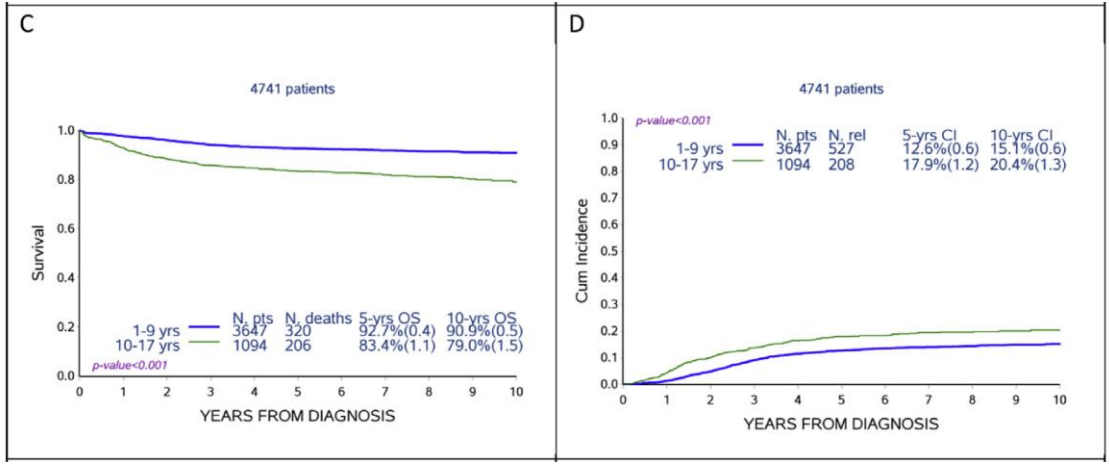


Expected effects by novel post-consolidation therapy in HR patients:

- Significant reduction of toxicity
- Overcoming resistance to chemotherapy in patients with insufficient response to earlier treatment elements

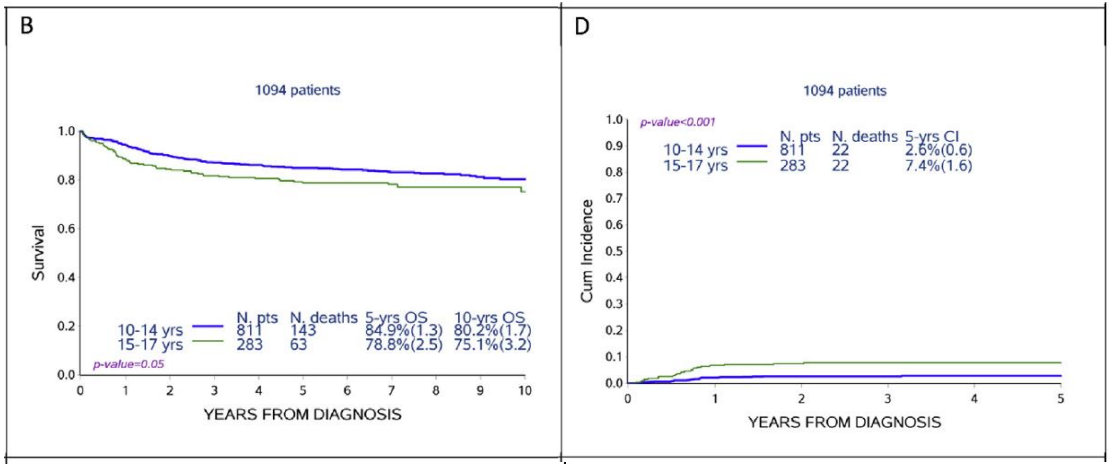
A brief focus on adolescents

Acute and late toxicities



(C) OS by age

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



(B) Overall survival (OS) by age

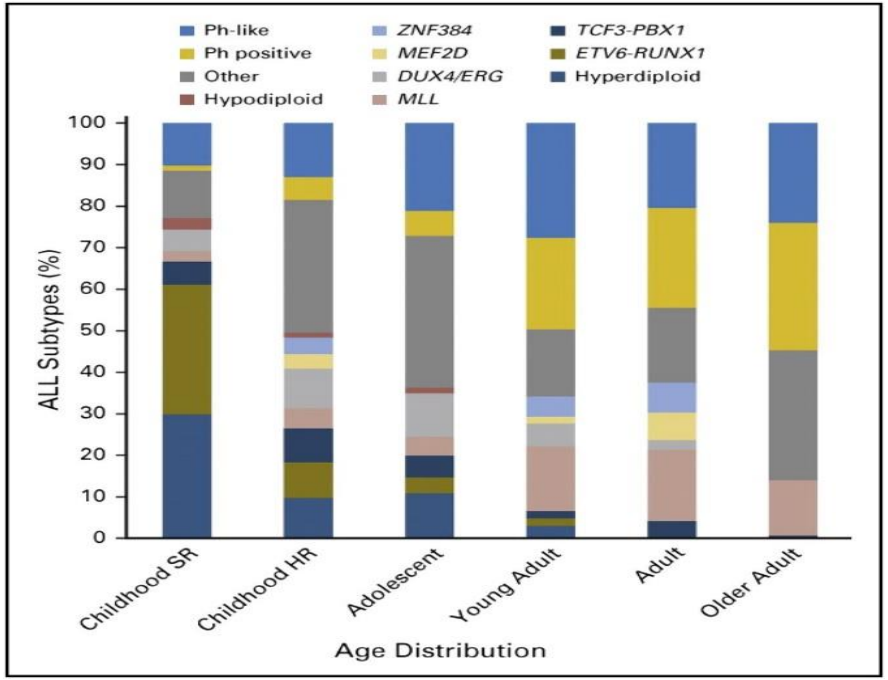
(D) Cumulative incidence of death in remission as a first event by age

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

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

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

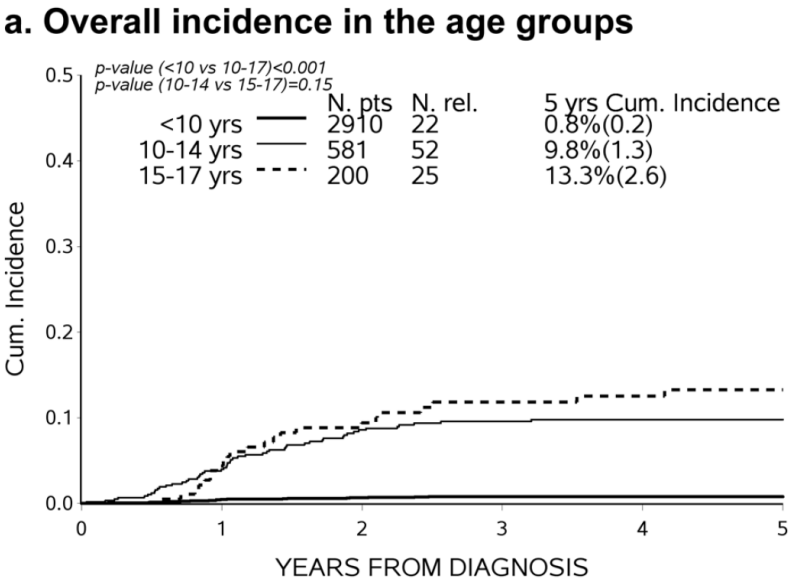


Late effects of treatment in ALL

- 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)

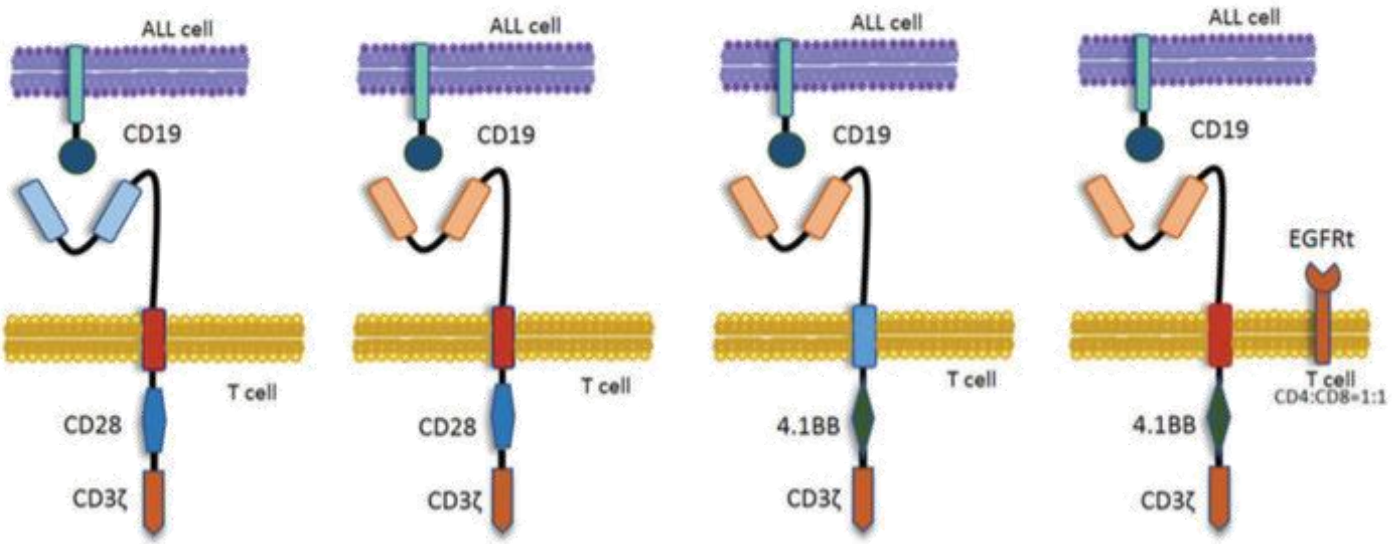
Parasole et al. *Blood Cancer Journal* (2018)8:115



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

Published constructs of 2nd generation CD19 CARs for ALL

CAR design important for persistence and sustained efficacy



Del Bufalo F & Locatelli F. Expert Review of Clinical Immunology 2019

Published studies of 2nd 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;371:1507–17	30 (18 post-HSCT)	FMC63-41BB-ζ lentivirus	27 CR; 22 MRD-negative **3 ➔** allogeneic HSCT
Lee DW, et al. Lancet 2015;385:517–28	20 (7 post-HSCT)	FMC63-CD28-ζ retrovirus	13 CR + 1 CRi; 12 MRD-negative **10 ➔** allogeneic HSCT
Gardner RA, et al. Blood 2017;129:3322–31	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;378:439–48	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;126:2123–38	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;378:449–59	53 (19 post-HSCT)	SJC25C1-CD28-ζ retrovirus	44 CR; 32 MRD-negative **17 ➔** allogeneic HSCT

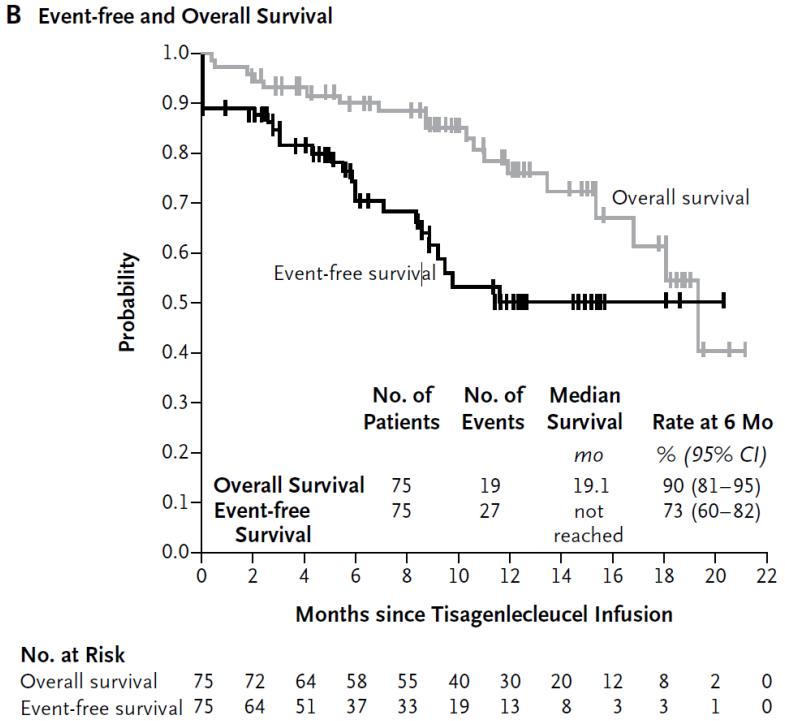
- **251 patients treated: 85% CR, 76% MRD-negative**

Summary of ELIANA study

ORIGINAL ARTICLE

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

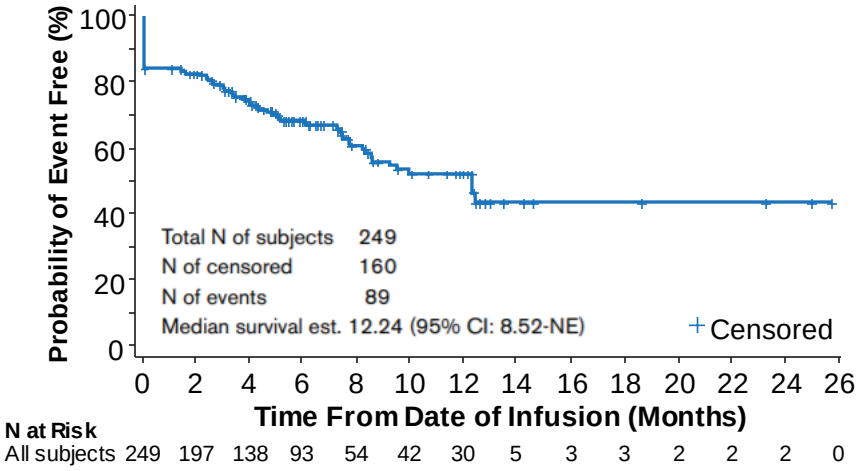
- 92 patients enrolled, 75 treated
- 73% Grade 3–4 AEs related to CAR-T:
- **81% → CR/CRi, all MRD negative; 66% in intention-to-treat analysis**
- 1 year EFS at 50%, no relapses after this
- **Demonstrates feasibility of delivery in multiple centres**



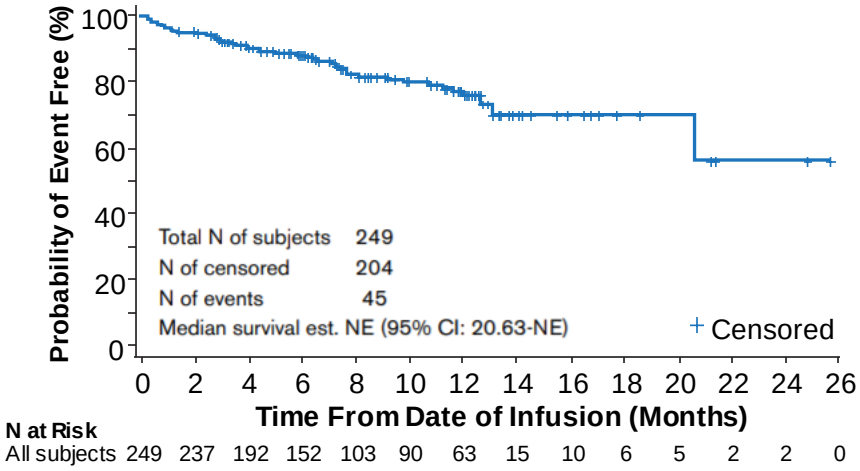
Maude SL, et al. N Engl J Med 2018;378:439–48;
KYMRIAH™ (tisagenlecleucel) Prescribing Information. Novartis Pharmaceuticals Corporation.

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)



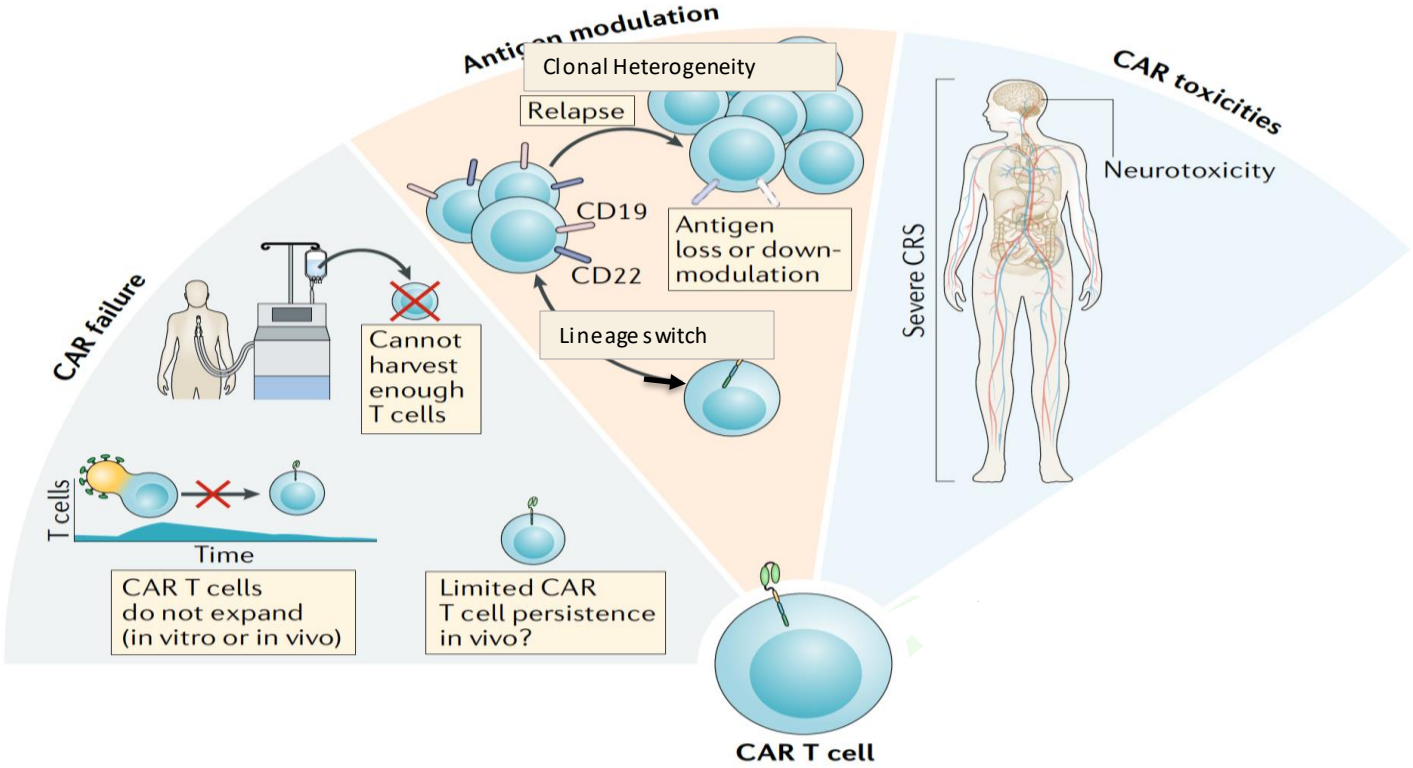
OS Rates Among All Infused Patients, % (95% CI) N = 249	
6 months	88.5 (83.6-92.0)
12 months	77.2 (69.8-83.1)



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.

Current Limitations of CAR T Cells



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

CD19-CAR_Lenti: peculiarities

Viral platform	**Lentivirus**
Viral supernatant	**Provided by Miltenyi Biotec**
Reagents	**Granted by Miltenyi Biotec at reduced costs**
Production	**Automated (CliniMACS Prodigy®)**
Starting material	**Fresh apheresis (0.75-1.5 x 10^9 total WBC)**
	CD4/CD8 enriched cells (20-200 x 10^6 cells)
Release	**Fresh drug product**
Time between apheresis and lymphodepletion	**9 days**
Time between apheresis and infusion	**14 days**

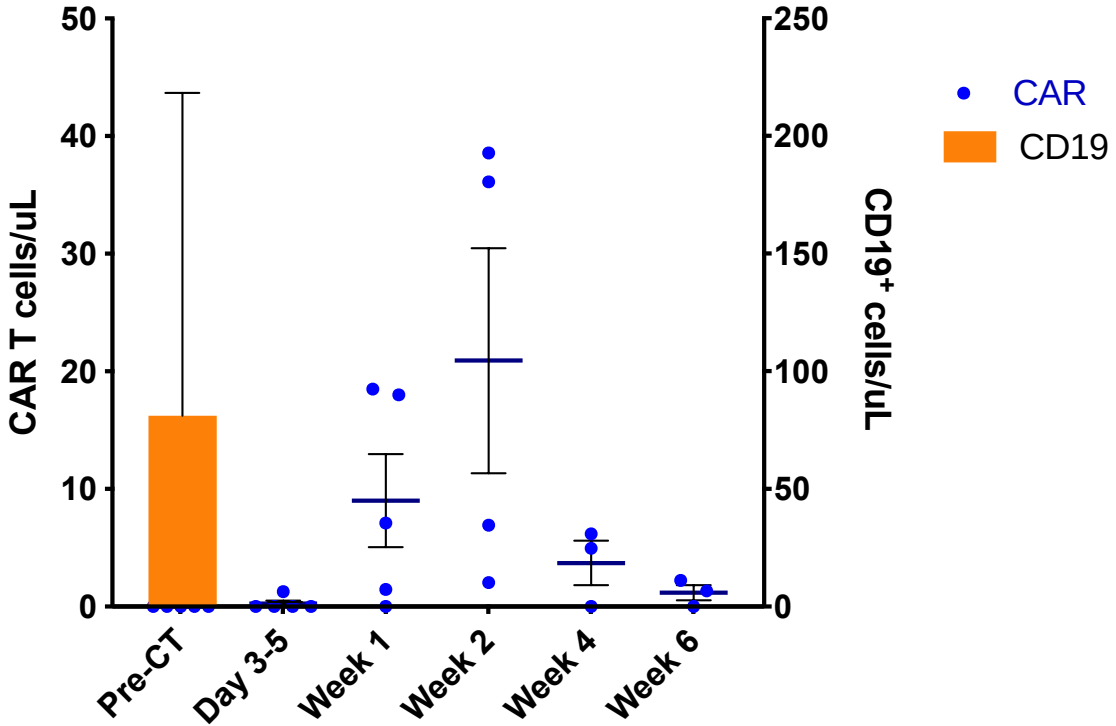
Bambino Gesù
OSPEDALE PEDIATRICO

Patients characteristics

	Pt ID	Gender	Age (y)	Cytogenetic anomalies	Disease phase at infusion	Previous allogeneic HSCT	BM blasts at lymphodepletion
DL1	001	M	7	None	ALL 2nd relapse	No	8,9%
	002	F	5	None	ALL 3rd relapse	Yes	15,7%
	003	F	7	47, XX (+21)	ALL 1st very early relapse	No	2,8%
DL2	004	M	4	None	ALL 2nd relapse (combined BM+CNS)	Yes	0,6%
	005	M	12	t(1;19)	ALL 1st refractory relapse (combined BM + bone and kidney)	No	2,3%

Bambino Gesù
OSPEDALE PEDIATRICO

CAR_Lenti expansion and outcome



All patients obtained CR

2 weeks after infusion

Bambino Gesù
OSPEDALE PEDIATRICO

Final considerations

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

Global Leukemia Academy

Bispecifics for Pediatric/AYA ALL

Patrick A. Brown, MD
Johns Hopkins University School of Medicine
USA

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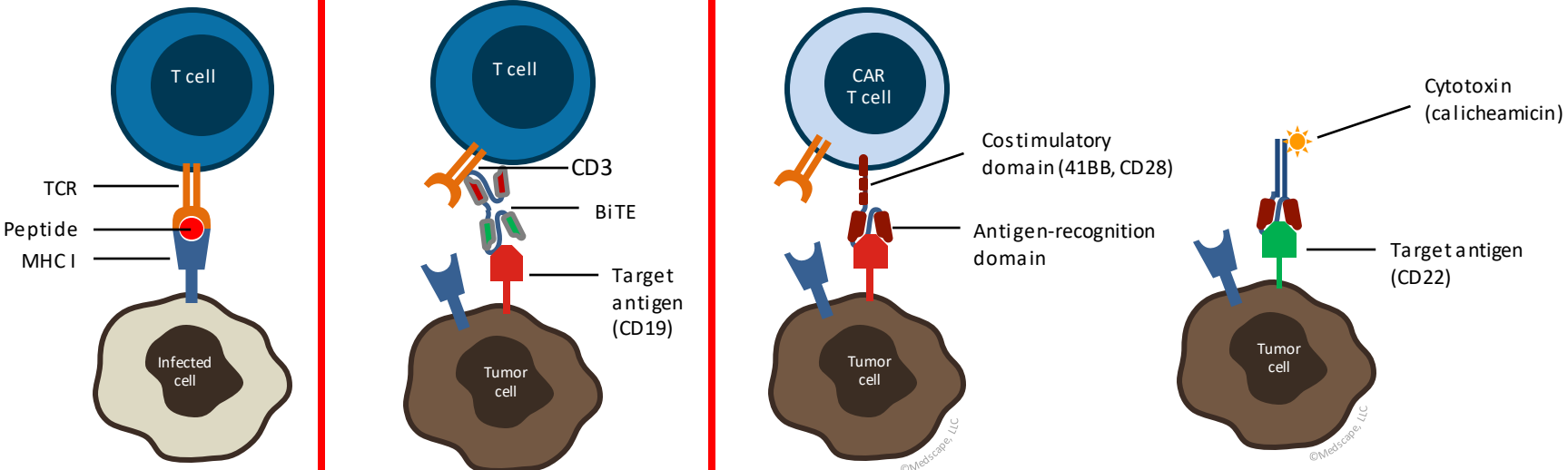
Bispecifics for Pediatric/AYA ALL

Patrick Brown, MD

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

Mechanism: Normal vs BiTE vs CAR vs ADC



- Off the shelf
- Continuous IV infusion

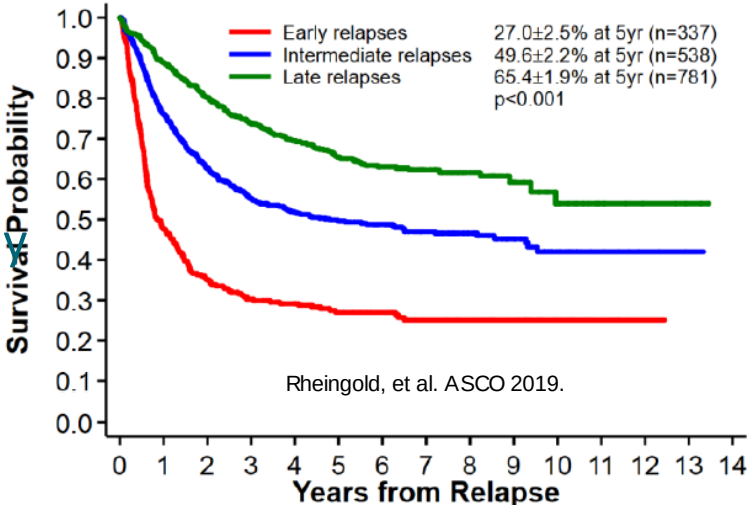
- Complicated and prolonged process
- Single infusion

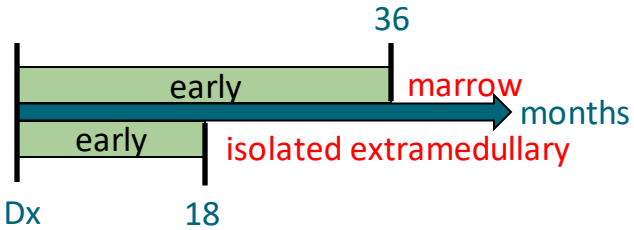
- Off the shelf
- Weekly short IV infusions

Adapted from Hinrichs CS, et al. *Nat Biotechnol.* 2013;31:999-1008.

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

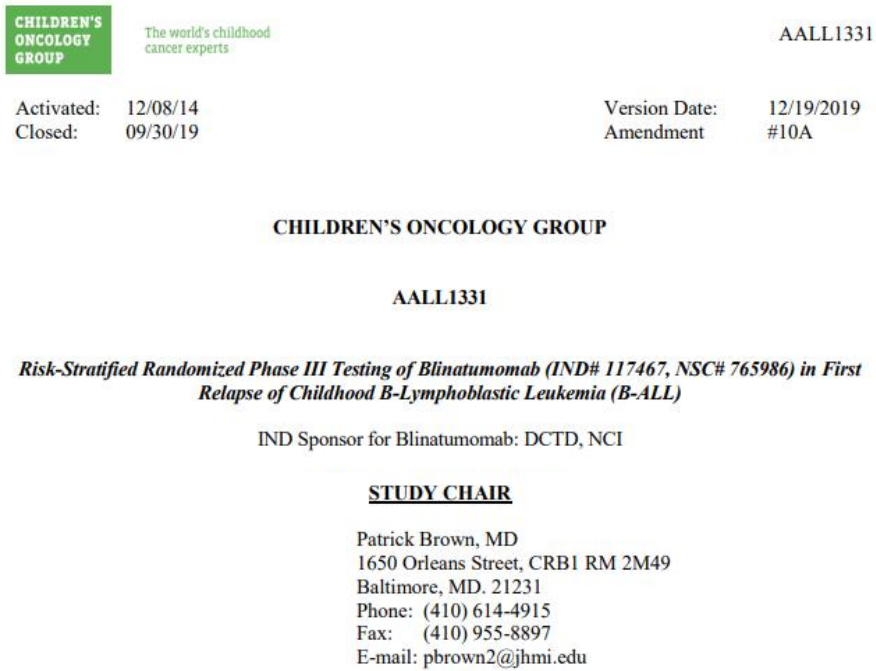
Blinatumomab (CD19 BiTE)

- In multiple relapsed/refractory setting (peds and adults)
  - CR 40%–45%
  - MRD-negative CR 20%–35%
  - Early survival benefit (adults)

von Stackelberg et al. *J Clin Oncol*. 2016;34:4381-4389
Kantarjian et al. *N Engl J Med*. 2017;376:836-847

- In MRD+ setting (adults)
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

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



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The world's childhood cancer experts

AALL1331

Activated: 12/08/14
Closed: 09/30/19

Version Date: 12/19/2019
Amendment #10A

CHILDREN'S ONCOLOGY GROUP

AALL1331

Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC# 765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

IND Sponsor for Blinatumomab: DCTD, NCI

STUDY CHAIR

Patrick Brown, MD
1650 Orleans Street, CRB1 RM 2M49
Baltimore, MD. 21231
Phone: (410) 614-4915
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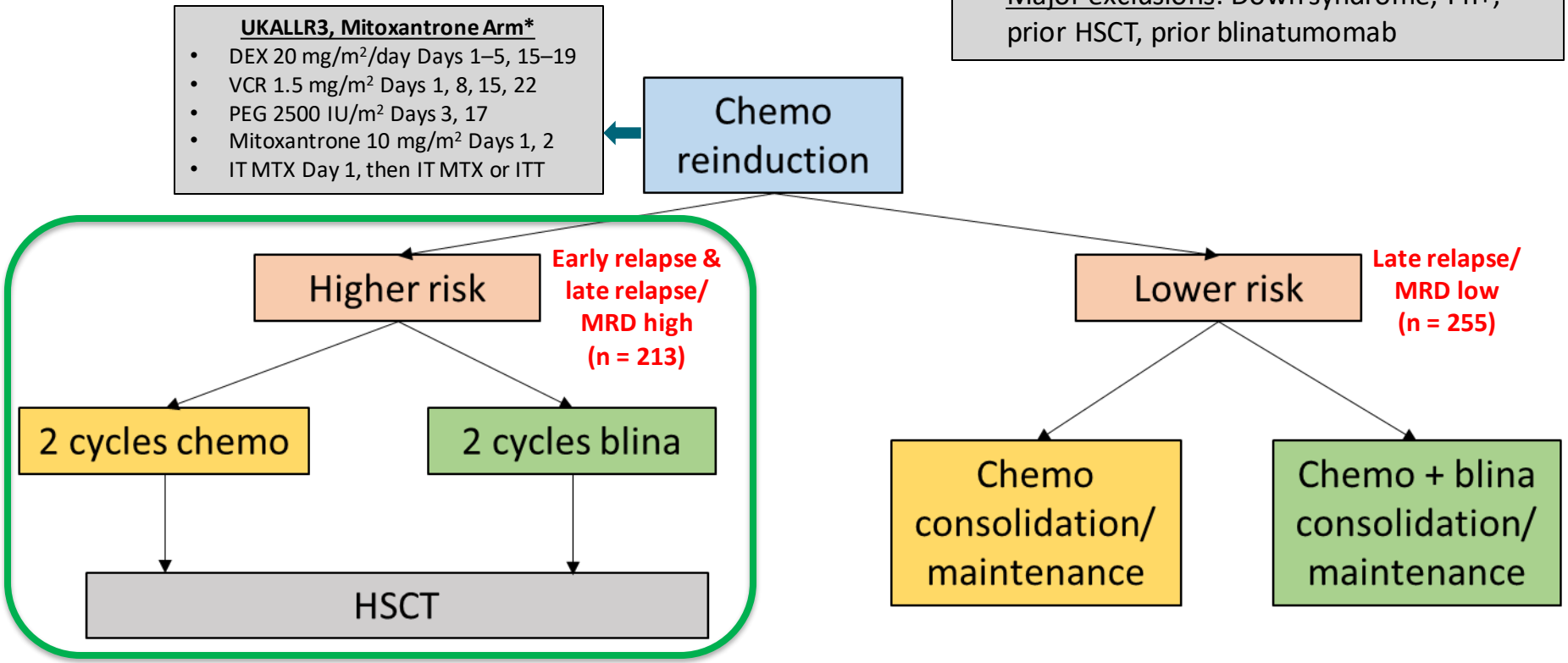
E-mail: pbrown2@jhmi.edu

CHILDREN'S ONCOLOGY GROUP

Overall objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in first relapse of childhood/AYA B-ALL

AALL1331: "Big Picture"

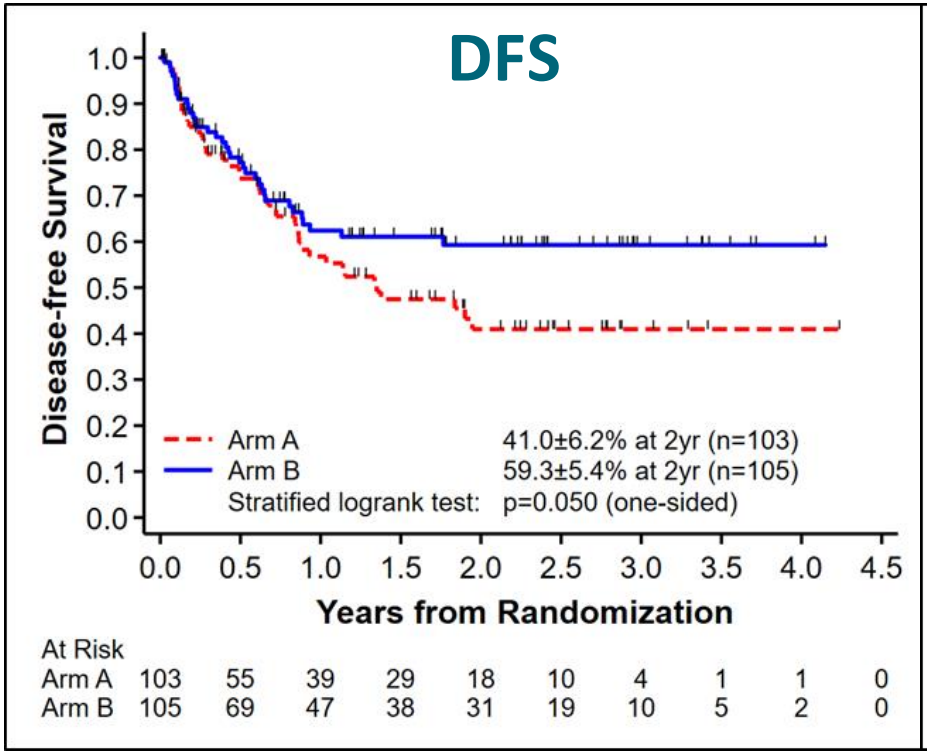
- All first relapse (any CR1 duration, any site)
- Ages 1–30
- Major exclusions: Down syndrome, Ph+, prior HSCT, prior blinatumomab

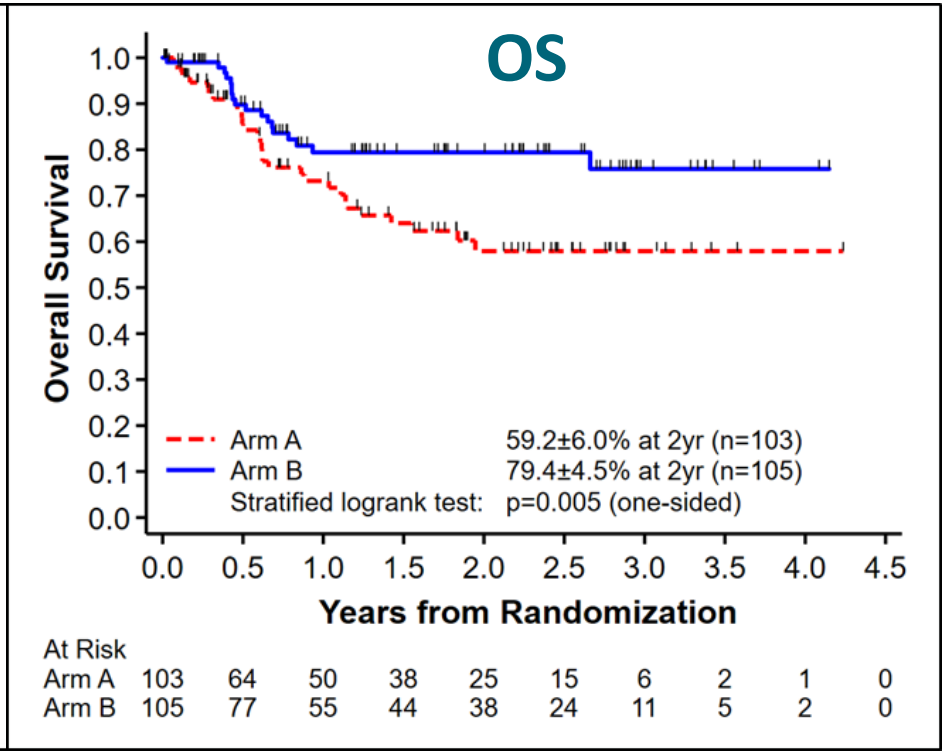


CHILDREN'S ONCOLOGY GROUP

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

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



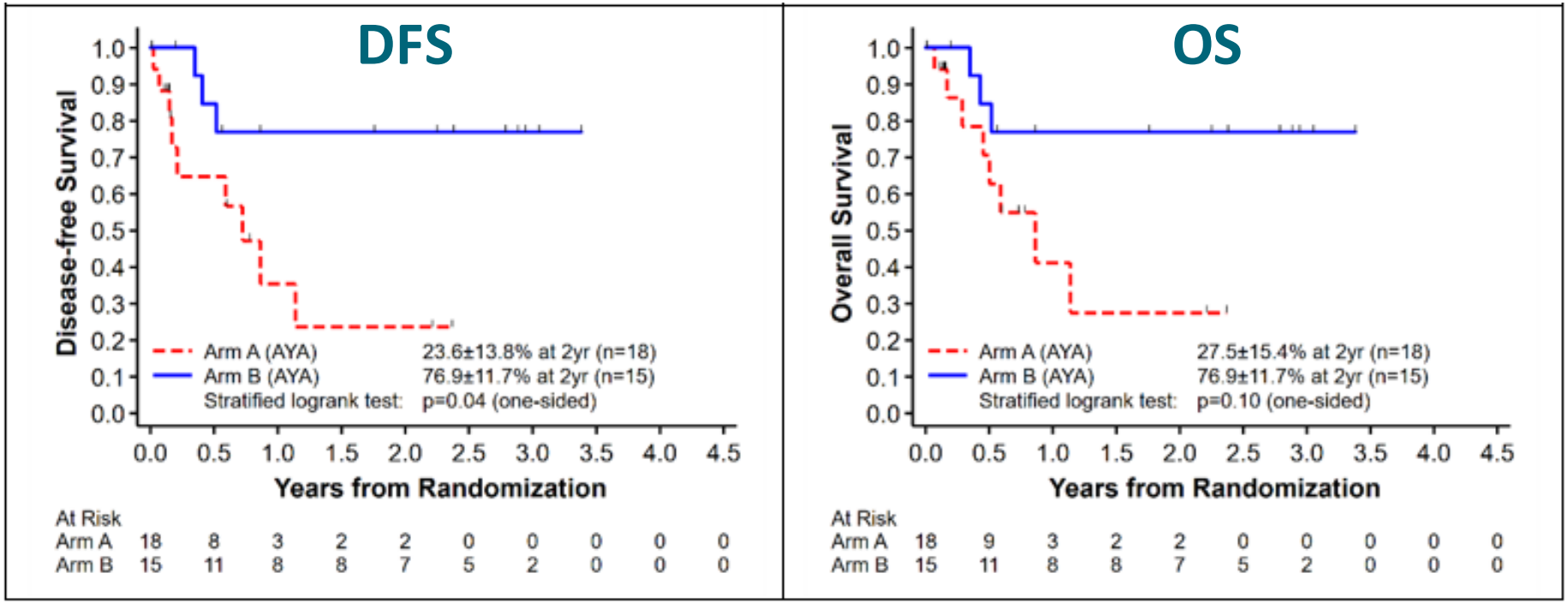


CHILDREN'S ONCOLOGY GROUP

Median follow up 2.9 years

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

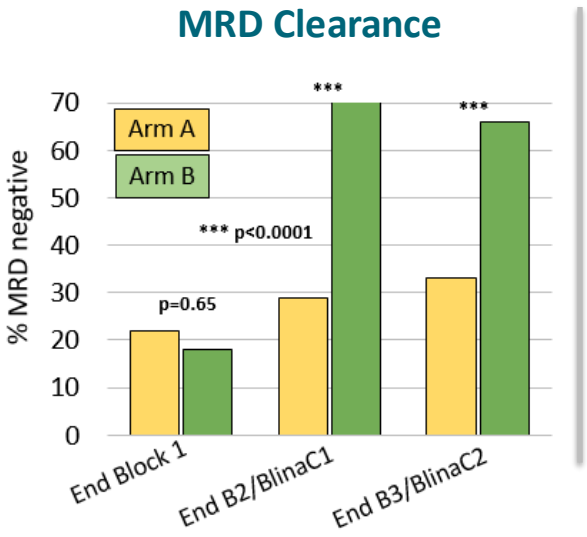
Results AYA Patients (Ages 18–30 at Relapse)

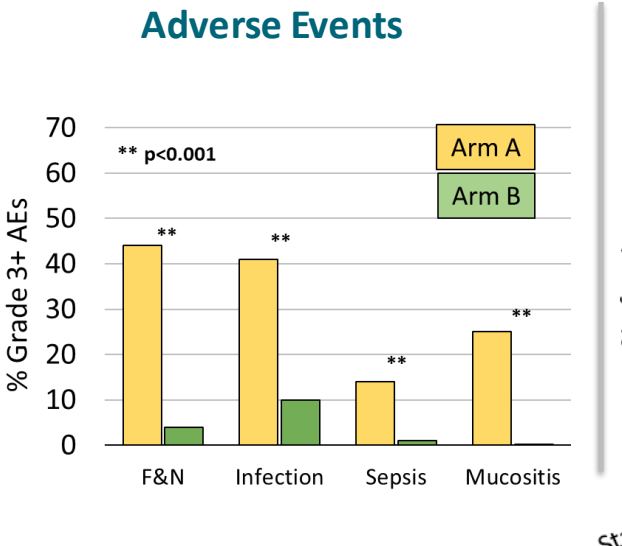


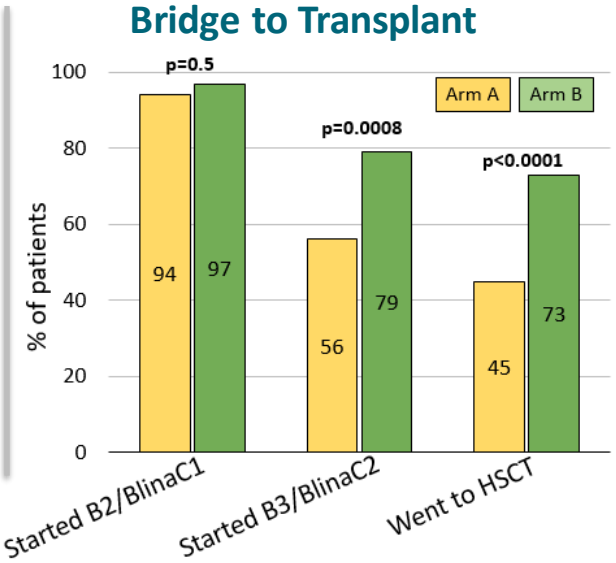
CHILDREN'S ONCOLOGY GROUP

Median follow up 1.4 years

Other Endpoints: MRD, AEs, HSCT Bridging







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

CHILDREN'S ONCOLOGY GROUP

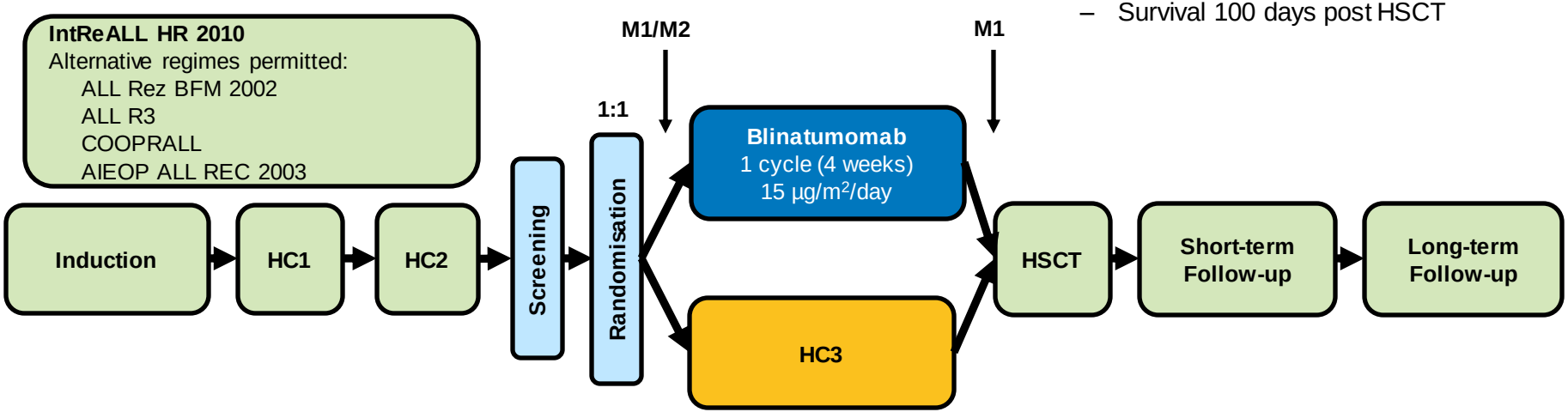
Brown P, et al. *JAMA*. 2021;325(9):833-842.

Amgen 20120215: Open-Label, Randomized, Phase III Trial: 47 Centers, 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

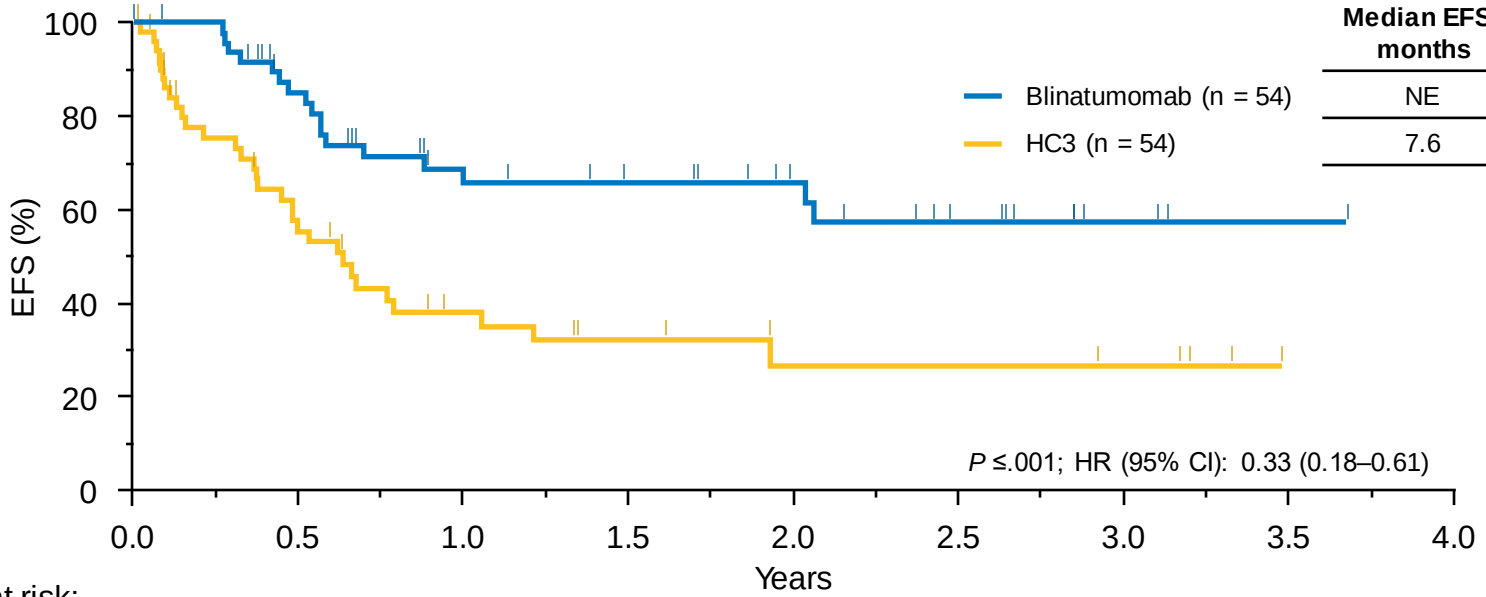
Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post HSCT



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

Locatelli F, et al. *JAMA*. 2021;325(9):843-854.

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

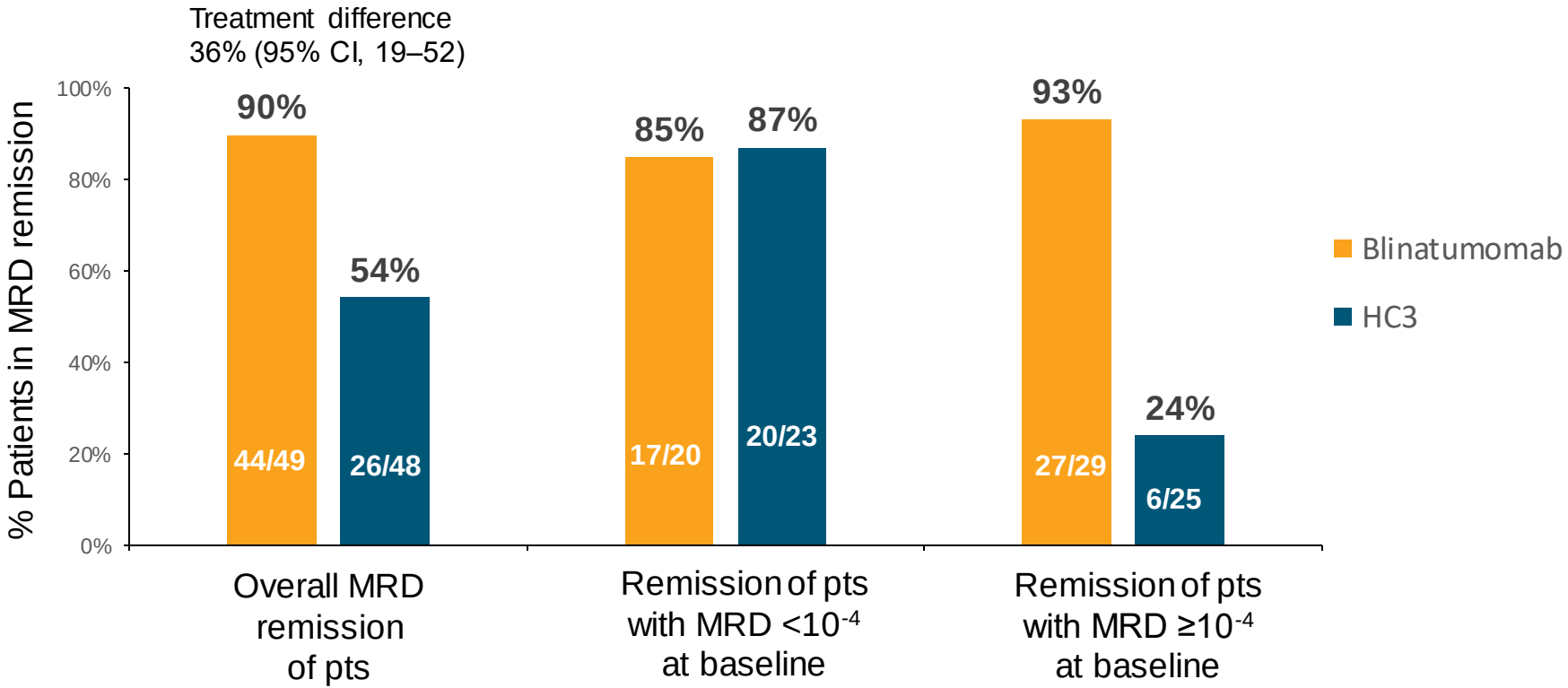
Subjects at risk:

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	

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

Locatelli F, et al. *JAMA*. 2021;325(9):843-854.

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

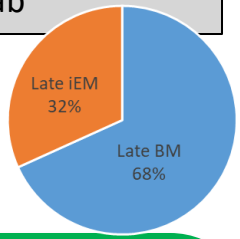


Locatelli F, et al. *JAMA*. 2021;325(9):843-854.

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

AALL1331: "Big Picture"

- All first relapse (any CR1 duration, any site)
- Ages 1–30
- Major exclusions: Down syndrome, Ph+, prior HSCT, prior blinatumomab



UKALLR3, Mitoxantrone Arm*

- DEX 20 mg/m²/day Days 1–5, 15–19
- VCR 1.5 mg/m² Days 1, 8, 15, 22
- PEG 2500 IU/m² Days 3, 17
- Mitoxantrone 10 mg/m² Days 1, 2
- IT MTX Day 1, then IT MTX or ITT

Chemo reinduction

Higher risk — Early relapse & late relapse/ MRD high (n = 213)

- 2 cycles chemo
- 2 cycles blina

HSCT

Lower risk — Late relapse/ MRD low (n = 255)

- Chemo consolidation/ maintenance
- Chemo + blina consolidation/ maintenance

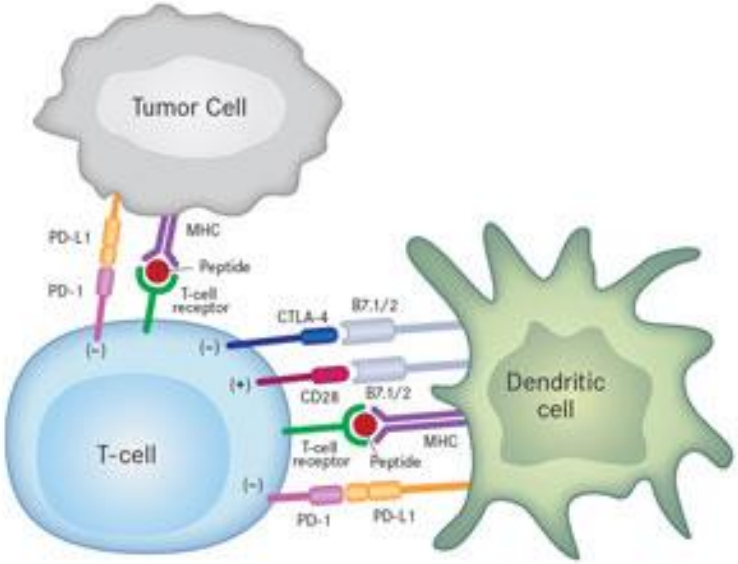
CHILDREN'S ONCOLOGY GROUP

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

What Happens When Blinatumomab Doesn't Work?

- Endogenous T-cell "exhaustion"

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

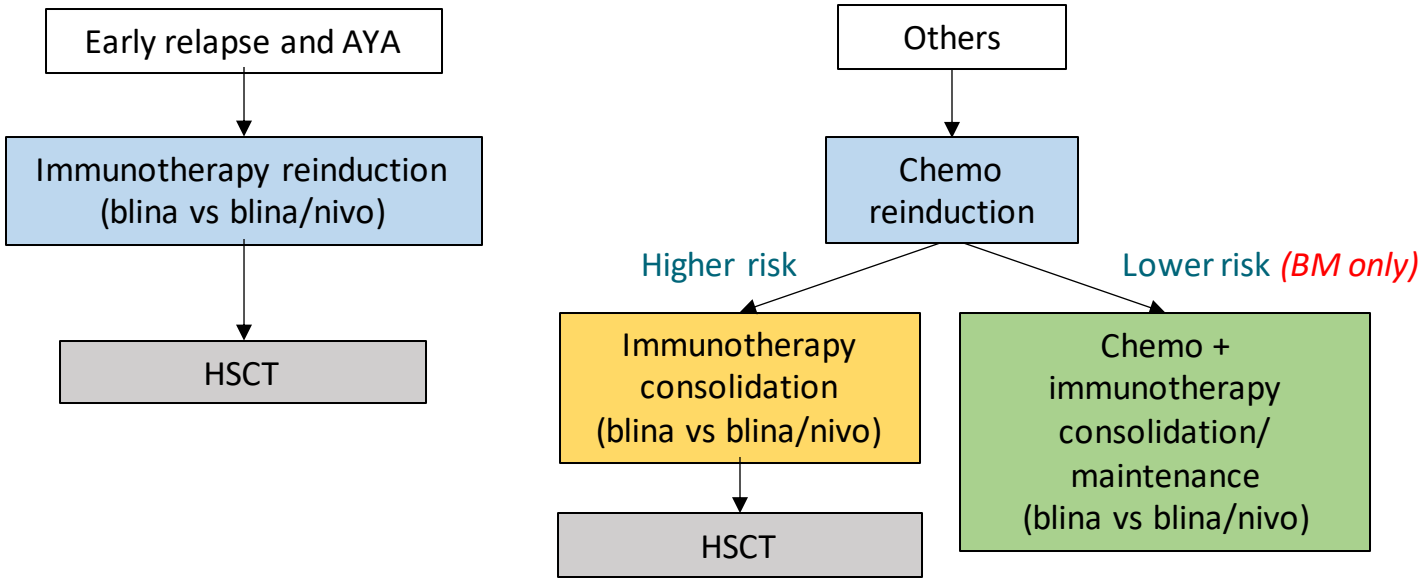


PD-1	PD-L1	CTLA-4
Nivolumab	Atezolizumab	Ipilimumab
Pembrolizumab*	Avelumab	
	Durvalumab	

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

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

AALL1821: Blinatumomab + Nivolumab



Can We Predict When Blinatumomab Won't Work?

bjh BRITISH JOURNAL OF HAEMATOLOGY

Correspondence | Free Access

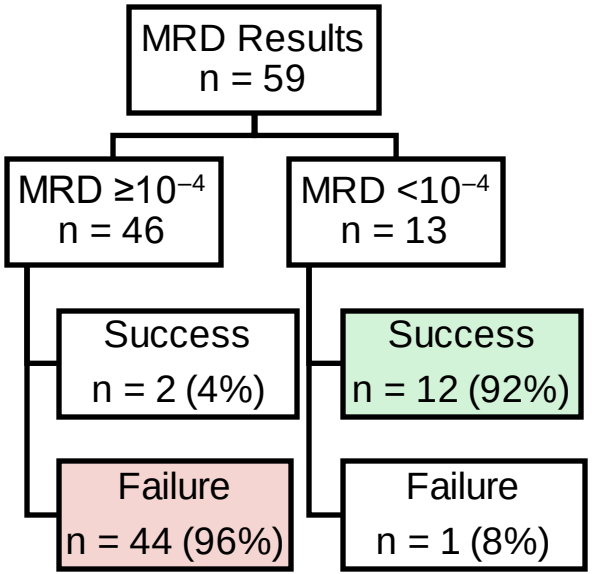
Day 15 bone marrow minimal residual disease predicts response to blinatumomab in relapsed/refractory paediatric B-ALL

Patrick Brown, Gerhard Zugmaier, Lia Gore, Catherine A. Tuglus, Arend von Stackelberg

First published: 03 December 2019 | https://doi.org/10.1111/bjh.16306

Biomarkers to Predict Blinatumomab Success/Failure

- Study definitions
  - "**Success**" was defined as complete MRD response in CR (n = 14)
  - "**Failure**" was defined as anything other than success (n = 50)
- Overall, Day 15 MRD results predicted best response after 2 cycles with 95% accuracy (correctly in 56 of 59 patients)



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***

CR, complete remission; MRD, minimal residual disease.

Clinical Trial Questions in COG: Molecularly/Immunologically Targeted Therapy in B-ALL

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

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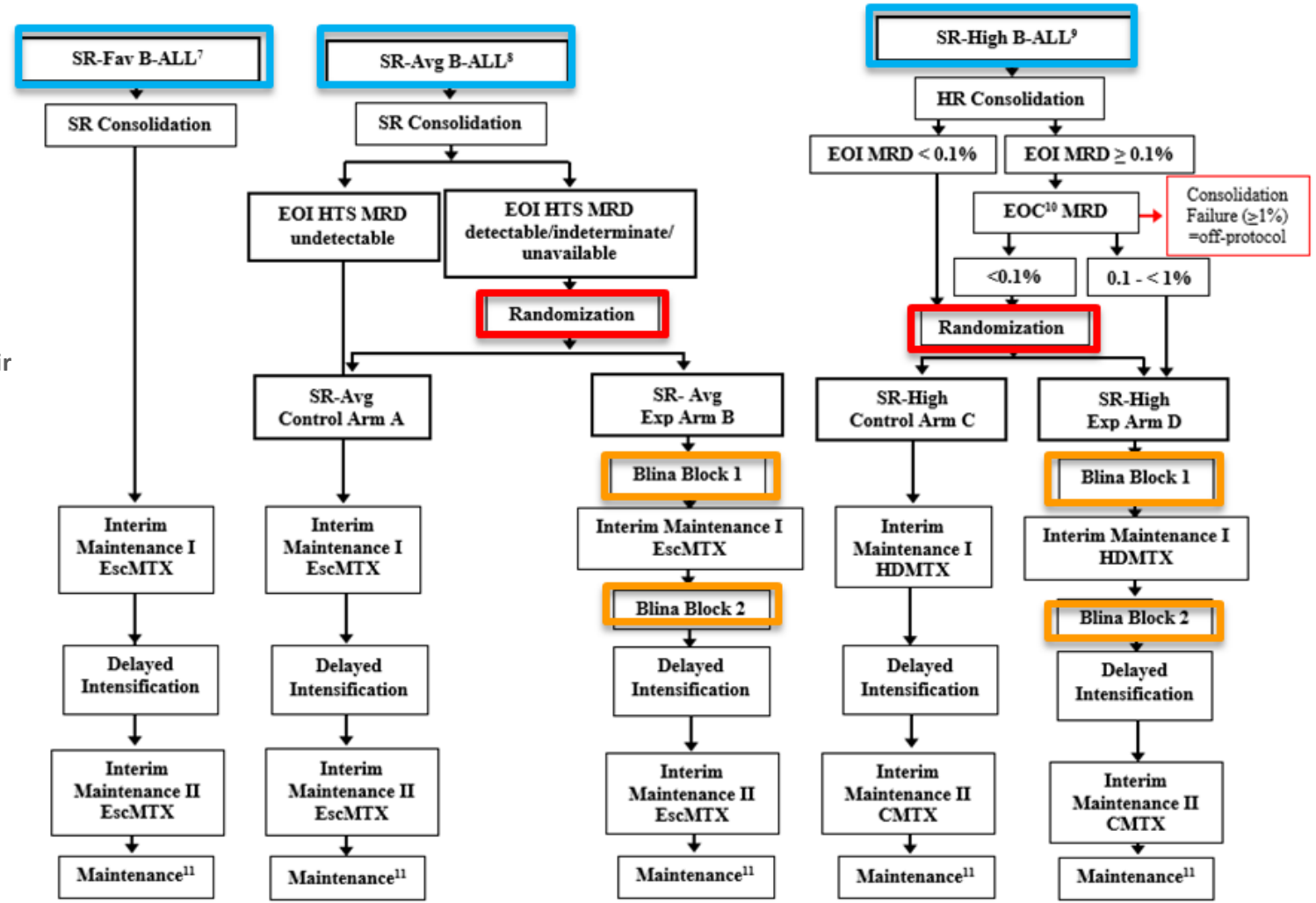
AALL1731: Post-Induction

Rachel Rau, Study Co-Chair
Sumit Gupta, Study Co-Chair

Opened June 2019
Accrued ~1800 of ~6400



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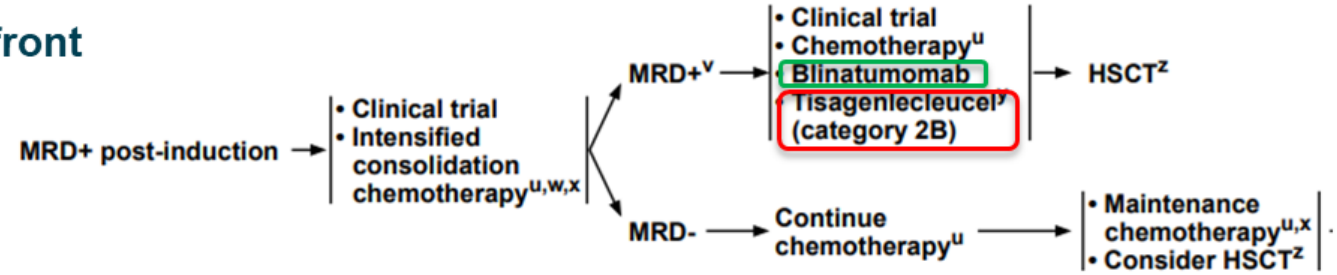
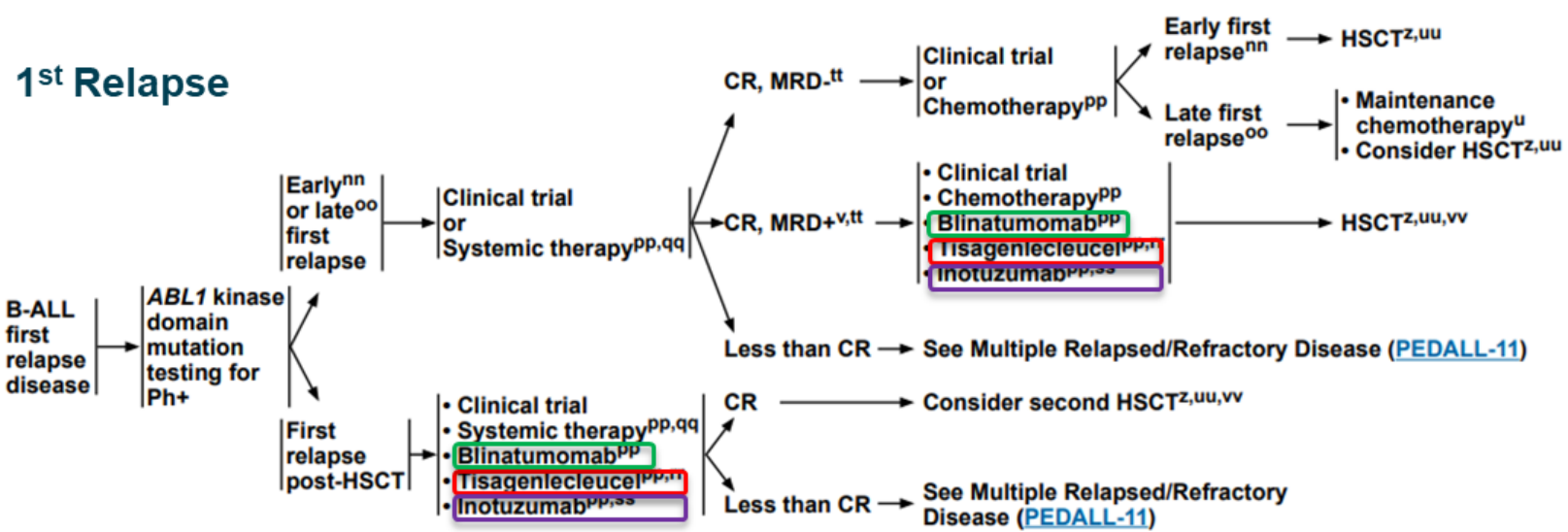
Upfront



1st Relapse



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?

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Questions to the Experts

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Closing

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Patrick A. Brown, MD
Johns Hopkins University School of Medicine
USA

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Thank you to all participants!

And thank you to Amgen for their sponsorship

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- 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/

Global Leukemia Academy

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

Webinar

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