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Emerging and Practical Concepts and Controversies in Leukemias

28 October 2021

Virtual Breakout – Pediatric Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

Welcome and meeting overview

Franco Locatelli

APTITUDE HEALTH

Global Leukemia Academy

Pediatric ALL

CHAIR

Franco Locatelli, MD, PhD
Professor of Pediatrics
Sapienza, University of Rome and IRCCS Bambino Gesù Children's Hospital, Italy

FACULTY

Rob Pieters, MD, PhD
Princess Máxima Center for Pediatric Oncology, University of Utrecht, The Netherlands

Christina Peters, MD
St. Anna Children's Hospital, Austria

Martin Schrappe, MD, PhD
University Medical Center Schleswig-Holstein, Germany

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Objectives of the program

- Understand current treatment patterns for acute leukemias including incorporation of new technologies
- Uncover when genomic testing is being done for acute leukemias, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in acute leukemias as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring acute leukemias
- 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 acute leukemias
- Review promising novel and emerging therapies in acute leukemias
- Explore regional challenges in the treatment of acute leukemias across Europe

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Virtual Breakout – Pediatric ALL Patients (Day 2) 17.00 – 19.45

Chair – Franco Locatelli

Time CET	Title	Speaker/Moderator
17.00 – 17.15	**Session open**	Franco Locatelli
17.15 – 17.40	**How to use MRD and genetics for risk stratification and therapy guidance in pediatric ALL**	Rob Pieters
17.40 – 18.05	**First-line treatment of pediatric ALL**	Martin Schrappe
18.05 – 18.30	**Current treatment options for relapsed ALL in children, including HSCT considerations**	Franco Locatelli
18.30 – 18.55	**Bispecific T-cell engagers for pediatric ALL**	Christina Peters
18.55 – 19.25	**Case-based panel discussion on management of long- and short-term toxicities in pediatric ALL patients** • Case presentation 1: Francesca Del Bufalo • Case presentation 2: Natalia Zubarovskaya	Moderator: Franco Locatelli *Faculty panel:* R. Pieters, F. Locatelli, P. Brown, C. Peters, M. Schrappe
19.25 – 19.45	**Final discussion, Q&A, and session close**	Franco Locatelli

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Educational ARS questions

Franco Locatelli

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Educational Questions Pediatric ALL

Question 1: Which of the following subsets of first-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 hypodiploidy
c) All patients with t(17;19) or t(1;19)
d) Each of the 3 previous subsets

Educational Questions Pediatric ALL

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

a) Inotuzumab is approved for induction treatment of relapsed B-ALL in childhood

b) Inotuzumab dosage is 3 mg/m^2

c) Blinatumomab is approved for consolidation treatment before HSCT in children with B-ALL

d) None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

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Educational Questions Pediatric ALL

Question 3: Which children with relapsed ALL should be transplanted after a TBI-containing regimen?

a) All children
b) Children above the age of 4 years
c) Children above the age of 10 years
d) Those with T-ALL

Educational Questions Pediatric ALL

Question 4: Which of the following statements is incorrect?

a) Leukemia recurrence in patients given CAR T cells is associated with early disappearance of CAR T cells in peripheral blood
b) Leukemia recurrence in patients given CAR T cells is associated with B-cell aplasia
c) Leukemia recurrence in patients given CAR T cells is associated with disease burden at time of infusion
d) Leukemia recurrence in patients given CAR T cells is associated with reappearance of MRD

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How to use MRD and genetics for risk stratification and therapy guidance in pediatric ALL

Rob Pieters

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How to use MRD and genetics for risk-stratification and therapy guidance

Rob Pieters
Chief Medical Officer

MRD and genetics to guide stratification and therapy

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

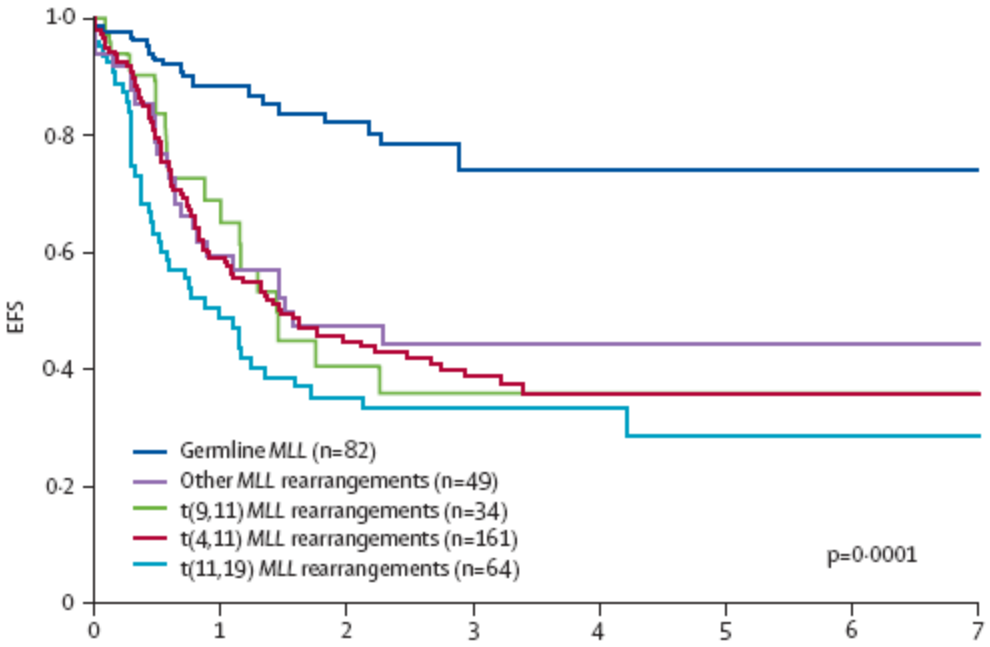
Question 1: Which of the following statements is NOT correct?

a) MRD at end of induction in infant *KMT2A*-rearranged ALL can be used to select the most effective subsequent myeloid-like or lymphoid-like type of consolidation therapy

b) MRD at end of induction and consolidation in *BCR-ABL1*–positive ALL is used to select patients who do not need a SCT

c) The prognostic relevance of MRD at end of induction depends on the genetic subtype of ALL

d) All types of *BCR-ABL1*–like ALL are sensitive to ABL-class tyrosine kinase inhibitors

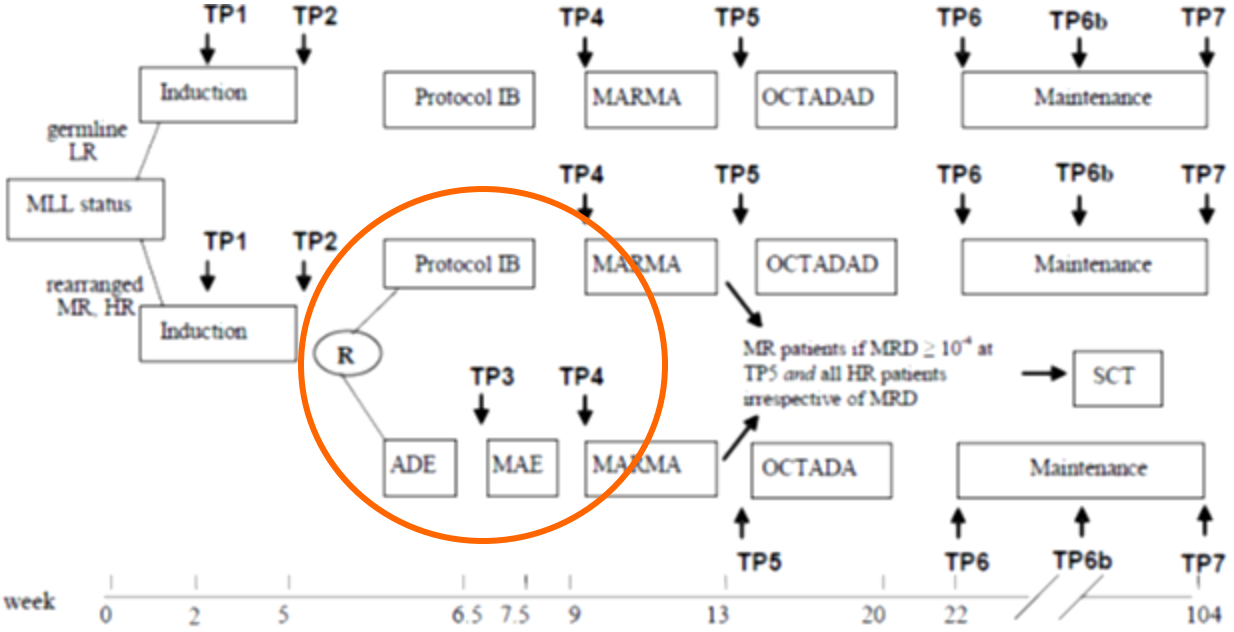


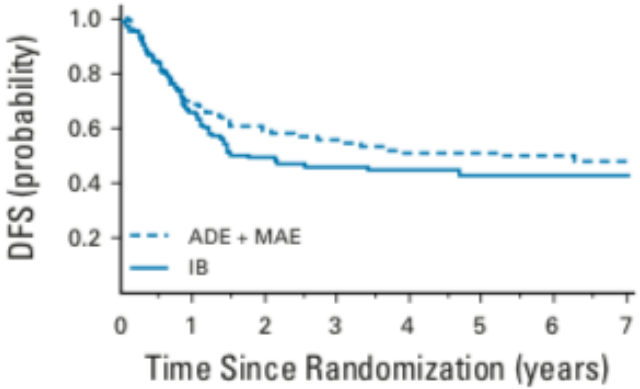
KMT2A germline

KMT2A rearranged

Pieters, Lancet 2007

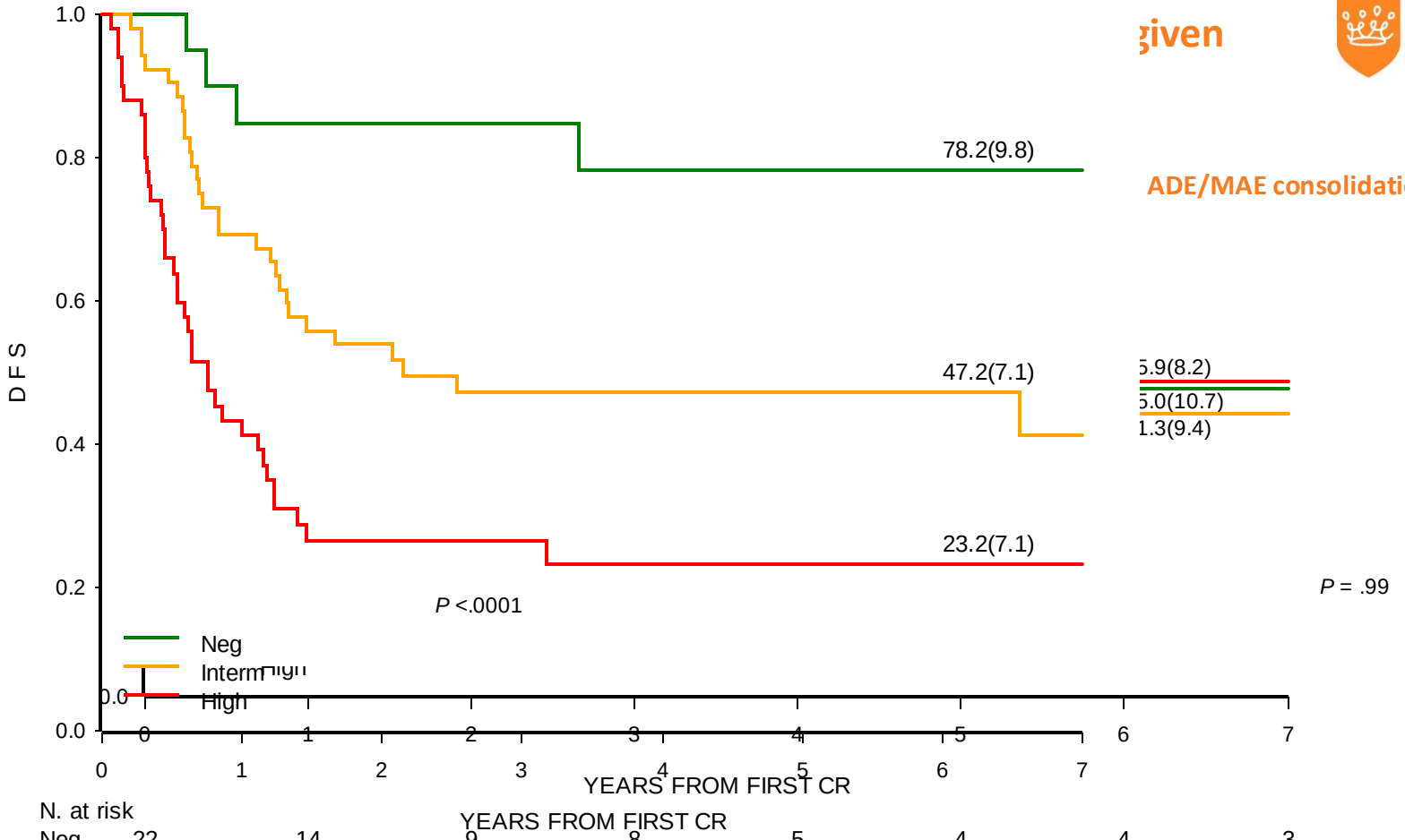
Interfant-06 treatment schedule



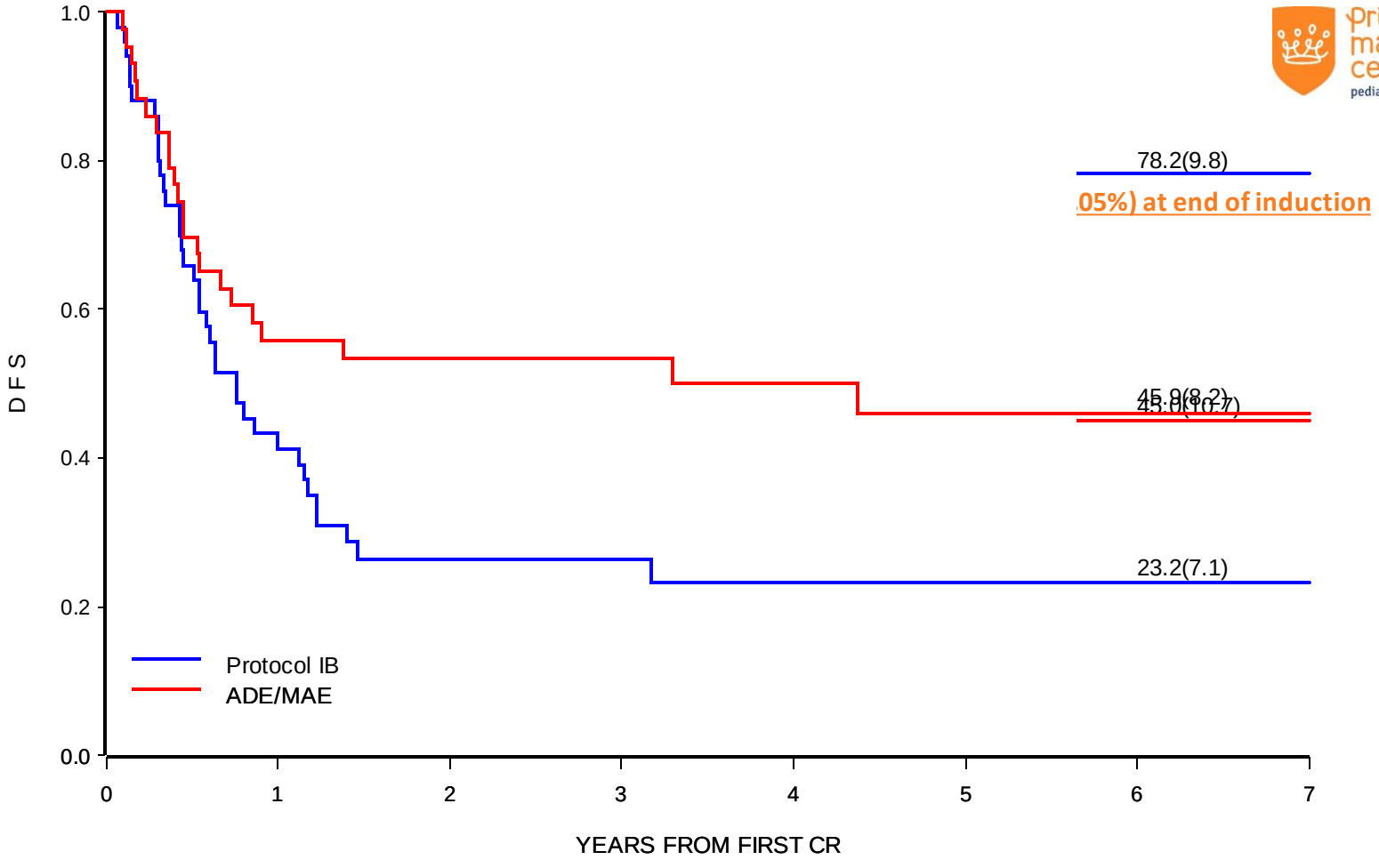


given

ADE/MAE consolidation



YEARS FROM FIRST CR
N. at risk
Neg 20 16 13 13 9 8 5
High 43



Stutterheim, J Clin Oncol 2021

Conclusions: EOI MRD Interfant-06

(ALL-like) induction leads to selection of patients

- Low MRD → "ALL-like leukemia" → benefit from ALL consolidation (IB)
- High MRD → "AML-like leukemia" → benefit from AML consolidation (ADE/MAE)

TKI studies and outcomes in Ph+ ALL (courtesy of Thai Ho Tran)

	AALL0031[1]	EsPhALL2004[2]	EsPhALL2010[3]	AALL0622[4]	AALL1122[5]	CCCG-ALL-2015[6]
Phase	3	2	2	2	2	3
TKI	Imatinib 340 mg/m^2	Imatinib 300 mg/m^2	Imatinib 300 mg/m^2	Dasatinib 60 mg/m^2	Dasatinib 60 mg/m^2	Imatinib 300 mg/m^2 vs Dasatinib 80 mg/m^2
Period	2002-2006	2004-2009	2010-2014	2008-2012	2012-2014	2015-2018
Patients	91	160	155	60	106	97 (imatinib) 92 (dasatinib)
CR1 HSCT	25%	83%	38%	32%	14%	0.5%
5-yr EFS	71% (Cohort 5)	60%	57%	60%	55%	4-yr EFS: 49% (imatinib) 4-yr EFS: 71% (dasatinib)
5-yr OS	81% (Cohort 5)	72%	72%	86%	82%	4-yr OS: 69% (imatinib) 4-yr OS: 88% (dasatinib)

1. Schultz KR, et al. *Leukemia.* 2014; 2. Biondi A, et al. *Haematologica.* 2018; 3. Biondi A, et al. *Lancet Haematol.* 2018; 4. Slayton WB, et al. *J Clin Oncol.* 2018; 5. Hunger SP, et al. SIOP Virtual Congress. 2020; 6. Shen S, et al. *JAMA Oncol.* 2020.

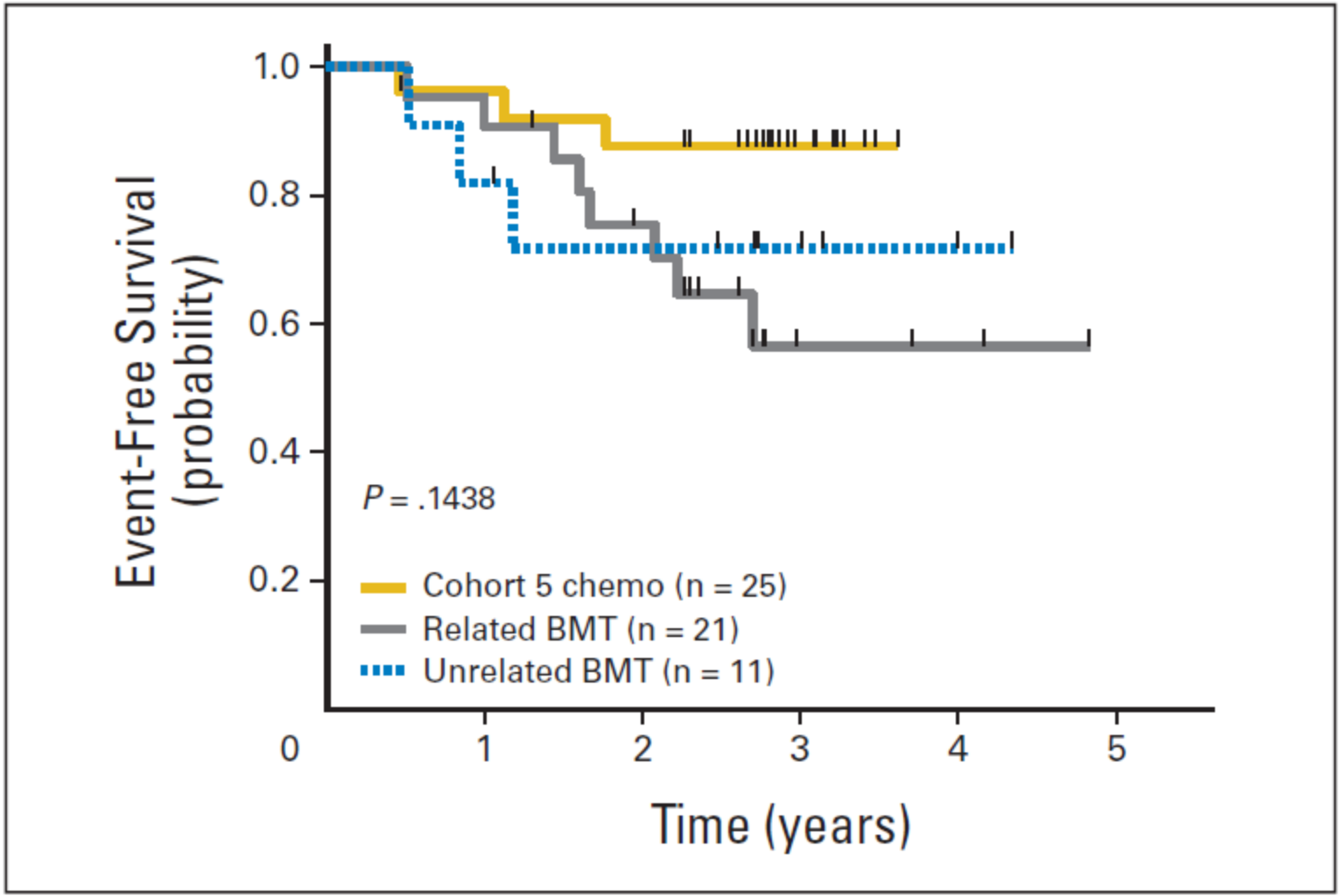


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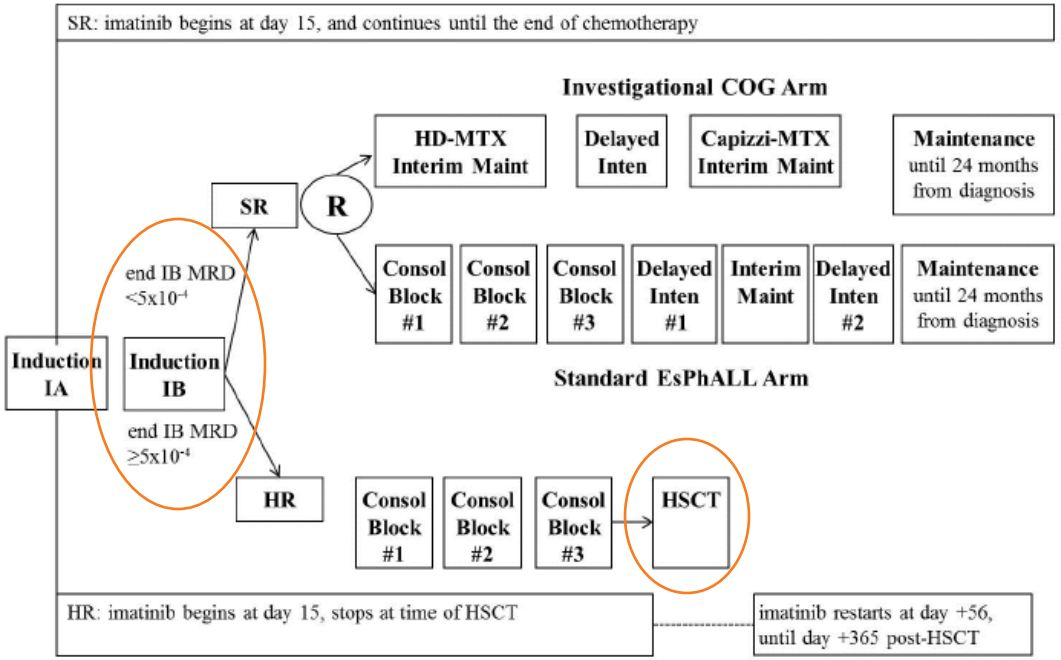
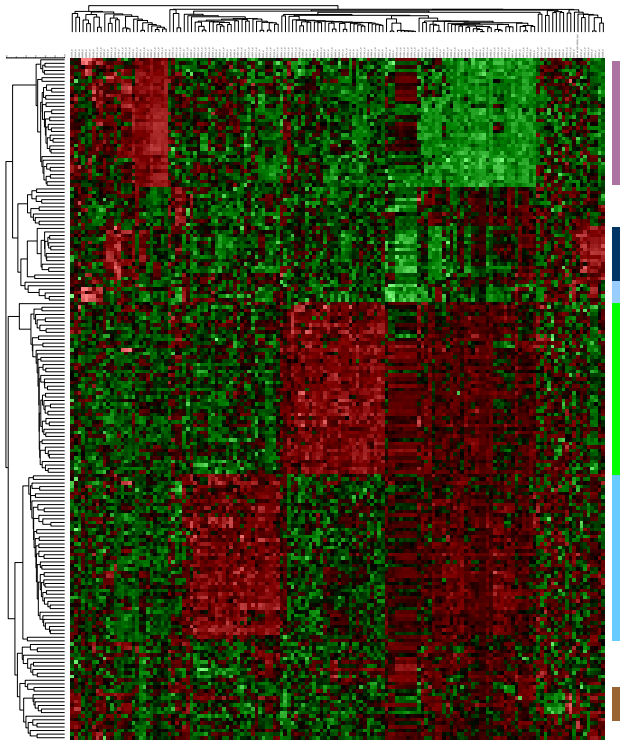
Fig 4. Comparison of event free survival (EFS) for Cohort 5 chemotherapy only

EsPhALL2017/COGAALL1631



Note. MRD: Minimal Residual Disease, SR:Standard Risk, HR: High Risk, **R**: Randomization, HD-MTX: High Dose Methotrexate, Maint: Maintenance, Inten: Intensification, Consol: Consolidation, HSCT: Hematopoietic Stem Cell Transplant

Discovery of *BCR-ABL1*–like ALL in 2009



T-ALL

***E2A*-rearranged**

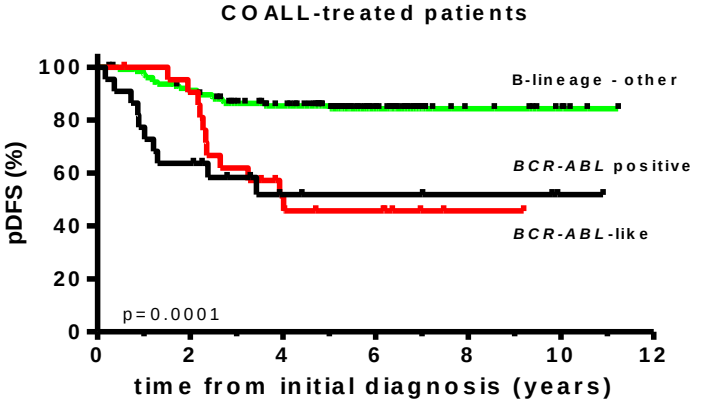
***MLL*-rearranged**

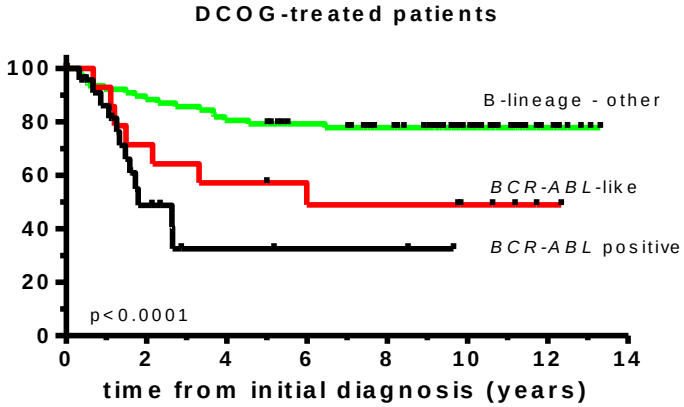
TEL-AML1

Hyperdiploid

BCR-ABL1

5 real *BCR-ABL1*
30 *BCR-ABL1*–like





Den Boer et al. Lancet Oncol. 2009

Frequency of identified tyrosine kinase fusion genes in *BCR-ABL1*–like ALL and remaining B-other ALL

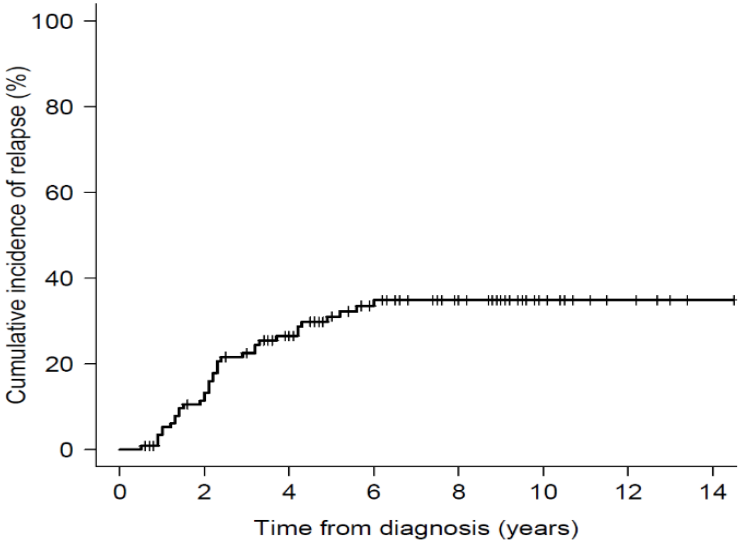
Marker	*BCR-ABL1*-like (n=77)	Remaining B-other (n=76)
***ABL1/ABL2* fusion**	**3.9%**	0%
ZMIZ1-ABL1	1	
FOXP1-ABL1	1	
RCSD1-ABL2	1	
***PDGFRB* fusion**	**5.2%**	0%
EBF1-PDGFRB	4	
***CSF1R* fusion**	**2.6%**	0%
SSBP2-CSF1R	2	
***JAK2* fusion**	**6.5%**	0%
PAX5-JAK2	3	
BCR-JAK2	1	
TERF2-JAK2	1	
CRLF2* high expression	15.6%	15.8%
PAR1 deletion**	10.5%	10.7%

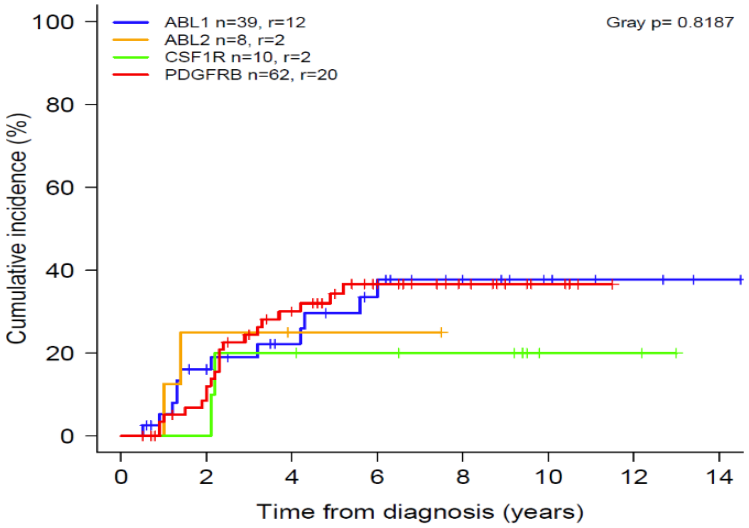
12% with **ABL-class** fusions
Targetable with TKI eg, imatinib/dasatinib

6% with *JAK2* fusions
Targetable with ruxolitinib????

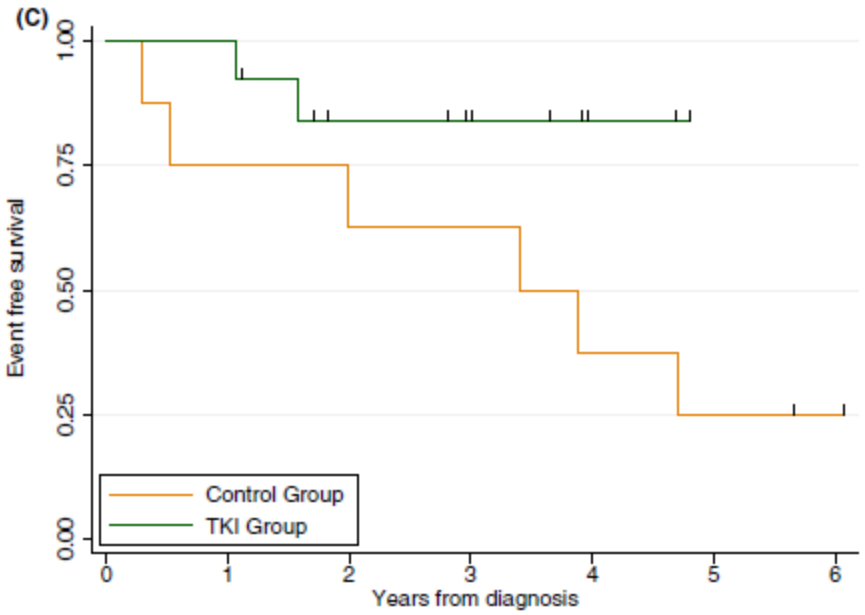
Boer, Oncotarget 2016

Cumulative incidence of relapse in ABL-class patients treated without TKI





Den Boer ML, Lancet Haematol 2020



without imatinib

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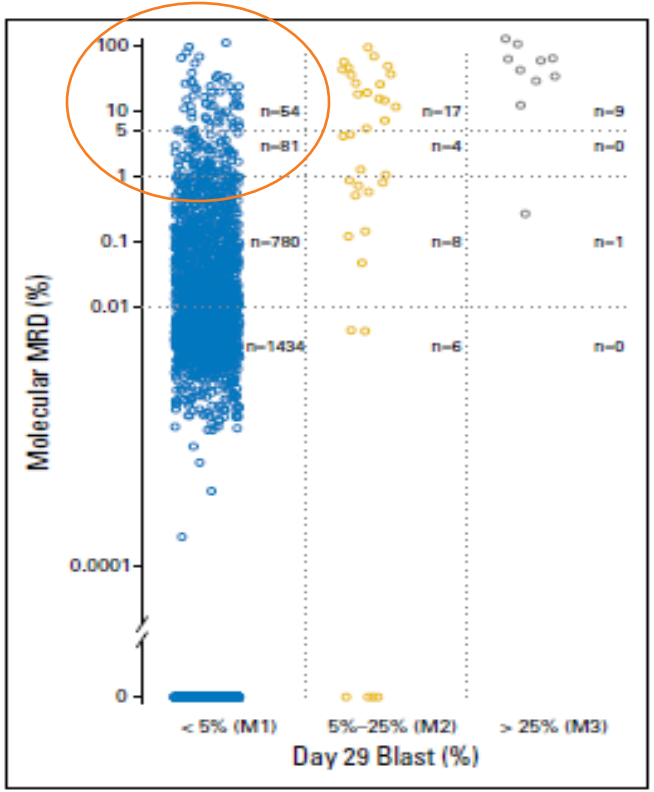
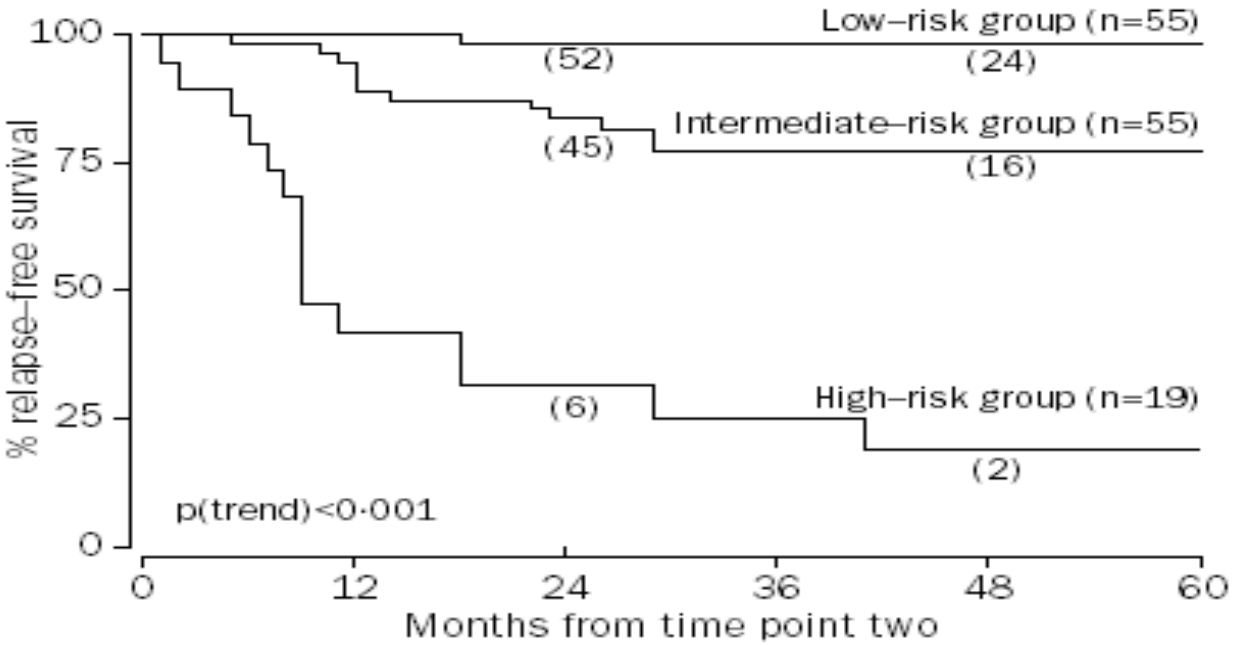
Morphologic vs molecular detection of MRD at end of induction

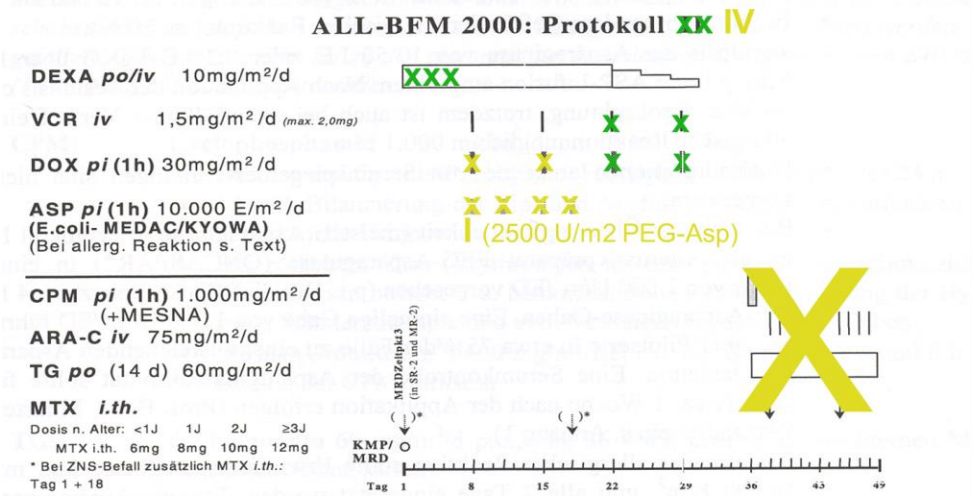


Minimal residual disease and outcome in ALL



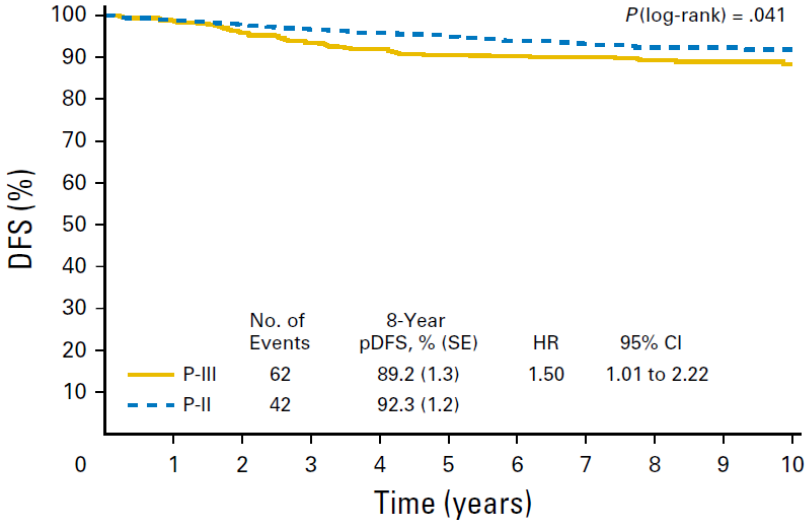
Relapse-free survival of the 3 MRD-based risk groups, as defined by MRD information at time points 1 and 2

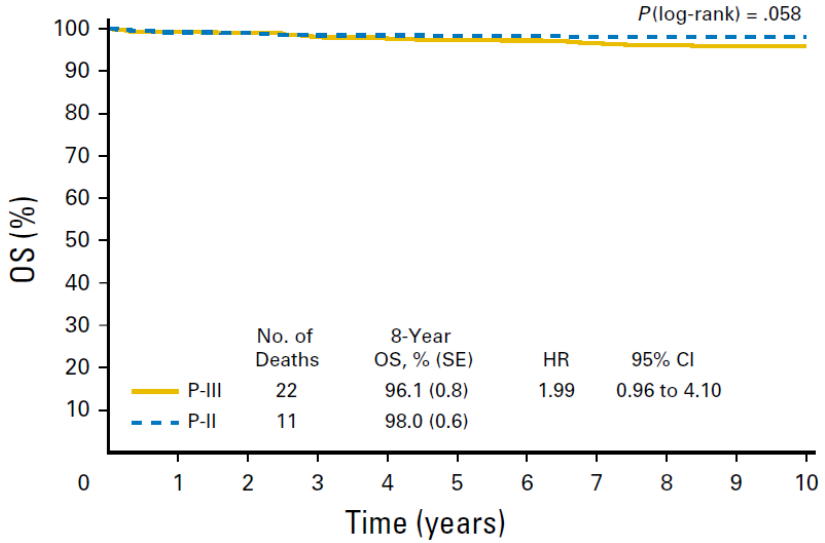
Therapy reduction in MRD-negative patients: BFM-II vs BFM-III vs DCOG-IV

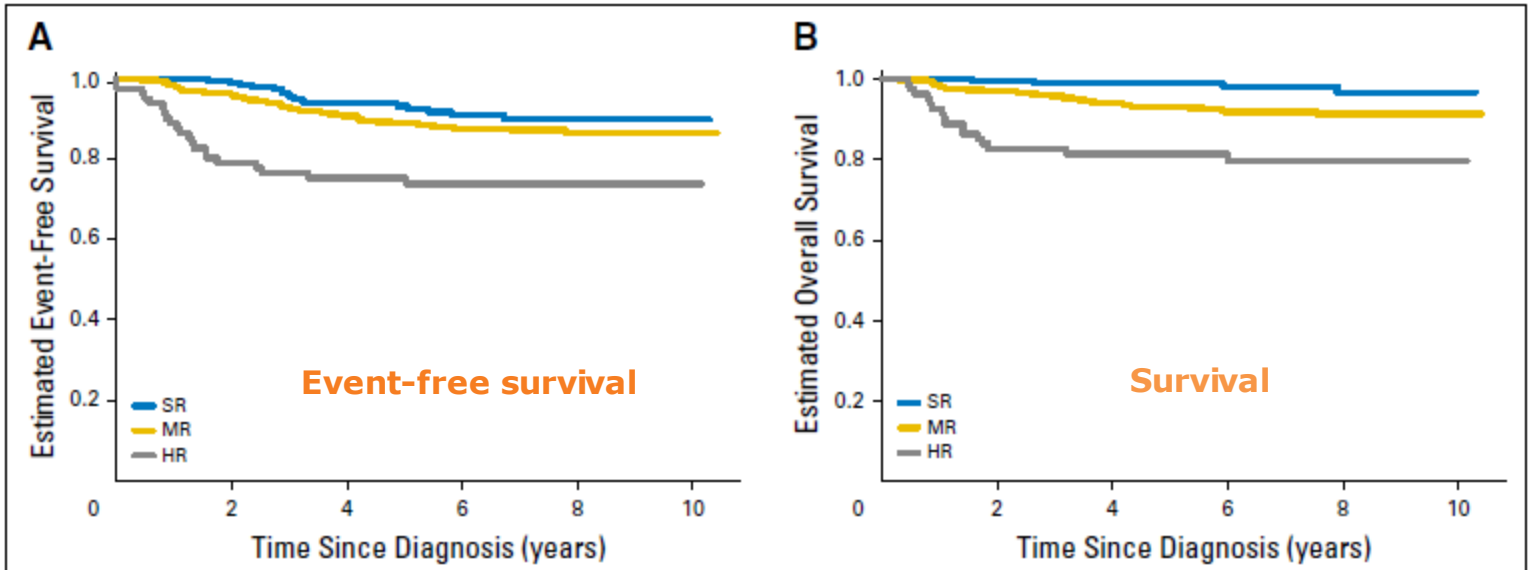


	BFM-II	BFM-III	DCOG-IV	Cum dose
Dexamethasone	250	180	180	mg/m2
VCR	6	3	3	mg/m2
Doxorubicin	120	60	0	mg/m2
Native Asp	40.000	40.000	0	U/m2
PEG-Asp	0	0	2.500	U/m2
Cyclophoshamide	1.000	500	0	mg/m2
araC	600	600	0	mg/m2
6-TG	840	840	0	mg/m2

Therapy reduction (P-II to P-III) in AIEOP-BFM 2000: DFS and OS







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Pieters, J Clin Oncol 2016

Outcome in MRD low-risk patients (25% of all patients)

	Prot II	Prot III	DCOG Prot IV
8yr OS	98%	96%	97%
5yr DFS	96%	91%	93%
5yr CIR	4%	8%	6%

- Therapy reduction: relapse rate ~4% higher but survival not different

Dilemma

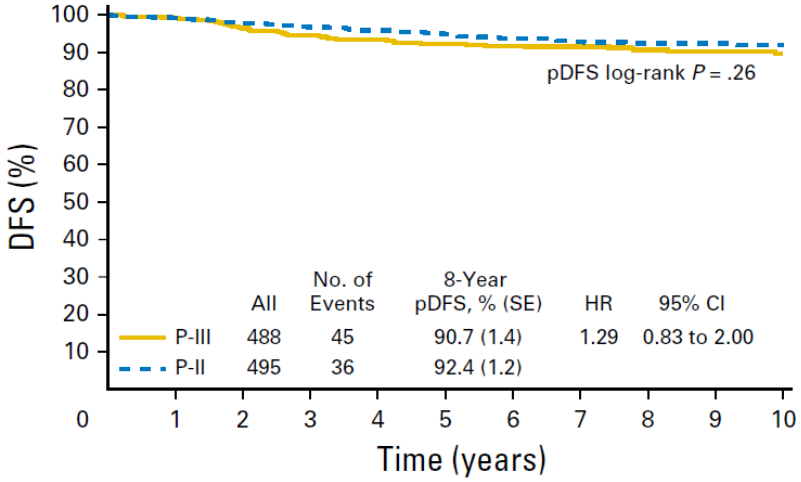
- Decrease of therapy for all MRD low-risk patients: an extra ~4% of them need relapse therapy

OR

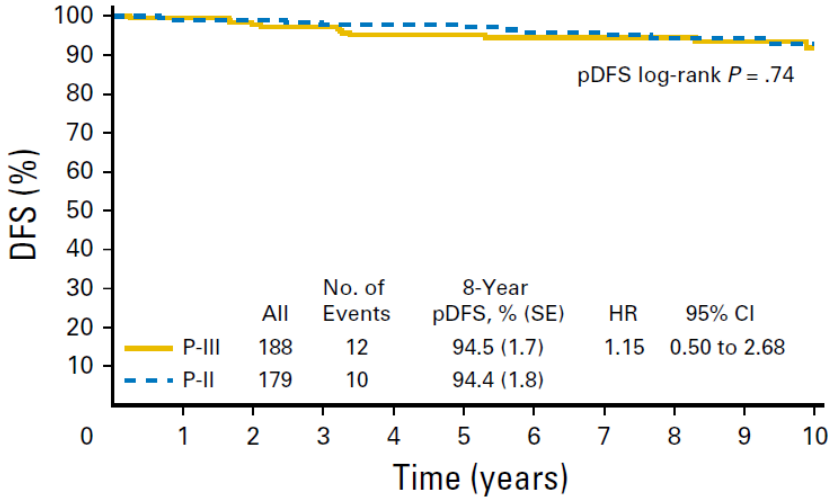
- More intensive therapy for all MRD low-risk patients

Therapy reduction in specific risk groups (AIEOP-BFM 2000)?

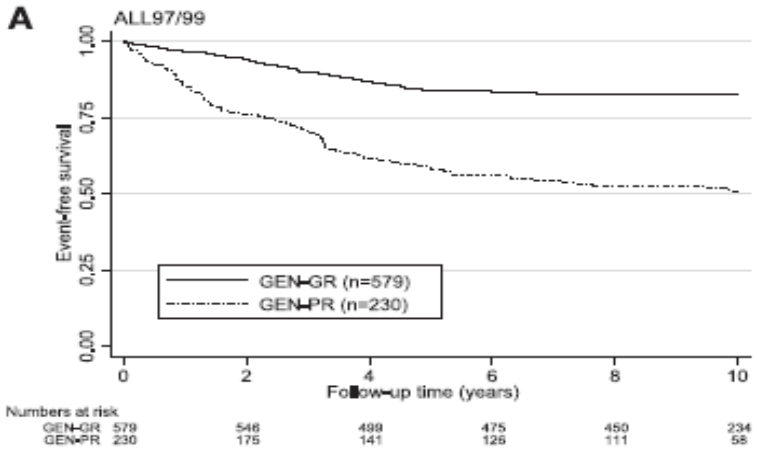
Age 1-9 yr

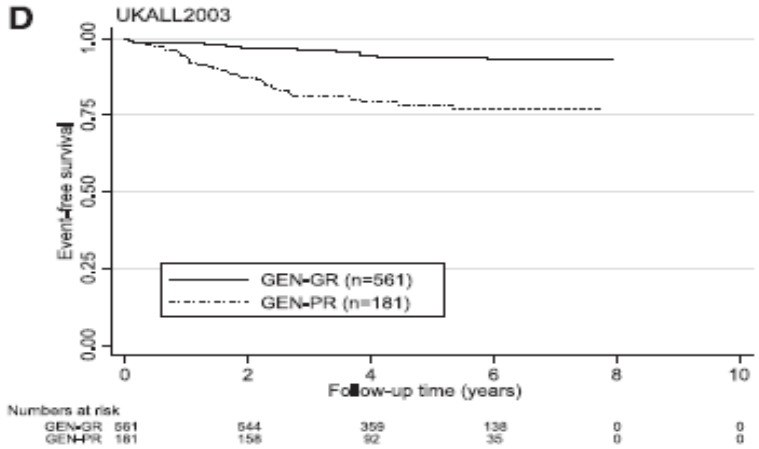


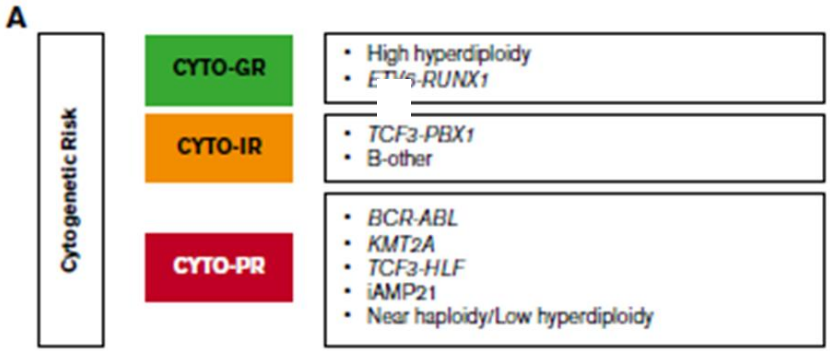
ETV6/RUNX1

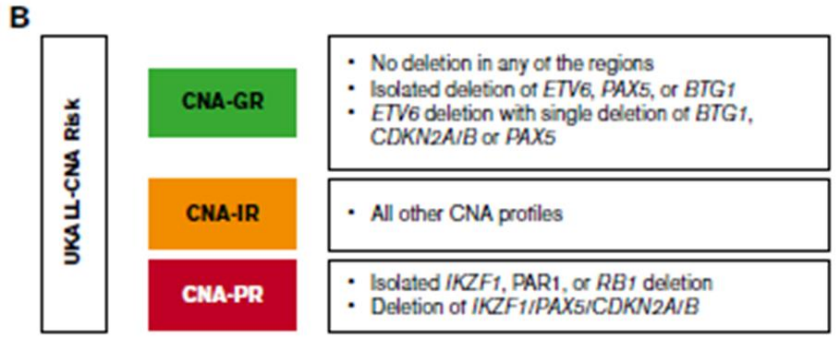


EFS ALL97/99 and UKALL2003 by genetic risk group





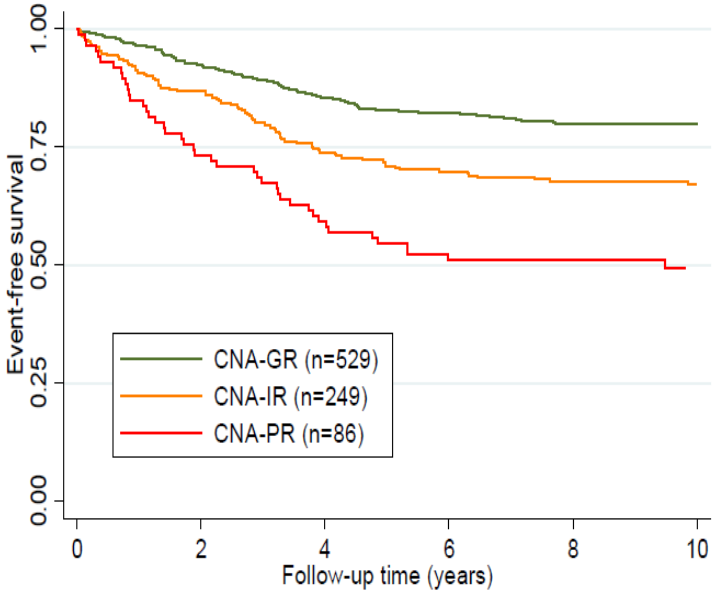




Moorman, Blood 2014

UK copy number alteration (CNA) classifier in UKALL

CNA profile defines risk groups



CNA profiles by MLPA

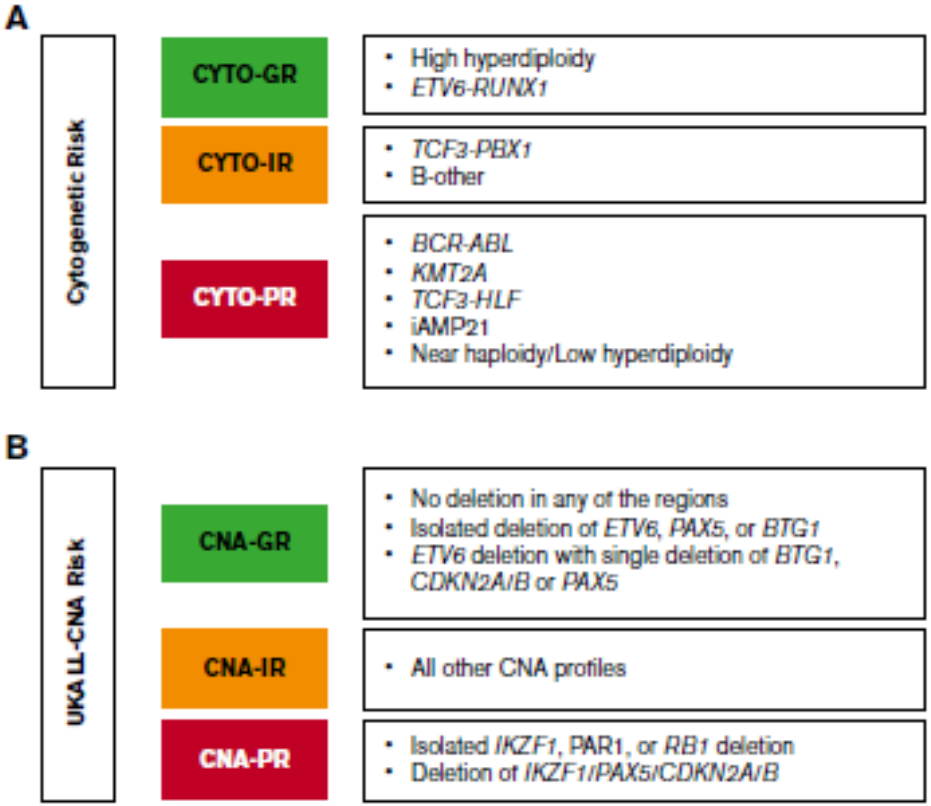
Good risk
- No deletion
- Isolated deletion of *ETV6, PAX5*, or *BTG1*
- *ETV6* deletion + *BTG1, CDKN2A/B* or *PAX5 deletion*

Intermediate risk
- All other CNA profiles

Poor risk
- Isolated *IKZF1, PAR1,* or *RB1* deletion
- Deletion of *IKZF1/PAX5/CDKN2A/B*

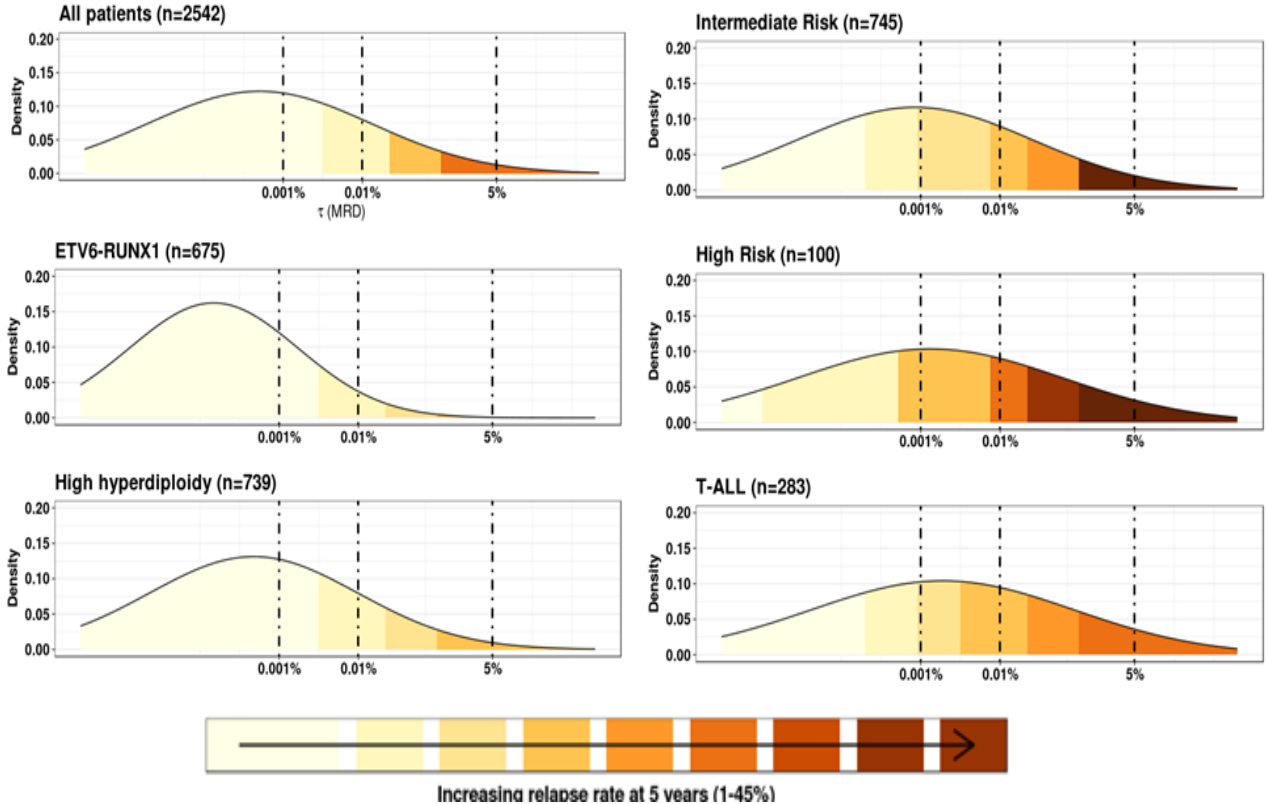
Moorman, Blood 2014

Novel genetic risk groups in B-lineage ALL by cytogenetics and by CNA



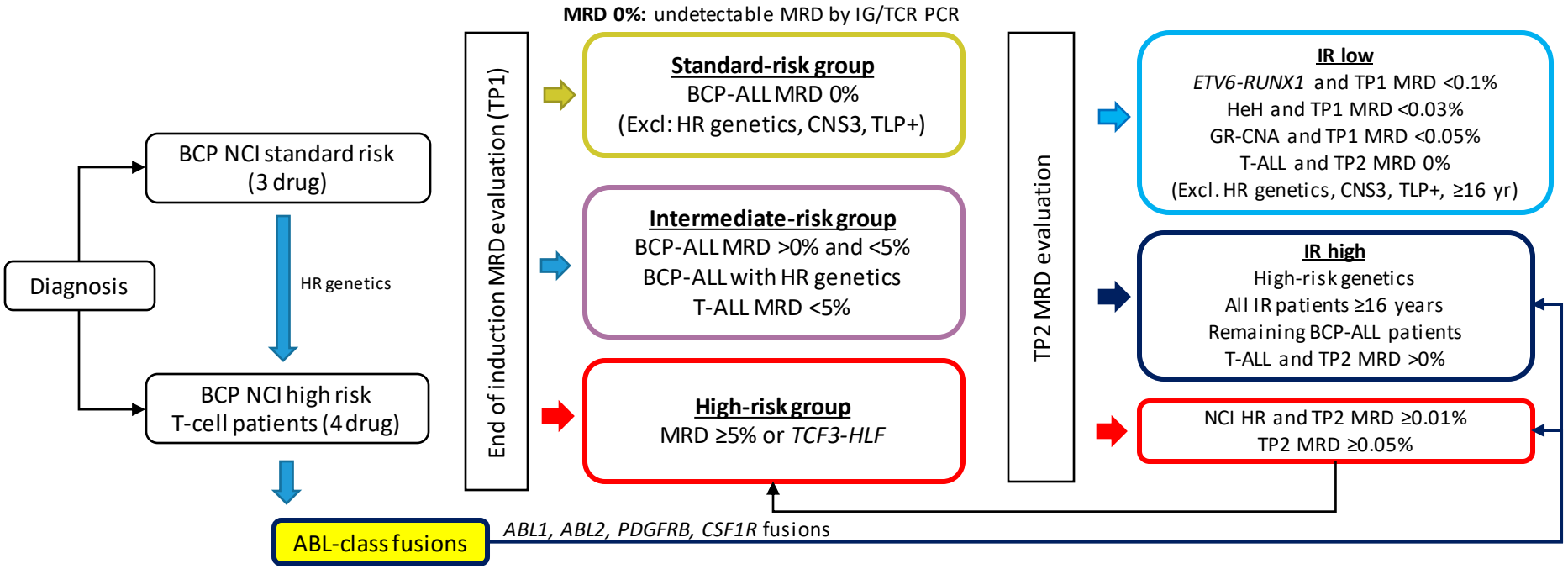
Hamadeh L, et al. *Blood Adv*. 2019;3(2):148-157.

Risk of relapse by MRD value varies by genetic subtype



O'Connor, J Clin Oncol 2018

Risk-stratification algorithm



High-risk genetics: *KMT2A/MLL* fusions, near haploidy, low hypodiploidy, iAMP21

GR-CNA profile

- No deletion of *IKZF1, CDKN2A/B, PAR1, BTG1, EBF1, PAX5, ETV6, RB1*
- Isolated deletions of *ETV6, PAX5, BTG1*
- *ETV6* deletions with a single additional deletion of *BTG1, PAX5, CDKN2A/B*

Risk groups by MRD and genetics: Outcomes and interventions

Risk group	Patients, %	5-yr EFS, %	5-yr OS, %	5-yr relapse, %	Treatment intervention
SR	23%	95	99	4	Random: reduction doxorubicin
IR-low	37%	94	98	4	Random: reduction doxorubicin Random: reduction VCR/Dexa pulses
IR-high	36%	82	89	15	Random: intensification inotuzumab Random: intensification 6TG/MP vs MP Down non-random: blinatumomab ABL-class: non-random imatinib
VHR	4%	78	78	14	B-lineage: non-random CD19 CAR T T-lineage: non-random nelarabine

MRD and genetics to guide stratification and therapy

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

[repeated question] Question 1 : Which of the following statements is NOT correct?

a) MRD at end of induction in infant *KMT2A*-rearranged ALL can be used to select the most effective subsequent myeloid-like or lymphoid-like type of consolidation therapy

b) MRD at end of induction and consolidation in *BCR-ABL1*–positive ALL is used to select patients who do not need a SCT

c) The prognostic relevance of MRD at end of induction depends on the genetic subtype of ALL

d) All types of BCR-ABL1–like ALL are sensitive to ABL class tyrosine kinase inhibitors

Thank you!

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Global Leukemia Academy

Q&A session

APTITUDE HEALTH

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First-line treatment of pediatric ALL

Martin Schrappe

APTITUDE HEALTH

First-line Treatment of ALL in Childhood and Adolescence

Global Leukemia Academy 2021

Prof Martin Schrappe, MD

Pediatrics I, University Medical Center Schleswig-Holstein

Kiel, Germany

schrappe-office@pediatrics.uni-kiel.de

Topics and Objectives

- Genetic subgroups of ALL - different by age
- Definitions for diagnostics and disease response - NEW
- Key components for stratification
- Key components of ALL therapy
- Contemporary trials for pediatric ALL in Europe
- Outlook

- *Only examples can be provided for most issues!*

Question 1

Genetic subgroups in pediatric ALL have been well described. Can you pick the most appropriate definition for a novel entity, called *IKZF1*-plus?

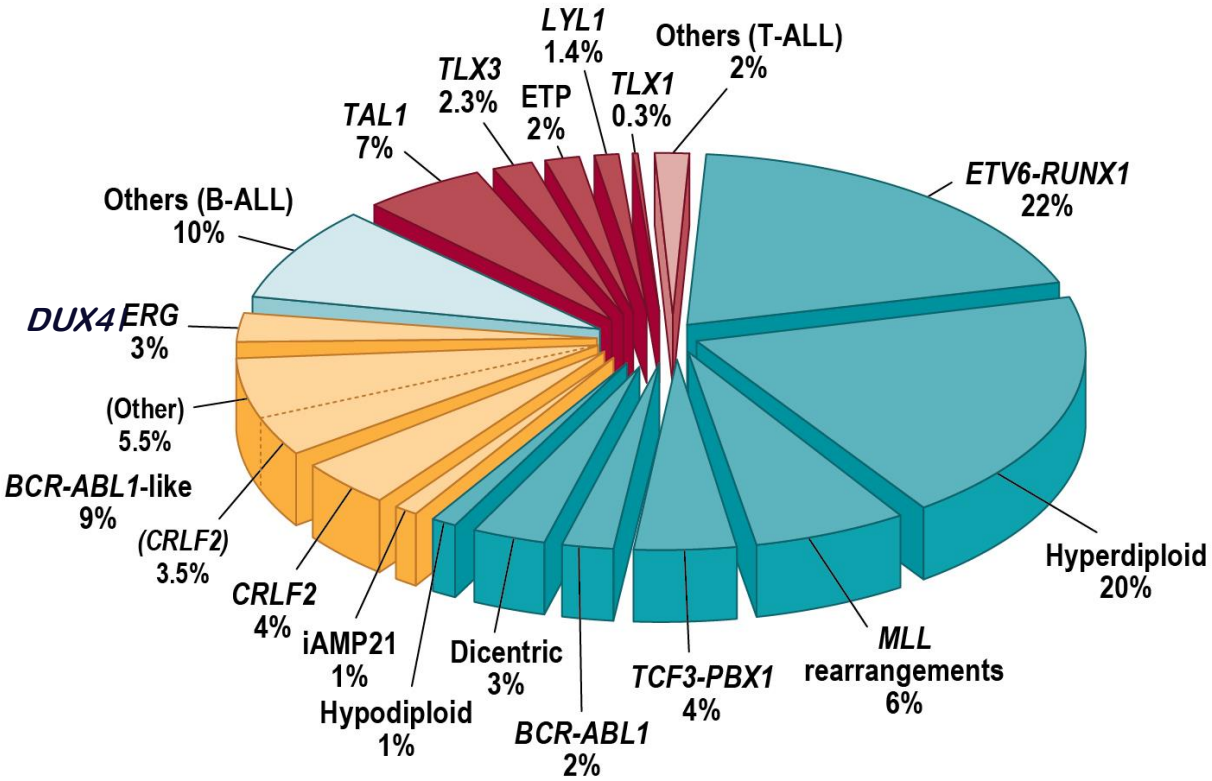
A. Novel mutation in the *bcr/abl* fusion gene
B. Simultaneous deletions in *IKZF1* and *PAX5* and/or *CDKN2A* and/or *CDKN2B* and/or *CRLF2 (PAR),* and negativity for *ERG* deletion
C. Gain of function in *IKZF1*
D. Novel term for hypodiploidy
E. Mutation in drug resistant patients with *ETV6/RUNX1* positivity

Question 2

Please indicate which of the following statements for positive testing of MRD at a level of 0.1% is most appropriate:

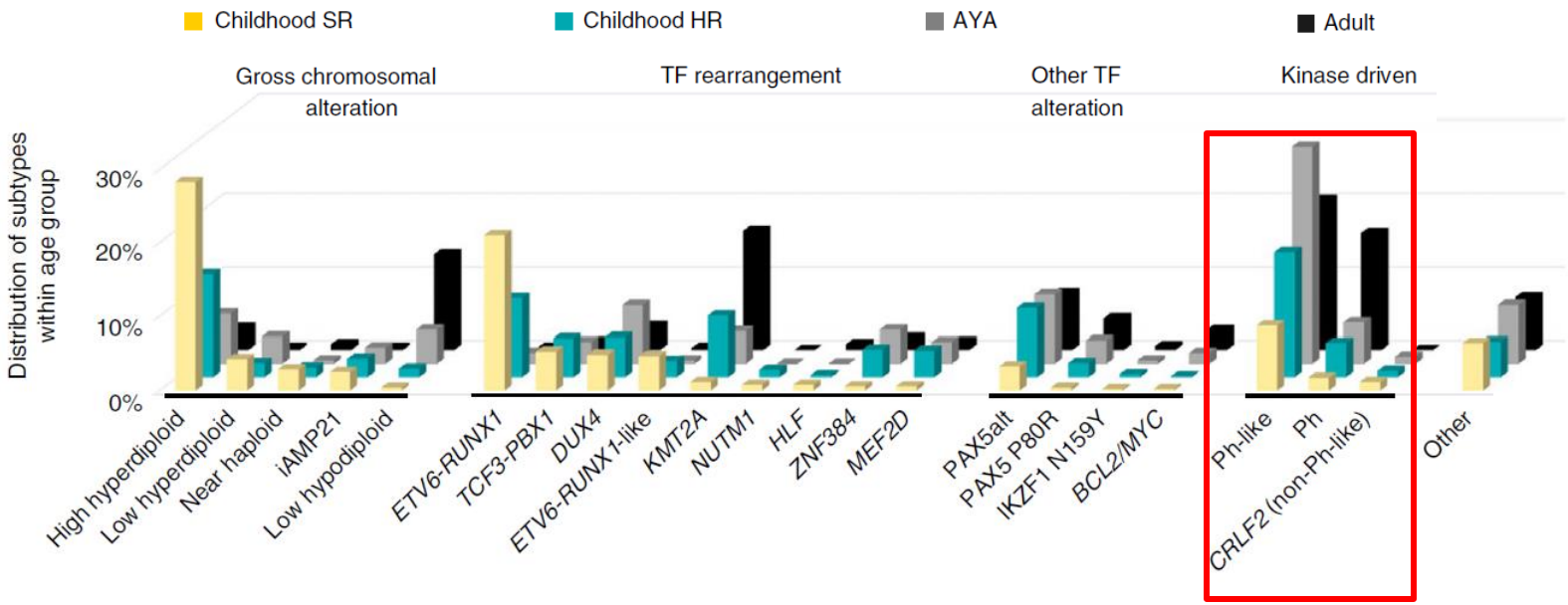
A. At the end of induction therapy for ALL, such a level of MRD equals induction failure
B. MRD at this level at the end of consolidation (approximately 12 weeks after start of treatment) can be considered a very favorable response
C. MRD at this level after allogeneic hSCT is a normal observation when measured at day +100
D. MRD at this level at any time of ALL therapy equals disease recurrence (relapse)
E. MRD at this level at the end of induction may indicate a more resistant leukemia, as compared to others with no detectable MRD at the end of induction

All Patients Have Specific Leukemic Genetic Abnormalities



Pui, Mullighan, et al. *J Clin Oncol.* 2015;33:2938-2948, Zhang et al. *Nat Genet.* 2016;48:1481-1489.

The Molecular Landscape of pB-ALL



Prognostic relevance?

Targetable activated signalling pathways?

Gu et al. *Nat Genet.* 2019.

JOURNAL OF CLINICAL ONCOLOGY

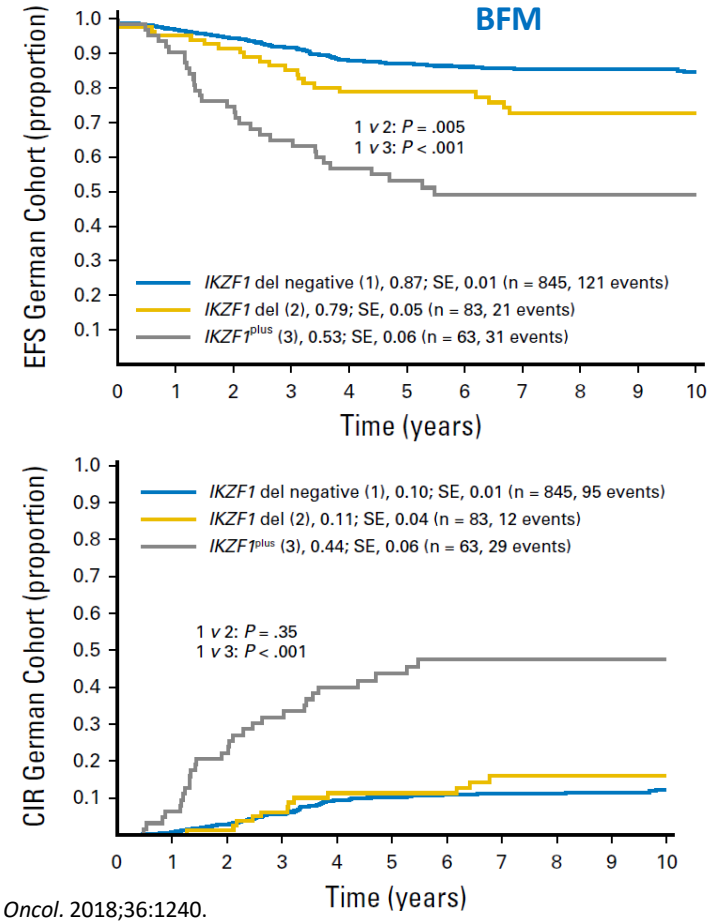
ORIGINAL REPORT

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

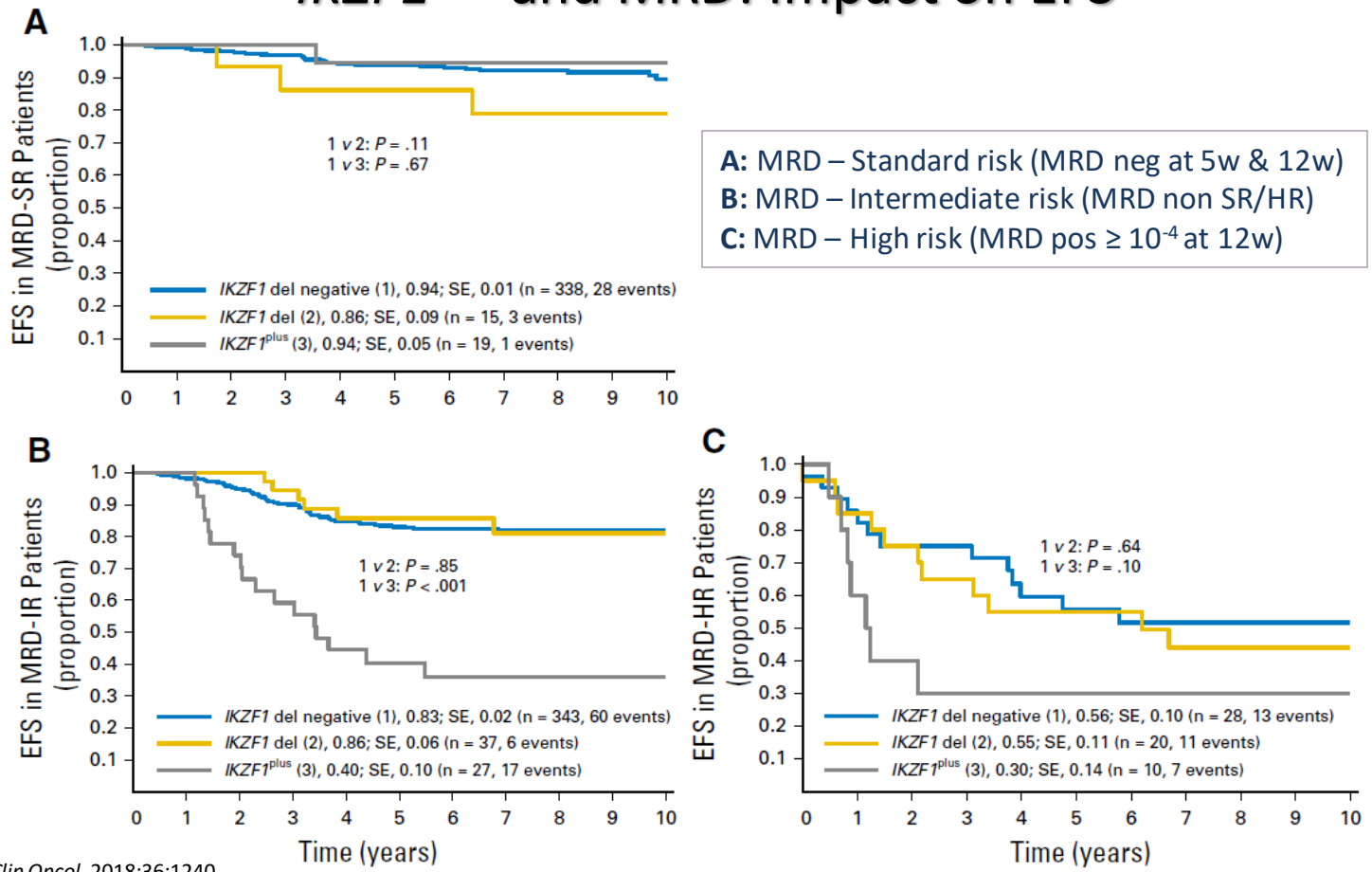
DOI: https://doi.org/10.1200/JCO.2017.74.3617

IKZF1 del and *IKZF1*^{plus} – Prognostic Impact



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

IKZF1^{plus} and MRD: Impact on EFS



A: MRD – Standard risk (MRD neg at 5w & 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;36:1240.

Remission, treatment failure, and relapse in pediatric ALL: An international consensus of the Ponte-di-Legno Consortium

Swantje Buchmann[1*], Martin Schrappe[1*§], Andre Baruchel[2], Andrea Biondi[3], Michael Borowitz[4], Myriam Campbell[5], Gunnar Cario[1], Giovanni Cazzaniga[3], Gabriele Escherich[6], Christine J. Harrison[7], Mats Heyman[8], Stephen P. Hunger[9], Csongor Kiss[10], Hsi-Che Liu[11], Franco Locatelli[12], Mignon L. Loh[13], Atsushi Manabe[14], Georg Mann[15], Rob Pieters[16], Ching-Hon Pui[17], Susana Rives[18], Kjeld Schmiegelow[19], Lewis B. Silverman[20], Jan Stary[21], Ajay Vora[22] and Patrick Brown[23] on behalf of the Ponte-di-Legno Consortium

https://doi.org/10.1182/blood.2021012328

Table 3.2: Bone marrow relapse (MRD unavailable)

BM #1		BM #2[@]
Cytomorphology	others	
M3	*	*
M2	1 other test^ with 1% blasts	*
M2	none	M2
M1	2 other tests^ with 1% blasts	*

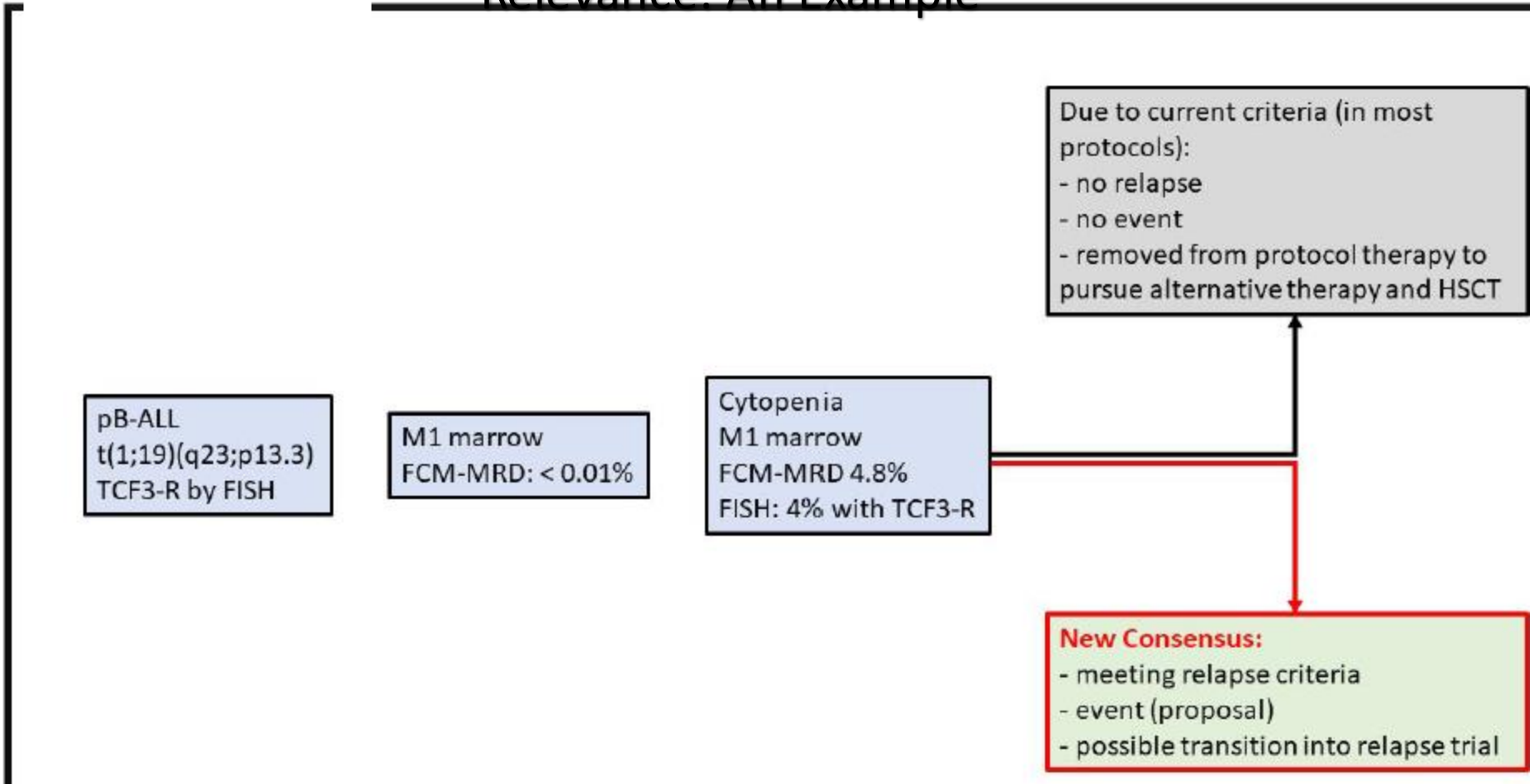
*: not necessary to define relapse; ^FISH/karyotype/PCR demonstrating leukemia-specific marker; [@]second evaluation at least one week later

1 to < 5 %	0 or 1 other test with 1% blasts	2 tests with 1% blasts

*: not necessary to define relapse; ^FCM/PCR/NGS-based MRD or FISH/karyotype/PCR demonstrating leu marker, or M2/M3 morphology; [@]second bone marrow evaluation at least one week later

Figure 1

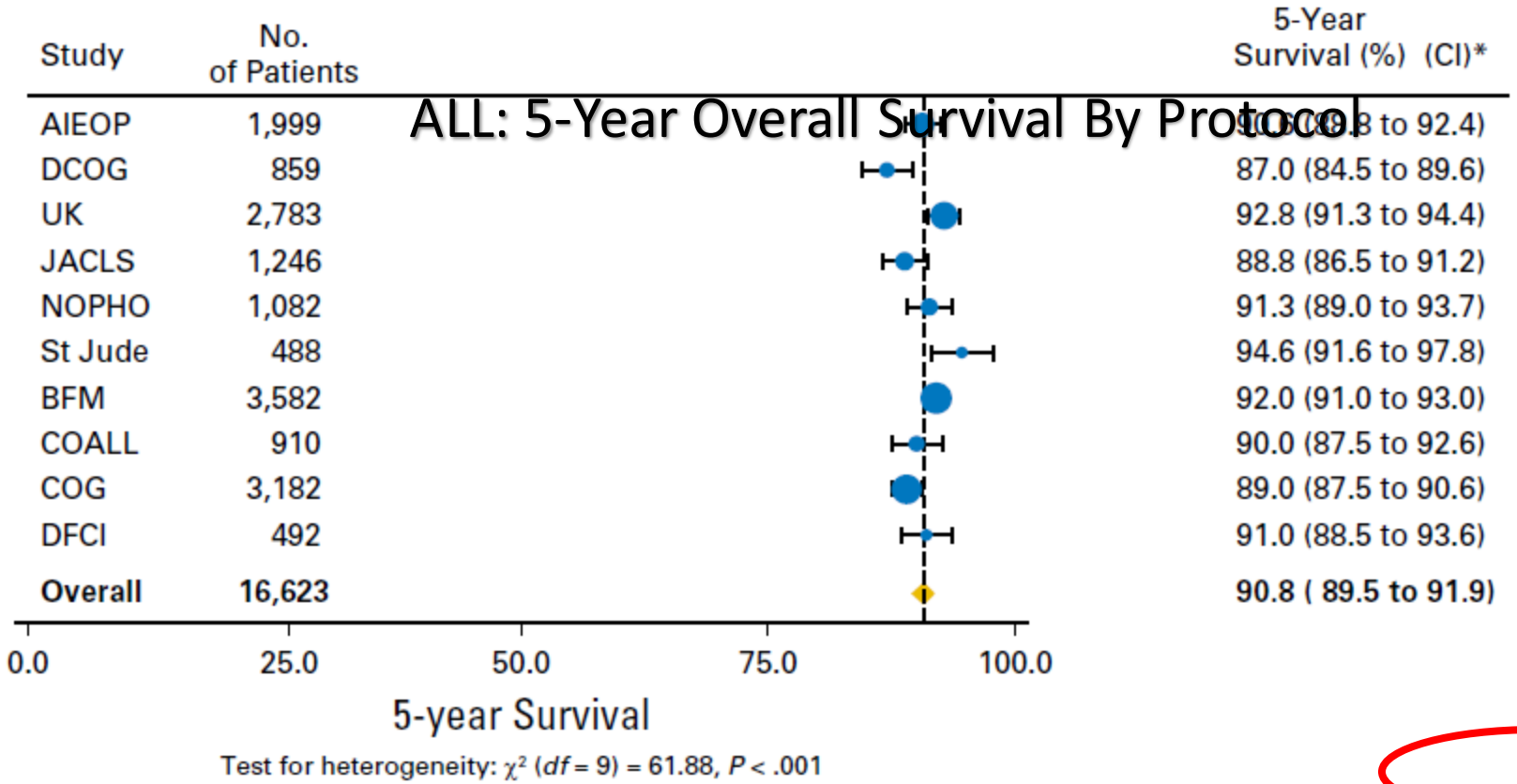
Relevance: An Example



Risk Stratification and Therapy

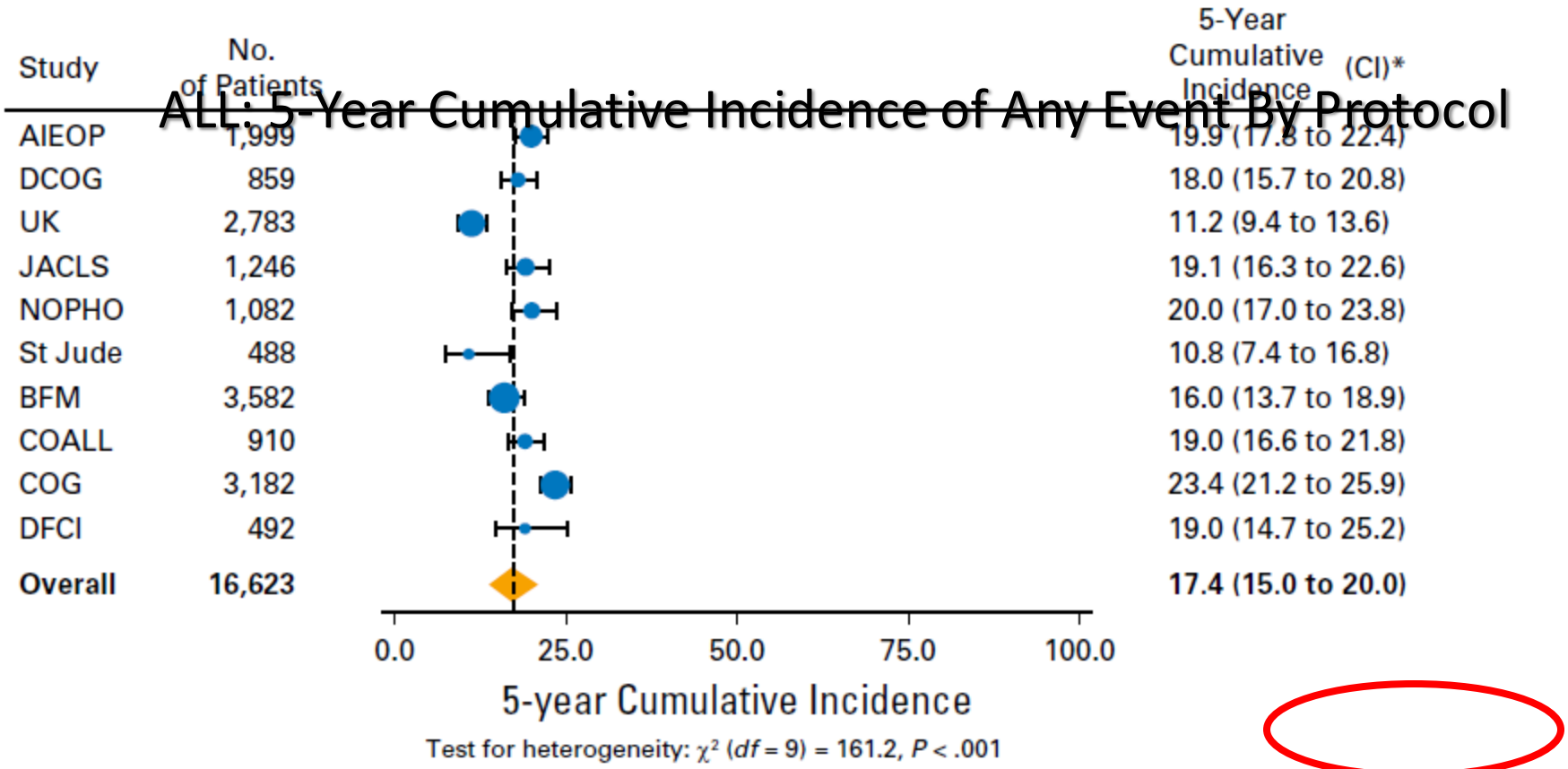
- The 2 main differences in stratification systems in pediatric ALL relate to the use of upfront criteria (e.g. NCI risk grouping) vs the use of “late” criteria such as response
- New subgroups have been described which use either a series of genetic markers, or the combination of genetic markers and treatment response: Ph-like or *BCR/ABL*-like pB-ALL; IKZF1*plus* pB-ALL
- Acute leukemias with ambiguous phenotype form another (rare) subgroup: MPAL
- Early response (through prednisone response, morphological CR, and in particular MRD detection) has been established as the strongest prognostic factor
- Treatment quality has moved to the focus of clinical research to avoid late effects and toxicity

ALL: 5-Year Overall Survival By Protocol



Vora A. *J Clin Oncol*. 2016;34:919-926.

ALL: 5-Year Cumulative Incidence of Any Event By Protocol



Vora A. *J Clin Oncol*. 2016;34:919-926.

Increased Knowledge Through Prospective Randomized Trials

Examples

- Dexamethasone vs prednisone in induction
- Reduction of delayed intensification in pB-ALL

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

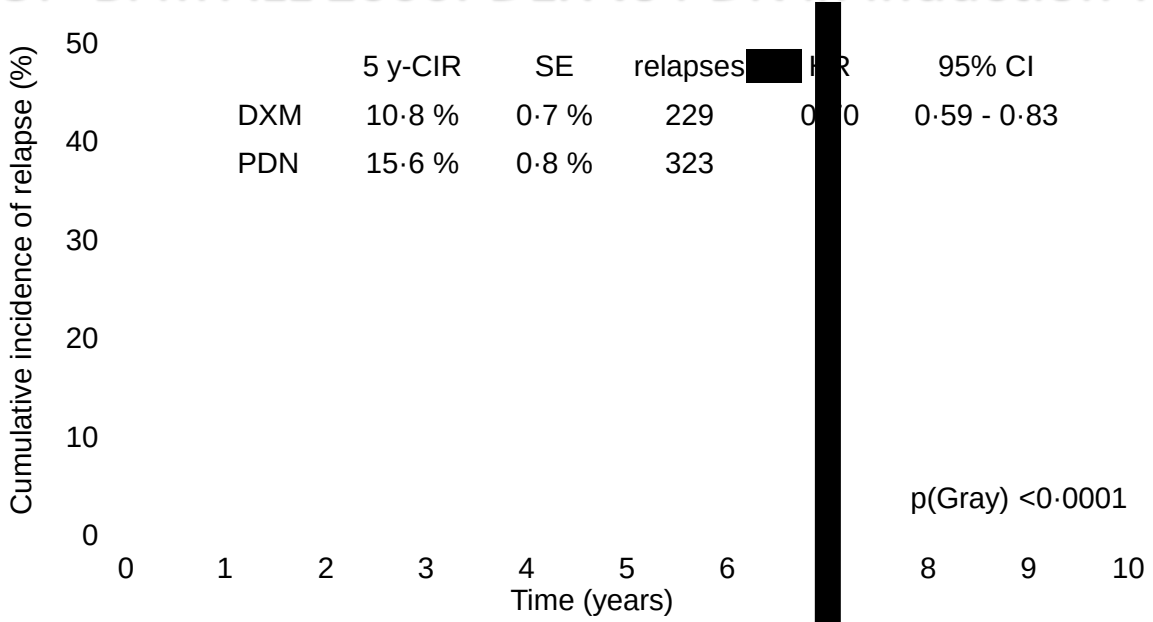
Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000

Anja Möricke,[1] Martin Zimmermann,[2] Maria Grazia Valsecchi,[3,4] Martin Stanulla,[2] Andrea Biondi,[4,5] Georg Mann,[6] Franco Locatelli,[7] Giovanni Cazzaniga,[5] Felix Niggli,[8] Maurizio Aricò,[9] Claus R. Bartram,[10] Andishe Attarbaschi,[6] Daniela Silvestri,[3,4] Rita Beier,[2,11] Giuseppe Basso,[12] Richard Ratei,[13] Andreas E. Kulozik,[14] Luca Lo Nigro,[15] Bernhard Kremens,[11] Jeanette Greiner,[16] Rosanna Parasole,[17] Jochen Harbott,[18] Roberta Caruso,[7] Arend von Stackelberg,[19] Elena Barisone,[20] Claudia Rössig,[21] Valentino Conter,[4,*] and Martin Schrappe[1,*]

[1]Department of Pediatrics, Christian-Albrechts-University Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany; [2]Division of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany; [3]Medical Statistics Unit, Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Monza, Italy; [4]Department of Pediatrics, University of Milano-Bicocca, Ospedale S. Gerardo, Monza, Italy; [5]Centro M. Tettamanti, Clinica Pediatrica Università Milano-Bicocca, Monza, Italy; [6]Department of Pediatrics, St. Anna Children's Cancer Research Institute and St. Anna Children's Hospital, Medical University School, Vienna, Austria; [7]Department of Pediatric Hemato-Oncology, Ospedale Bambin Gesù, Rome, University of Pavia, Pavia, Italy; [8]Department of Pediatric Oncology, University Children's Hospital, Zürich, Switzerland; [9]Direzione Generale, Azienda Sanitaria Provinciale, Ragusa, Italy; [10]Institute of Human Genetics, Ruprecht-Karls-University, Heidelberg, Germany; [11]Department of Pediatric Hematology and Oncology, University Hospital, Essen, Germany; [12]Pediatric Hemato-Oncology, Department of Women's and Children's Health, University of Padova, Padova, Italy; [13]Hematology/Oncology, Robert-Rössle-Klinik at the HELIOS Klinikum, Charité, Berlin, Germany; [14]Department of Pediatric Oncology, Hematology and Immunology, University of Heidelberg, Heidelberg, Germany; [15]Department of Pediatric Hemato-Oncology, Azienda Policlinico–Ospedale Vittorio Emanuele, Catania, Italy; [16]Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland; [17]Department of Pediatric Hematology and Oncology, Santobono-Pausilipon Hospital, Napoli, Italy; [18]Pediatric Hematology and Oncology, Justus-Liebig University, Gießen, Germany; [19]Pediatric Hematology and Oncology, Charité Medical Center, Humboldt University, Berlin, Germany; [20]Department of Pediatric Hemato-Oncology, Regina Margherita Children's Hospital, Torino, Italy; and [21]Department of Pediatric Hematology and Oncology, University Children's Hospital, Münster, Germany

Blood. 2016;127(17):2101-2112

AIEOP-BFM ALL 2000: DEX vs PDN in Induction Therapy



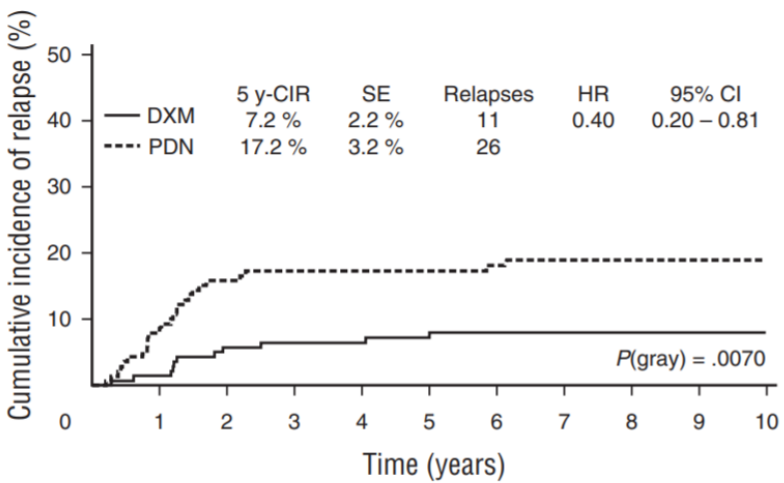
	DXM N (%)	PDN N (%)	p
Death before CR	37 (2·0)	15 (0·8)	0·00
Death in 1st CR	42 (2·3)	32 (1·7)	0·24
related to induction	10 (0·5)	2 (0·1)	0·022
not related to induction	32 (1·7)	30 (1·6)	0·80

Moericke A, et al. *Blood.* 2016.

Dexamethasone in Induction in T-ALL

Prednisone good-response, T-ALL

Di **Incidence of relapse and mortality rate**



	DXM N (%)	PDN N (%)	*P*
Death before CR	3 (2.1)	1 (0.7)	.62
Death in 1st CR	3 (2.1)	2 (1.4)	1.00
Related to induction	0 (0.0)	0 (0.0)	–
Not related to induction	3 (2.1)	2 (1.4)	1.00

Moericke A, et al. *Blood.* 2016.

JOURNAL OF CLINICAL ONCOLOGY

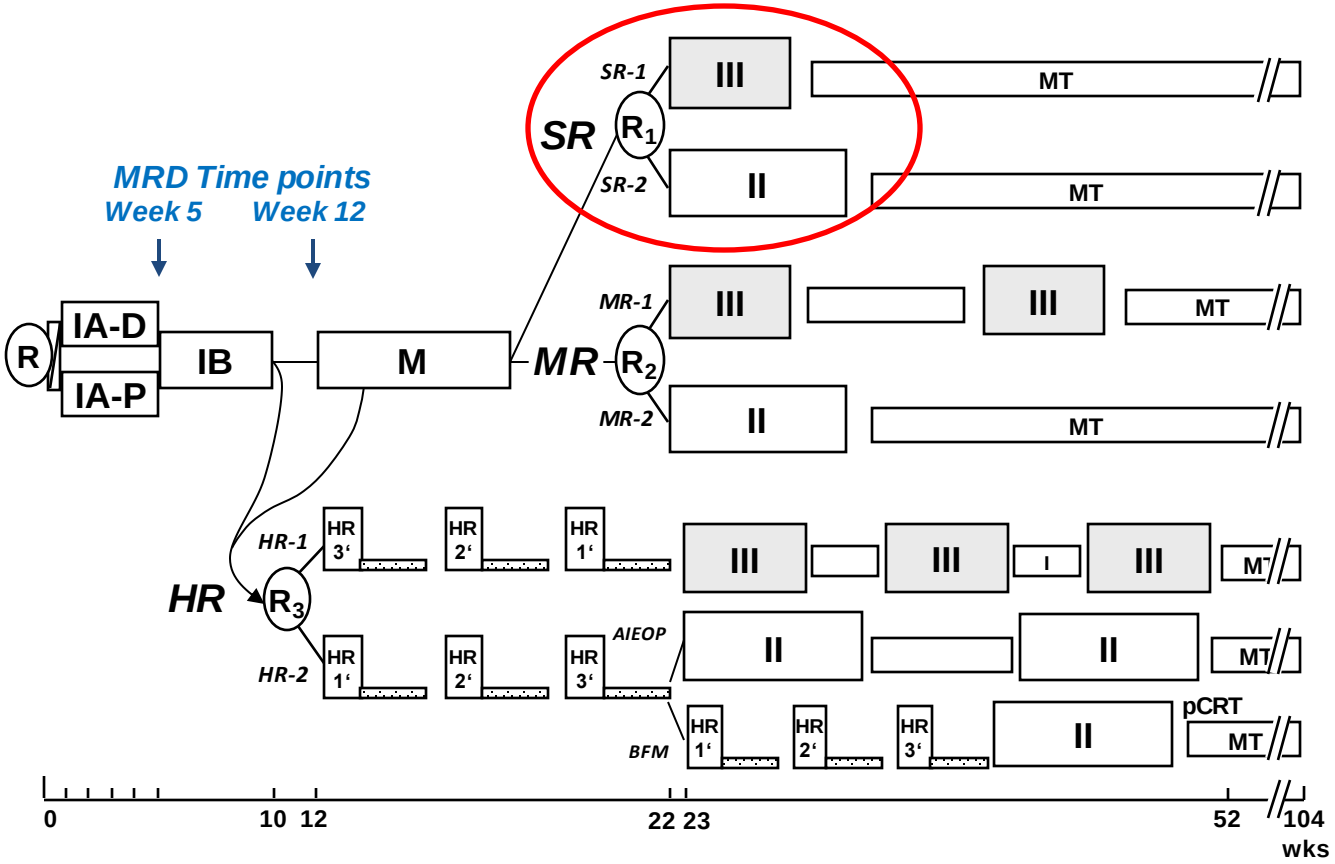
ORIGINAL REPORT

Reduced-Intensity Delayed Intensification in Standard-Risk Pediatric Acute Lymphoblastic Leukemia Defined by Undetectable Minimal Residual Disease: Results of an International Randomized Trial (AIEOP-BFM ALL 2000)

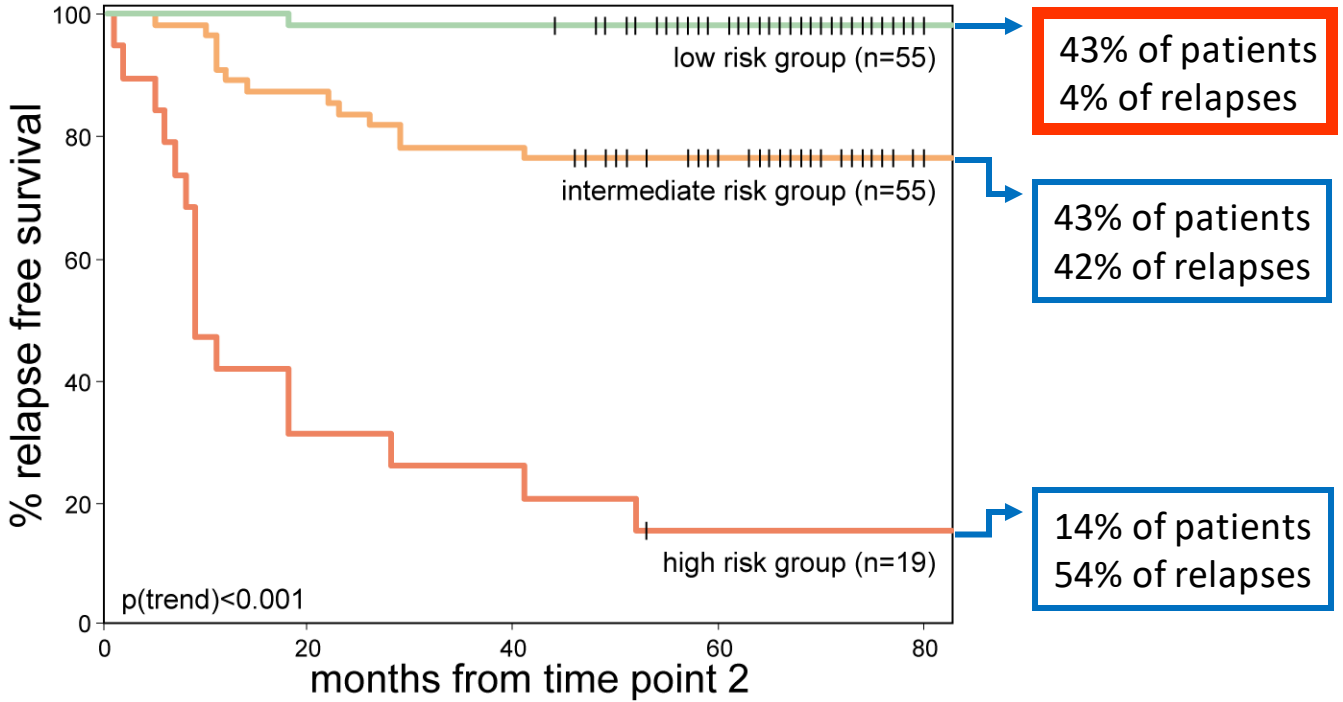
Martin Schrappe, Kirsten Bleckmann, Martin Zimmermann, Andrea Biondi, Anja Möricke, Franco Locatelli, Gunnar Cario, Carmelo Rizzari, Andishe Attarbaschi, Maria Grazia Valsecchi, Claus R. Bartram, Elena Barisone, Felix Niggli, Charlotte Niemeyer, Anna Maria Testi, Georg Mann, Ottavio Ziino, Beat Schäfer, Renate Panzer-Grümayer, Rita Beier, Rosanna Parasole, Gudrun Göhring, Wolf-Dieter Ludwig, Fiorina Casale, Paul-Gerhardt Schlegel, Giuseppe Basso, and Valentino Conter

DOI: https://doi.org/10.1200/JCO.2017.74.4946

AIEOP-BFM ALL 2000

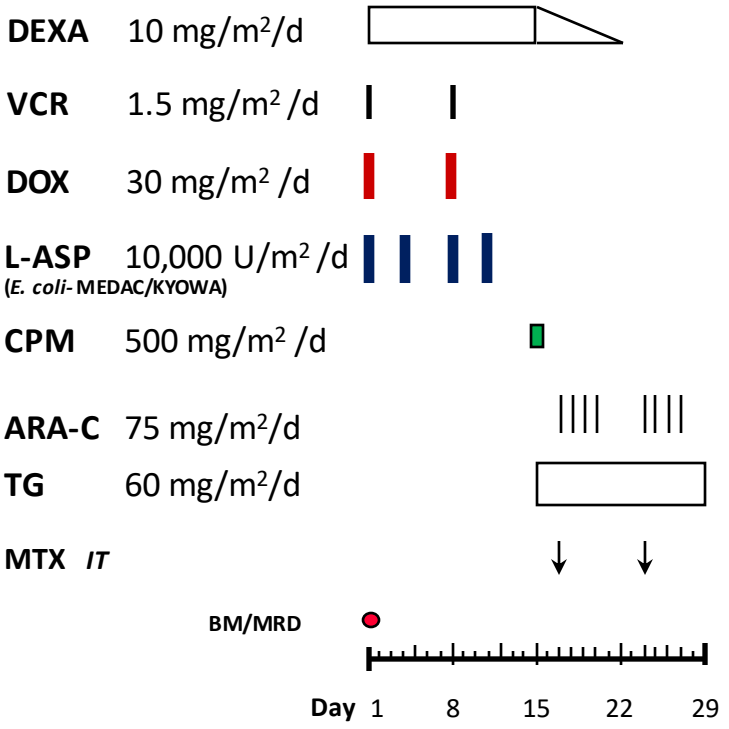


Relapse-free Survival in I-BFM-SG Study According to the Combined MRD Information at Time Points 1 and 2 (n=129)

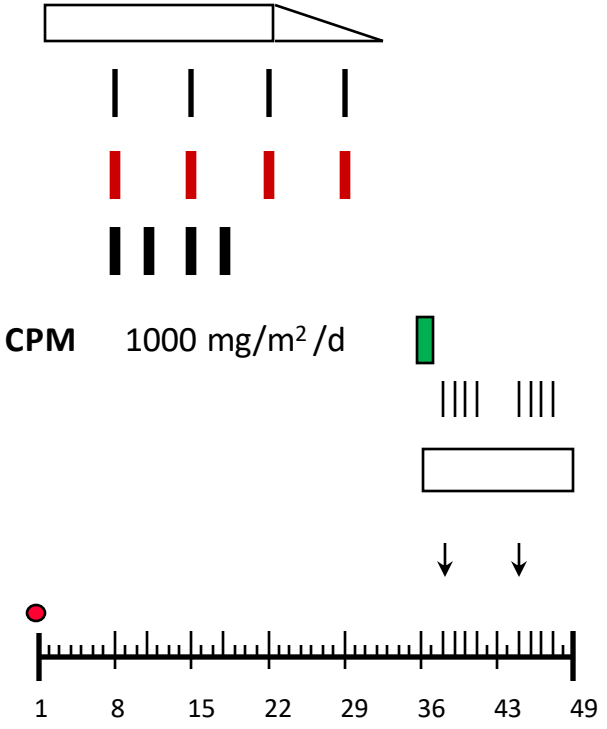


I-BFM-SG Report: van Dongen JJM, et al. *Lancet.* 1998;352:1731-1738.
See also: van Dongen JJM, et al. *Blood.* 2015;125:3996.

Reduced Intensity Delayed Intensification *Protocol III*



Standard Intensity Delayed Intensification *Protocol II*

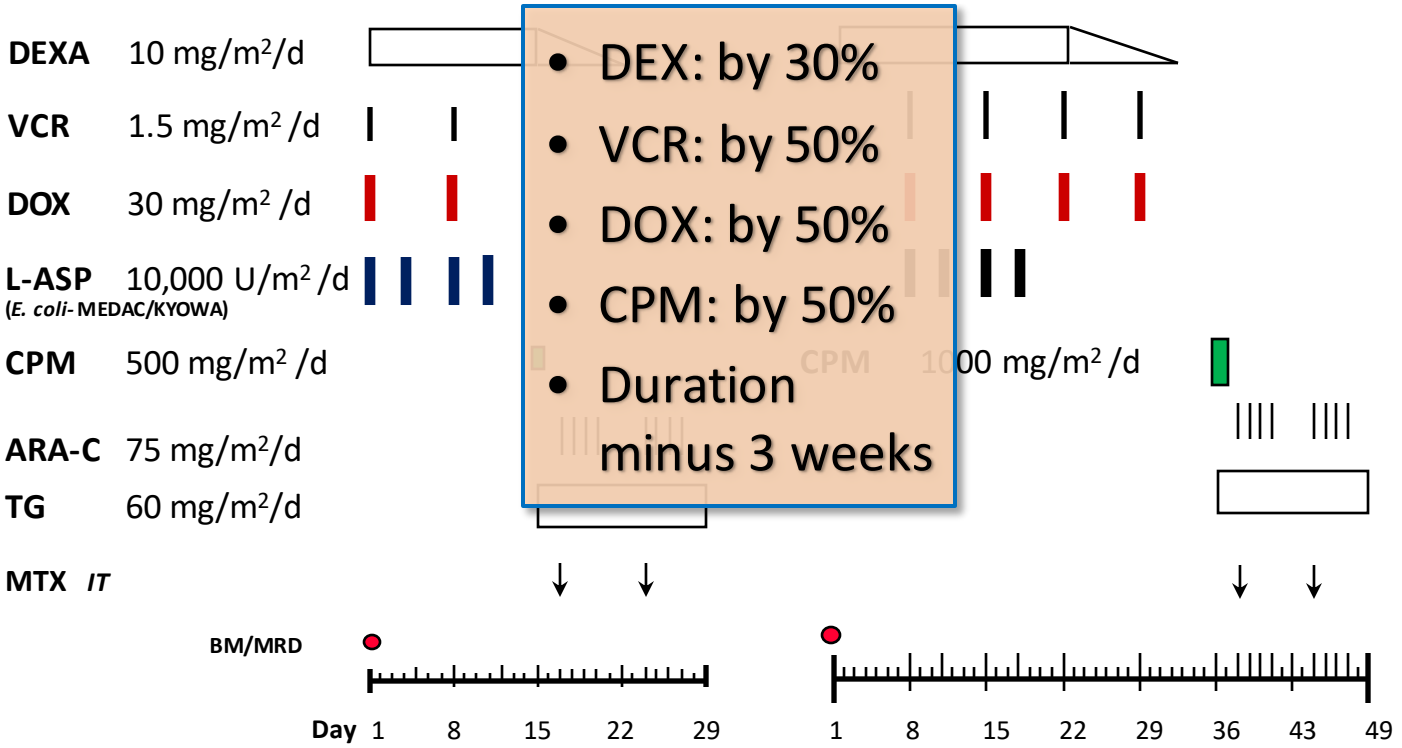


Reduced Intensity Standard Intensity

Delayed Inte nsification

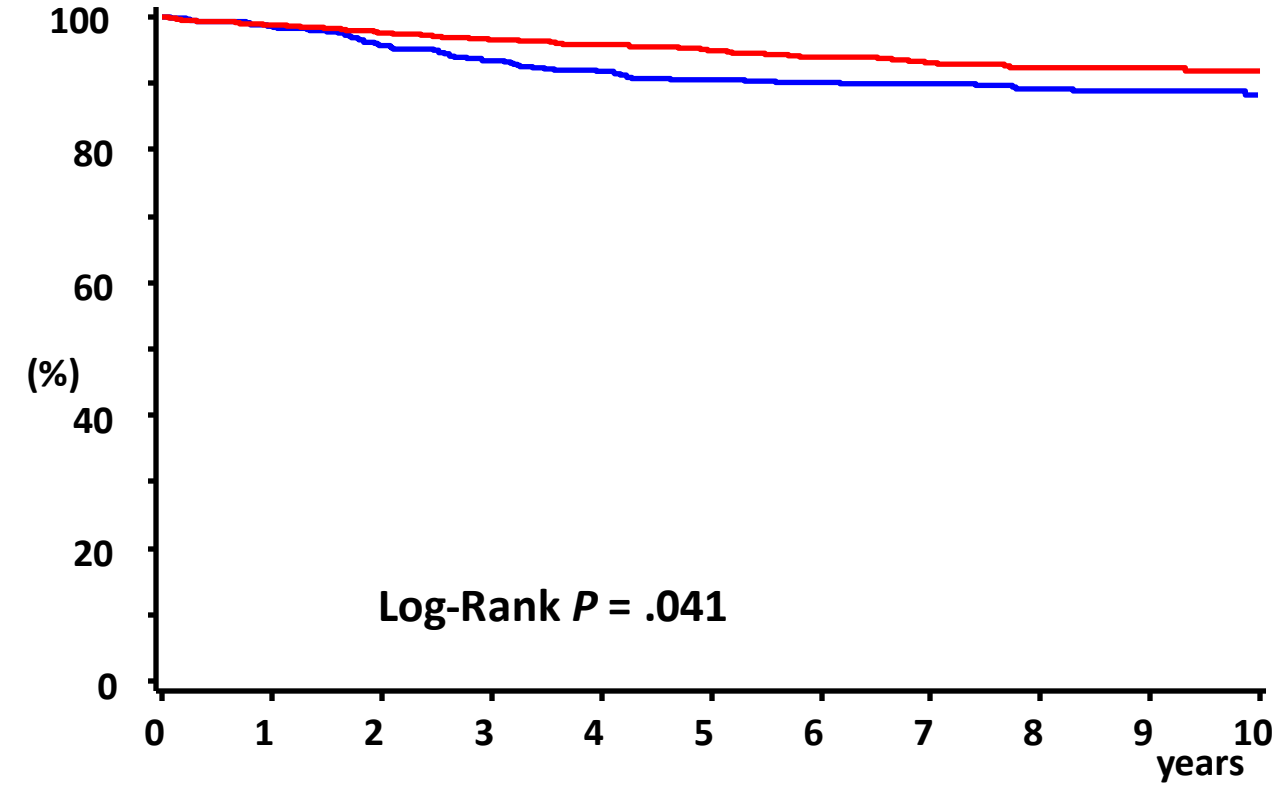
Protoc Protocol II

Reduction of Treatment

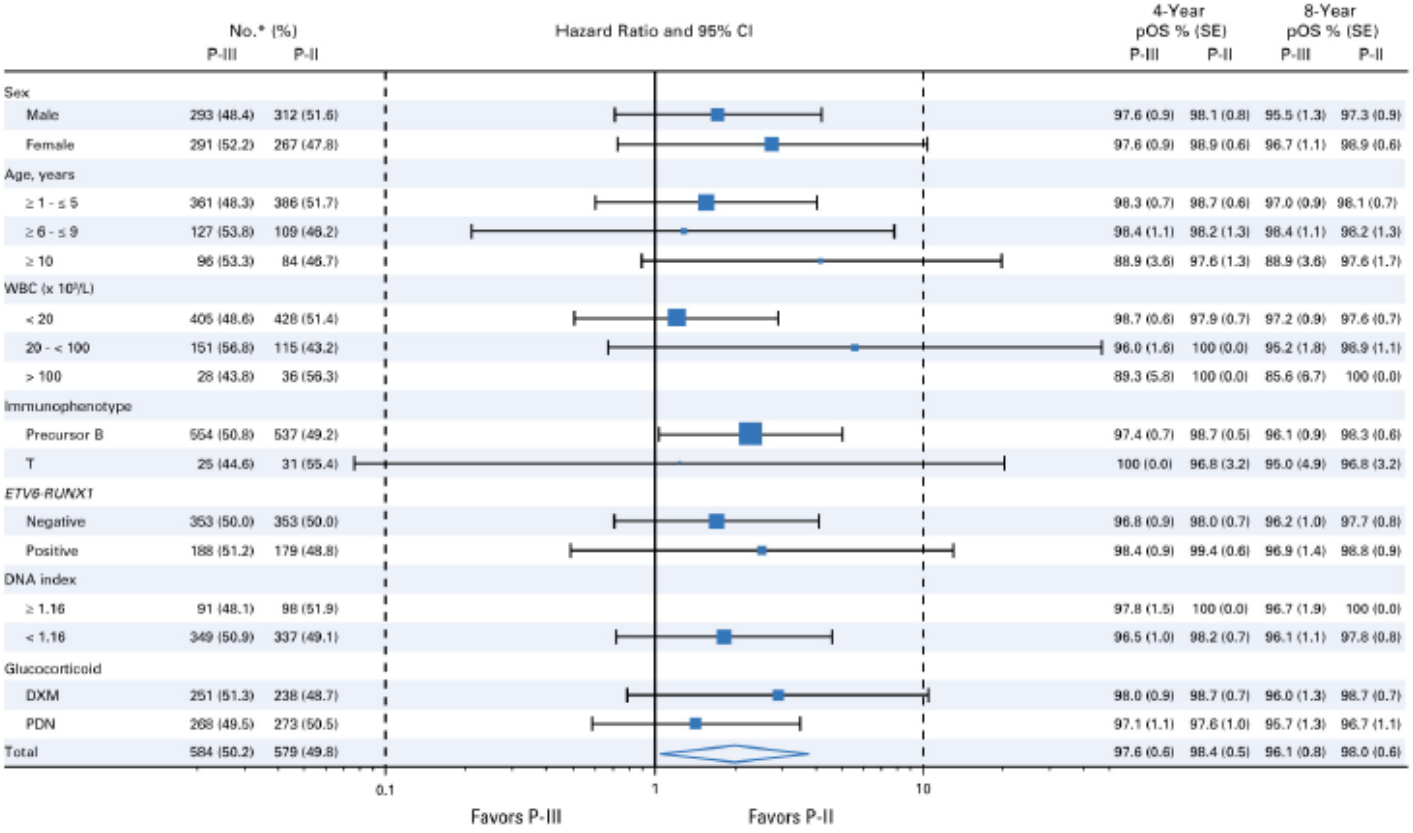


- DEX: by 30%
- VCR: by 50%
- DOX: by 50%
- CPM: by 50%
- Duration minus 3 weeks

AIEOP-BFM ALL 2000: SR - As Treated
Event-free survival (EFS) at 5 years



Overall Survival by Type of DI



DOI: https://doi.org/10.1200/JCO.2017.74.4946

SR-ALL Defined by PCR-based MRD: Recent clinical trials[1-3]

	% pts in SR	N / % randomized	Randomiz. question	Cumul. incid. of relapses	pEFS	*P*
AIEOP-BFM	39.0	1164 / 86.5	P-III vs -II	7.5 vs 4.1%	94.9 vs 90.6	.041
UKALL	38.9	521 / 49.2	1 DI vs 2 DI	5.6 vs 2.4%*	94.4 vs 95.5	n.s.
DCOG	24.9	--	--	6.2%	93.2	--

*Actuarial percentage (at 5y)

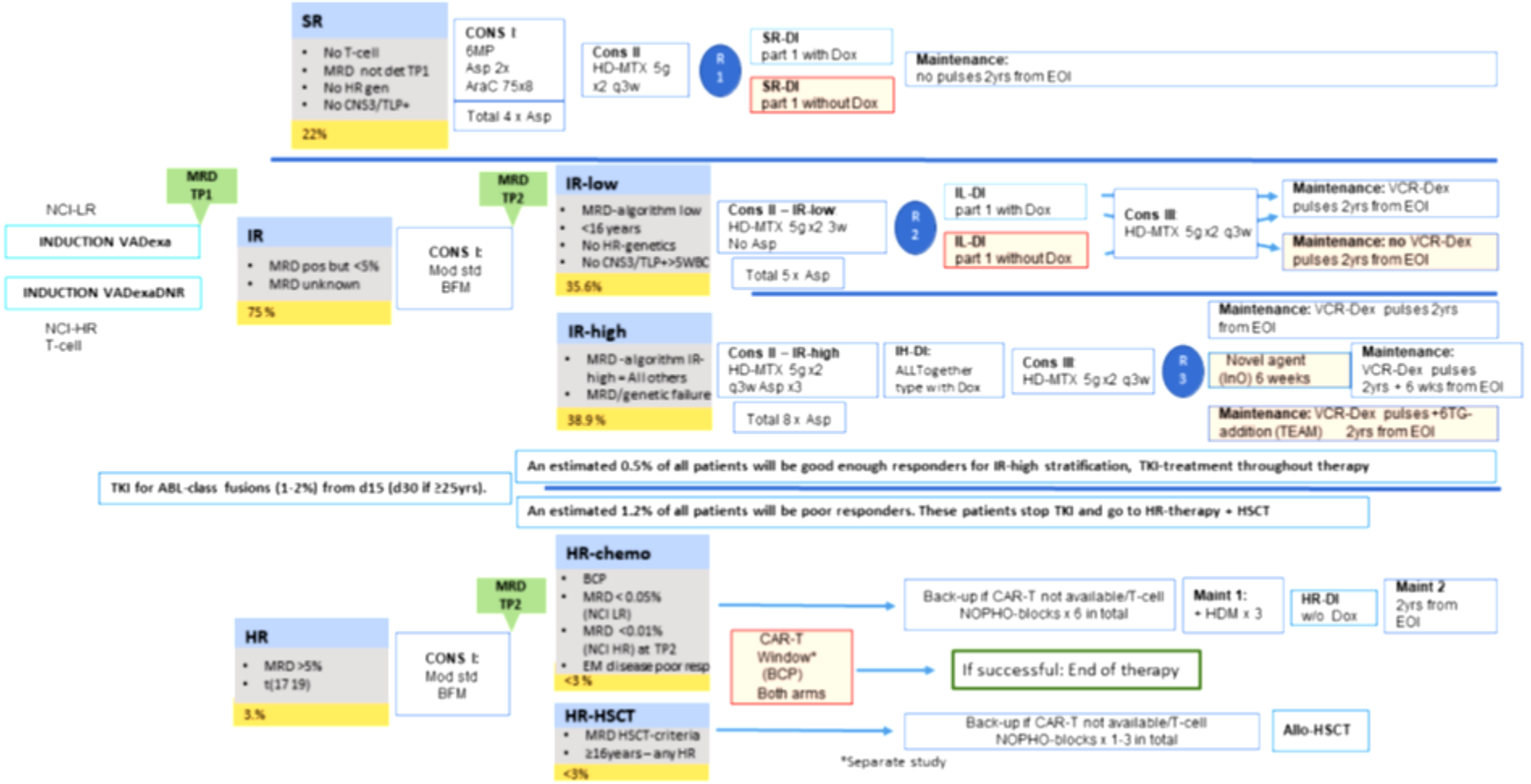
1. Schrappe M, et al. *J Clin Oncol.* 2017; 2. Vora A, et al. *Lancet Oncol*. 2013; 3. Pieters R, et al *J Clin Oncol.* 2016.

Contemporary Trials For Pediatric ALL in Europe

EUDRACT number: 2018-001795-38

ALLTogether

Therapy overview ALLTogether – including interventions



AIEOP-BFM ALL 2017

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

Stratification and Treatment Questions

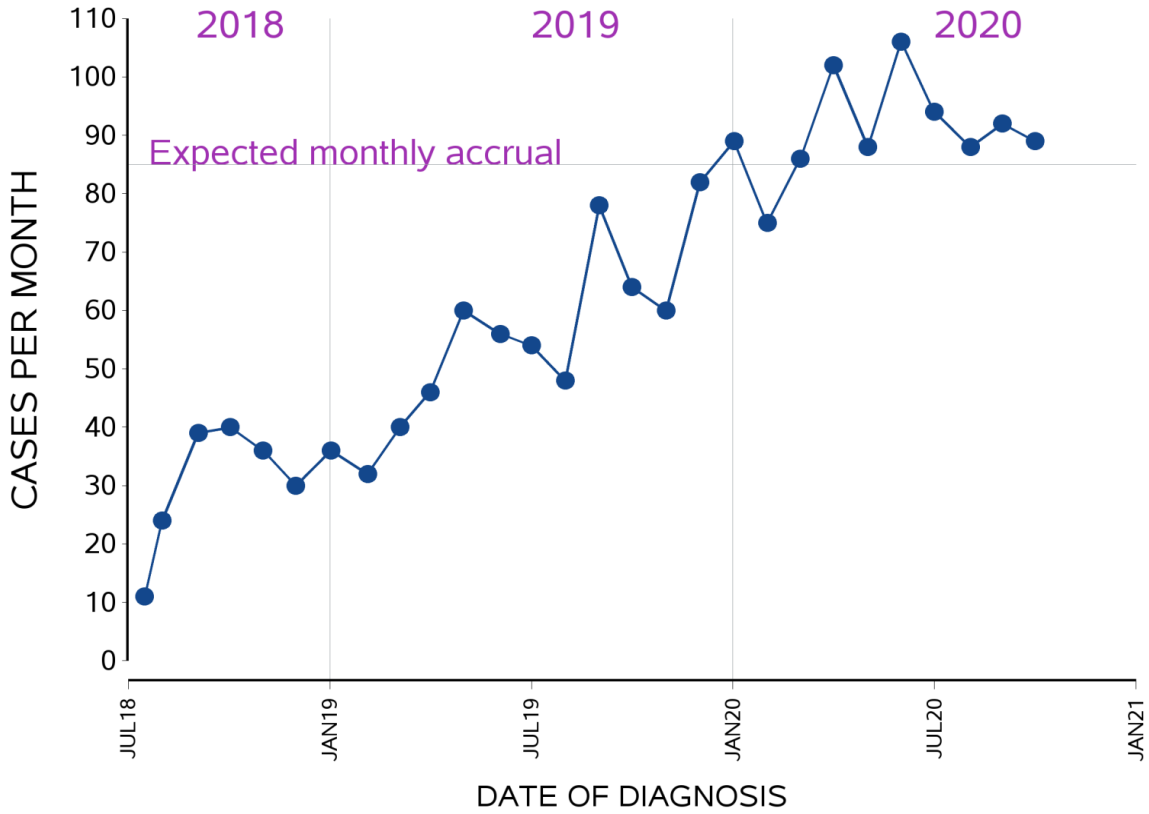
A. Biondi (AIEOP), J. Starý (CPH), S. Elitzur (INS),
A. Kolenova (SPHOS), G. Mann (BFM-A), D. Barbaric (ANZCHOG),
F. Niggli (BFM-CH), M. Schrappe (BFM-G)

Sponsor:
University Medical Center Schleswig-Holstein (Kiel, Germany)
EudraCT Number: 2016-001935-12

AIEOP-BFM ALL 2017

Participating countries (study groups)	• Australia (ANZCHOG) • Austria (BFM-A) • Czech Republic (CPH) • Germany (BFM-G) • Israel (INS) • Italy (AIEOP) • Slovakia (SPHOS) • Switzerland (BFM-CH)
Planned recruitment	5 years Approx. 1000 pts p.a.
Start	7-2018

Recruitment in trial AIEOP-BFM ALL 2017

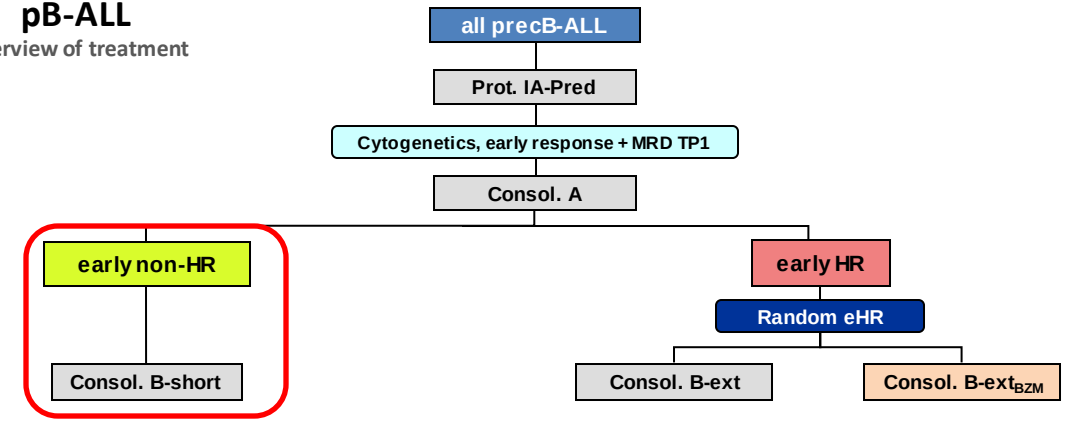


AIEOP-BFM ALL 2017: Risk Criteria for pB-ALL

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* *not* *ETV6-RUNX1* positive or • *IKZF1*^{plus} *and* PCR-MRD at TP1 positive or inconclusive *and* *not* positive for *ETV6-RUNX1*, *TCF3-PBX1* or *KMT2A* rearrangement 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
Standard Risk (SR)	• No HR criteria and • PCR-MRD negative at TP1

Combined use of FCM-based and ASO-PCR-based MRD-detection

AIEOP-BFM ALL 2017
pB-ALL
Overview of treatment



precB-ALL: early HR (20%)

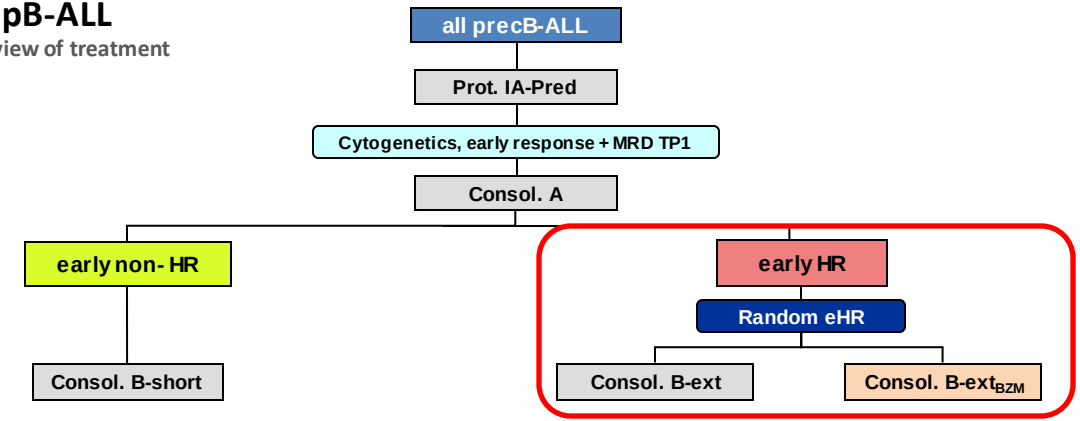
- **no complete remission on day 33, *or***
- positivity for *KMT2A-AFF1 (MLL-AF4)*, *or*
- hypodiploidy <45 chromosomes, *or*
- FCM-MRD in BM on day 15 ≥ 10%, *and* *not* *ETV6-RUNX1* positive, *or*
- **positivity for *TCF3-HLF (E2A-HLF)*, or**
- ***IKZF1*^{plus} *and* PCR-MRD at TP1 positive, or**
- **PCR-MRD at TP1 ≥ 5x10^{-4}, or**
- **age < 1 year and any *KMT2A (MLL)* rearrangement**

***IKZF1*^{plus}**

Deletion of *IKZF1* and:

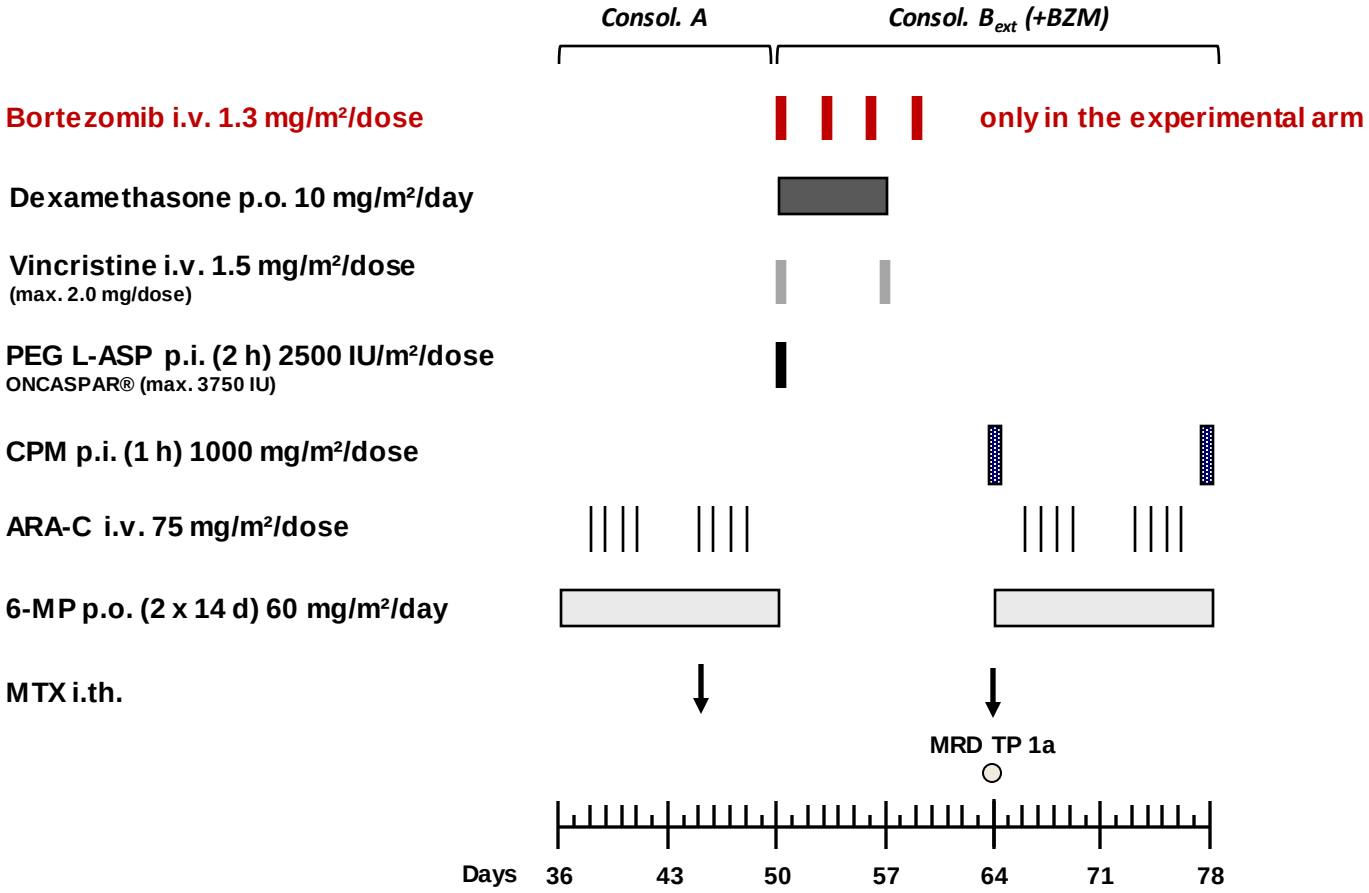
- ***PAX5* and/or**
- ***CDKN2A* and/or**
- ***CDKN2B* and/or**
- ***CRLF2* *(PAR)* and**
- **Negativity for *ERG* *d*eletion**

AIEOP-BFM ALL 2017
pB-ALL
Overview of treatment

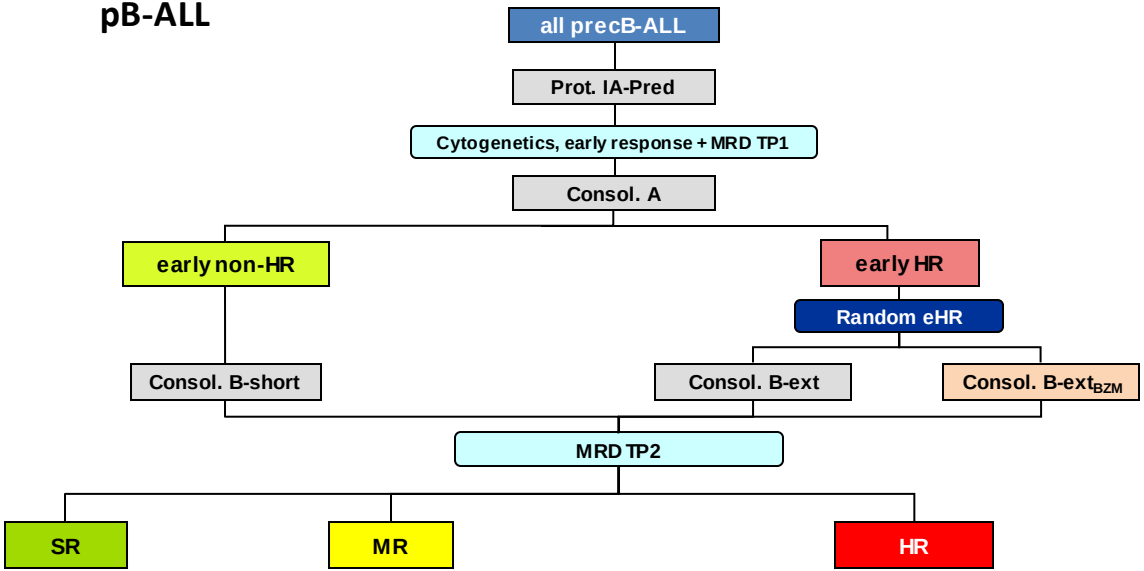


Can pEFS in pcB-early HR pts be improved by additional therapy with Bortezomib during an extended consolidation treatment phase compared to a standard extended consolidation?

Extended Consolidation for early HR pB-ALL
Random eHR

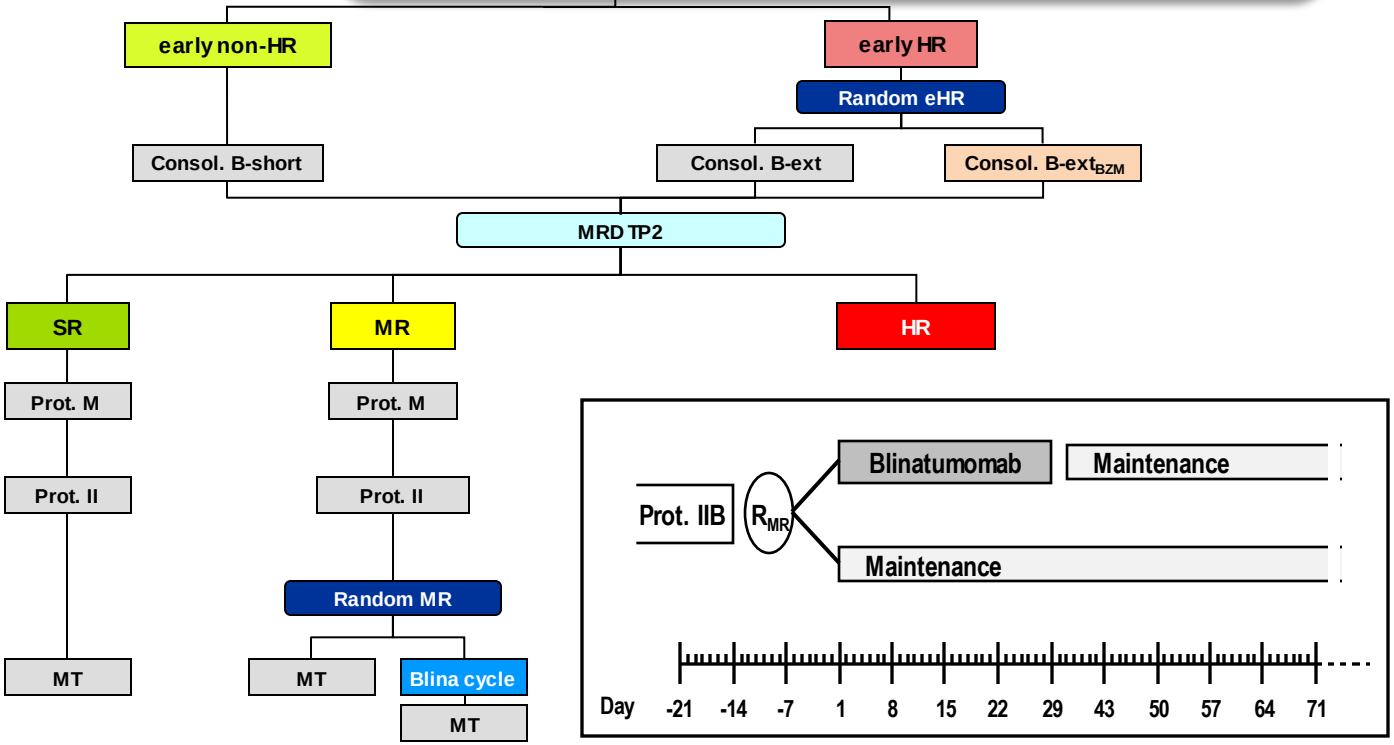


AIEOP-BFM ALL 2017
pB-ALL

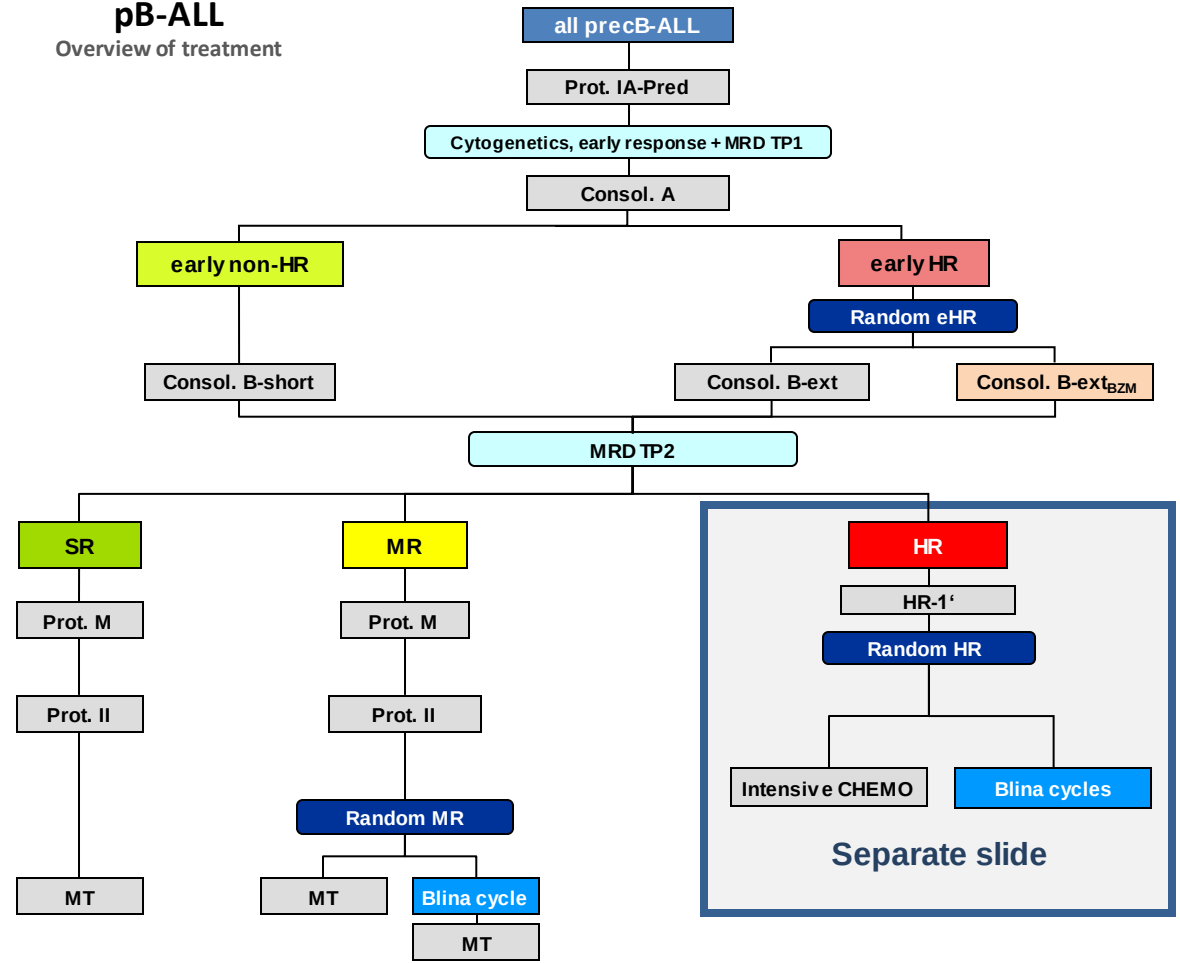


AIEOP-BFM ALL 2017
pB-ALL

Can pDFS of MR pts be improved by additional therapy with one cycle of post-reintensification immunotherapy with **Blinatumomab**?

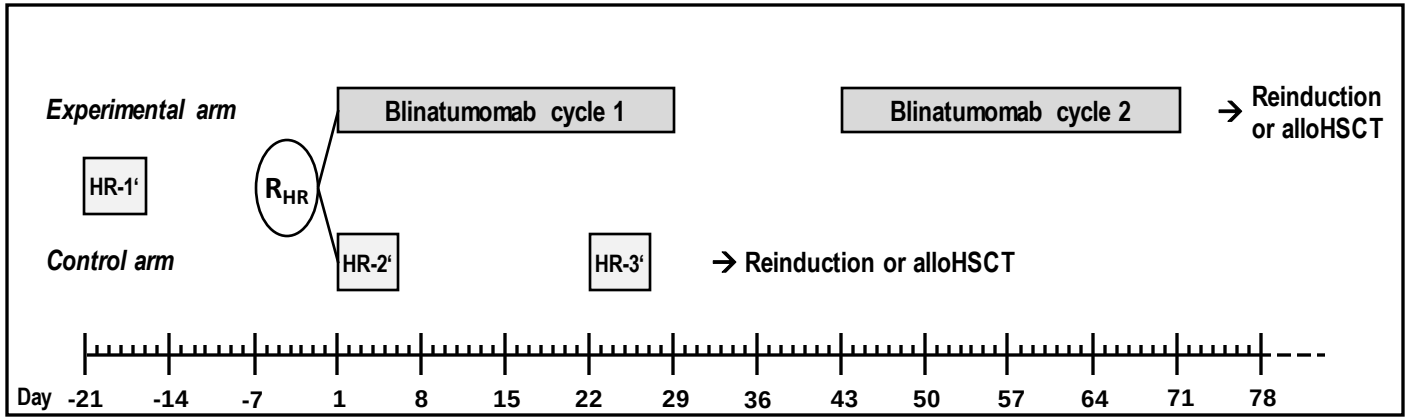


AIEOP-BFM ALL 2017
pB-ALL
Overview of treatment



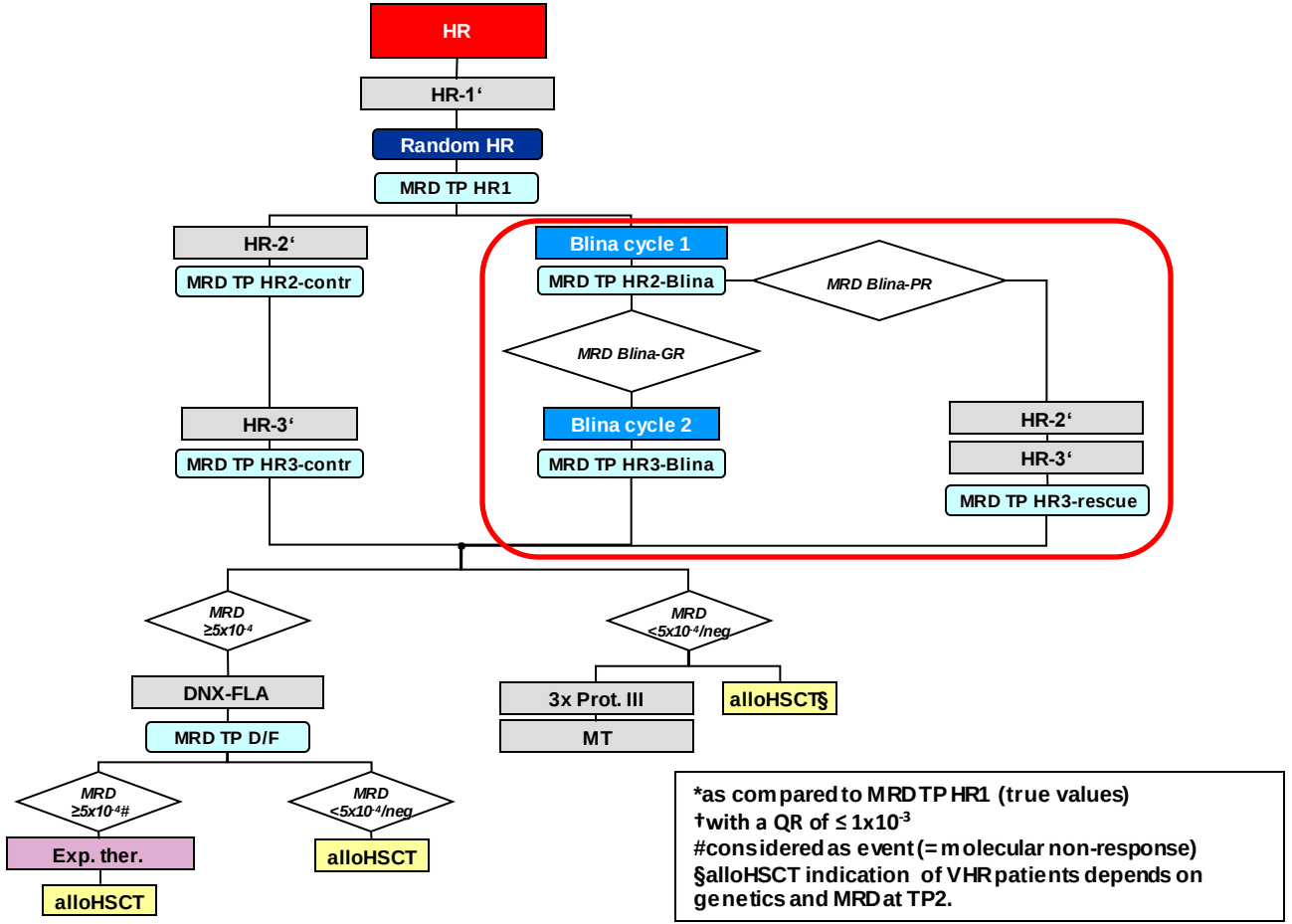
AIEOP-BFM ALL 2017: pB-ALL
Approach for HR patients: Randomization HR

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?



- Combination of two effects desired for a novel HR post-consolidation therapy:
  - Significant reduction of toxicity
  - More effective therapy for patients with insufficient response to the HR chemotherapy blocks by overcoming resistance to chemotherapy

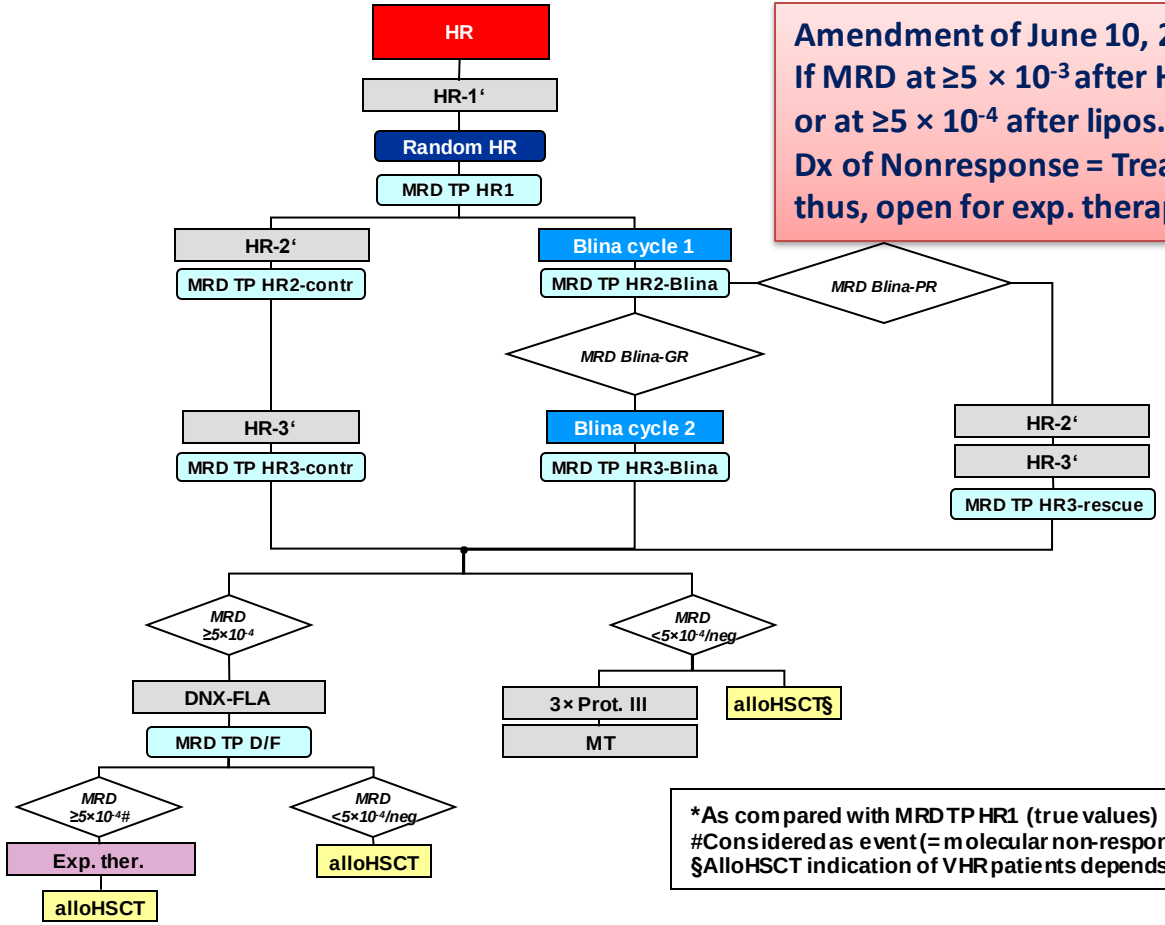
AIEOP-BFM ALL 2017: pB-ALL
Approach for HR patients: Randomization HR



*as compared to MRD TP HR1 (true values)
†with a QR of ≤ $1x10^{-3}$
#considered as event (= molecular non-response)
§alloHSCT indication of VHR patients depends on genetics and MRD at TP2.

AIEOP-BFM ALL 2017: pB-ALL

Approach for HR Patients: Randomization HR



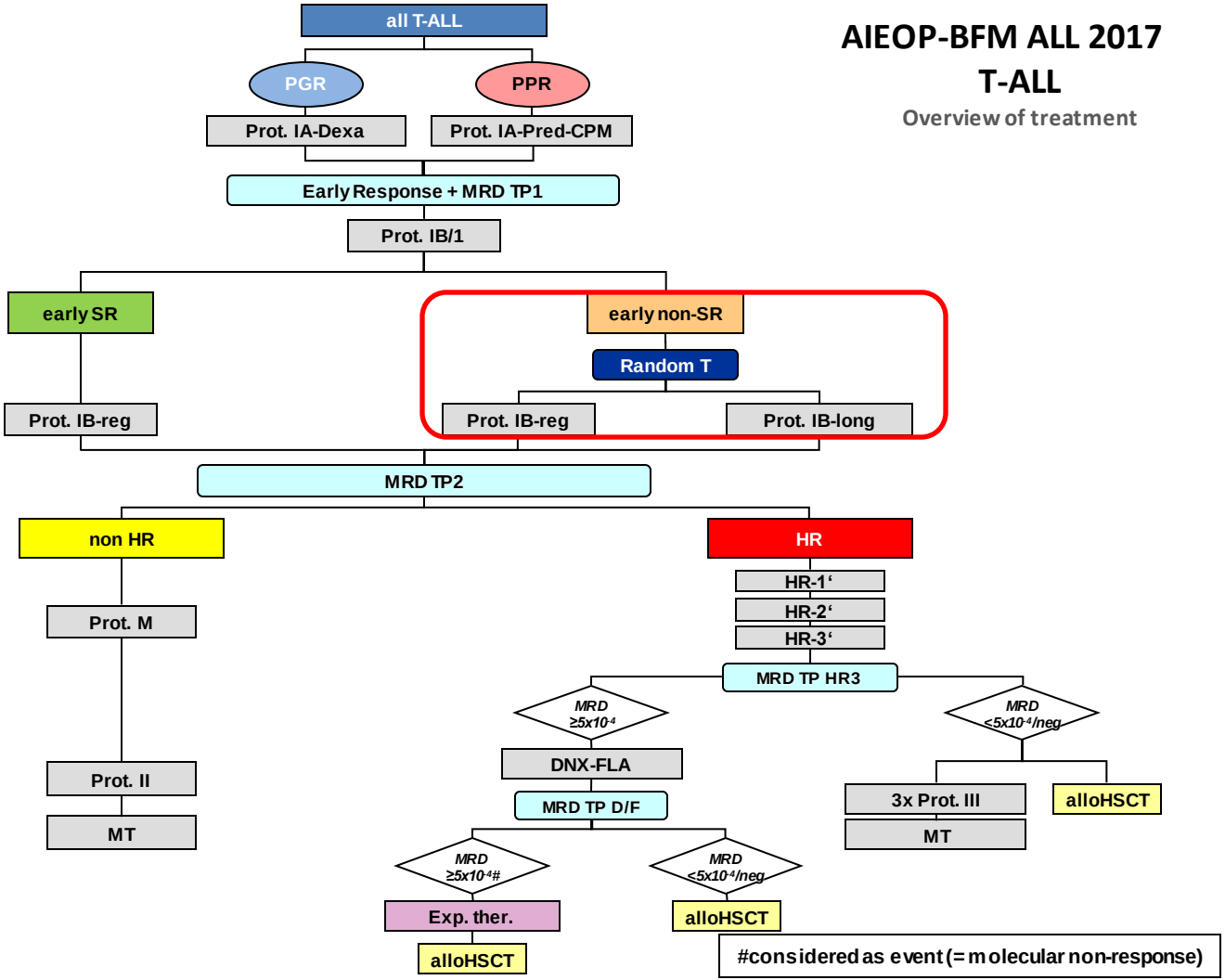
Amendment of June 10, 2020:
If MRD at ≥5 × 10^{-3} after HR-3‘ or 2nd cycle Blina, or at ≥5 × 10^{-4} after lipos. DOX-FLA:
Dx of Nonresponse = Treatment failure = Event, thus, open for exp. therapy

*As compared with MRD TP HR1 (true values)
#Considered as event (= molecular non-response)
§AlloHSCT indication of VHR patients depends on genetics and MRD at TP2

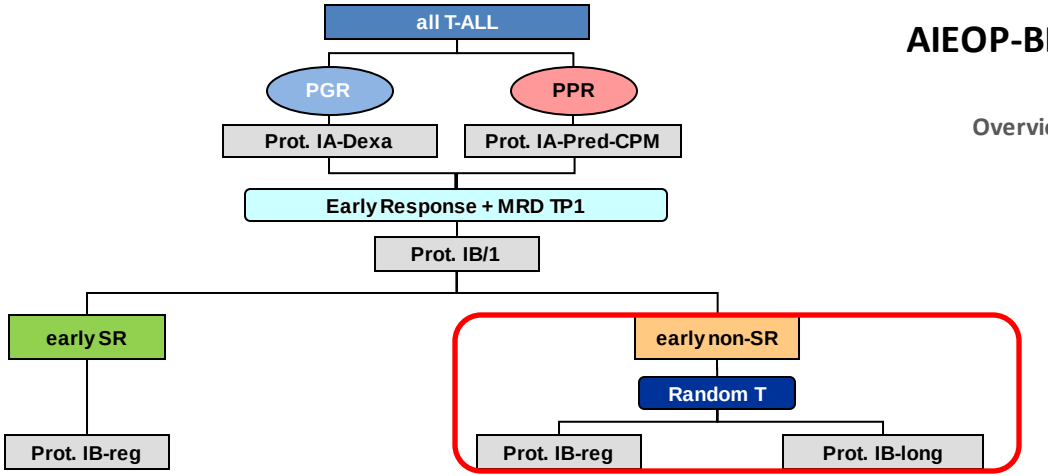
Treatment plan

T-ALL

AIEOP-BFM ALL 2017
T-ALL
Overview of treatment



AIEOP-BFM ALL 2017
T-ALL
Overview of treatment



Can the pEFS be improved by the extension of the standard of care consolidation by 14 days with an increase of the consolidation cumulative doses of Cyclophosphamide, Cytarabine and 6-Mercaptopurine by 50%?

Protocol IB-regular

CPM p.i. (1 h) 1000 mg/m²/dose

ARA-C i.v. 75 mg/m²/dose

6-MP p.o. (28 d) 60 mg/m²/day

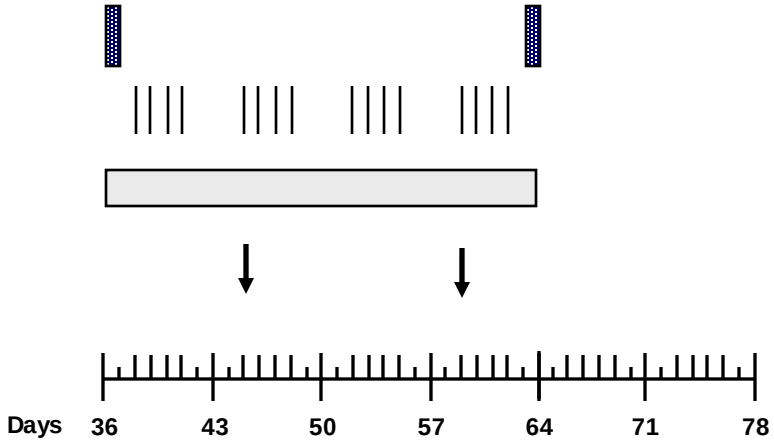
MTX i.th.

Age-adjusted dose:

1 to < 2 years: 8 mg

2 to < 3 years: 10 mg

≥ 3 years: 12 mg



Protocol IB-long

CPM p.i. (1 h) 1000 mg/m²/dose

ARA-C i.v. 75 mg/m²/dose

6-MP p.o. (42 d) 60 mg/m²/day

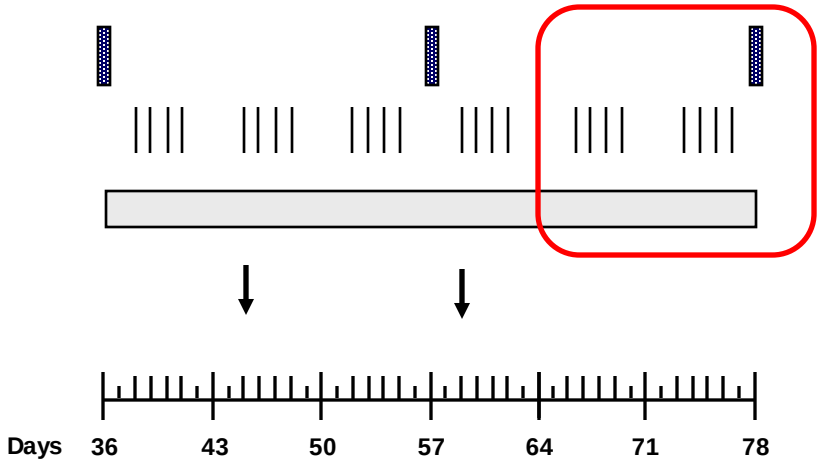
MTX i.th.

Age-adjusted dose:

1 to < 2 years: 8 mg

2 to < 3 years: 10 mg

≥ 3 years: 12 mg



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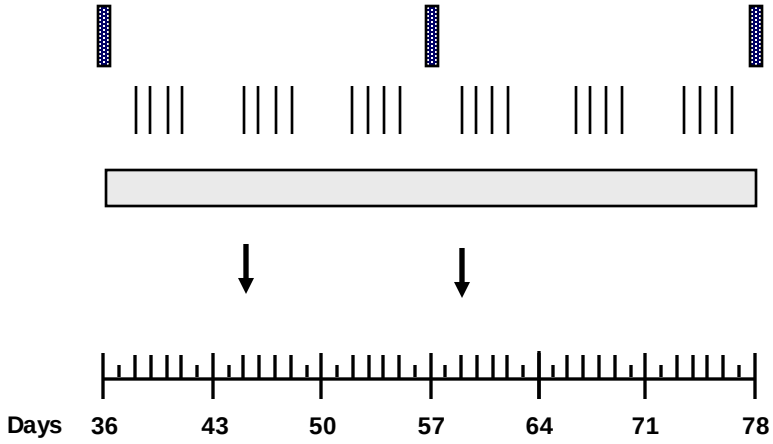

Protocol IB-regular

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Age-adjusted dose:

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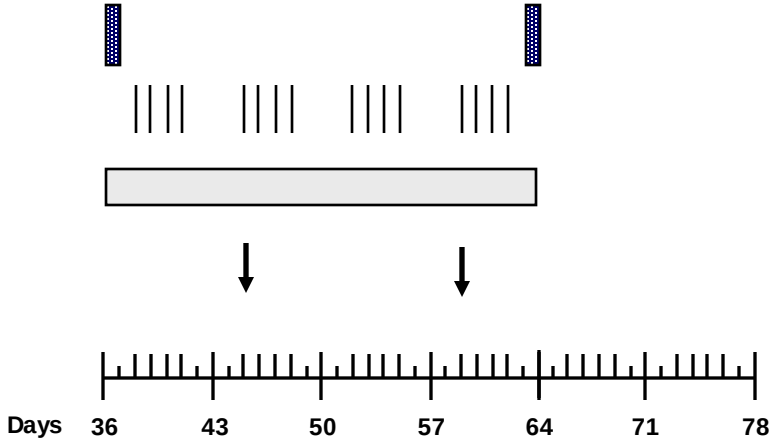
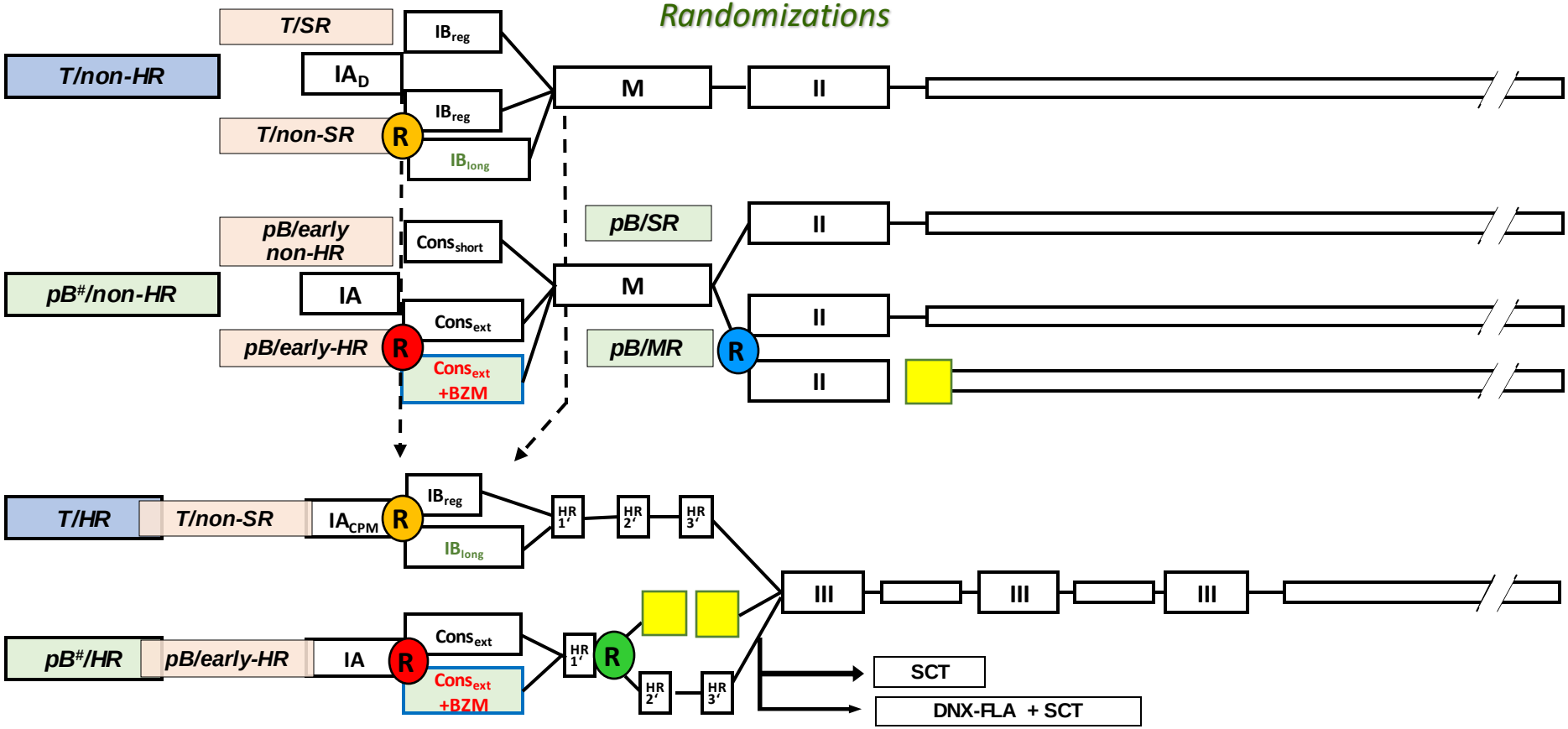


AIEOP-BFM ALL 2017: Genetic Screening and Consequences in Special Subgroups

- See flow chart: Combination of array-based techniques and FISH, sometimes RT-PCR
- Targetable lesions will be identified (Ph-like pos pts may enter EsPhALL/COGAALL1631
- Therapeutic consequences: Due to limited evidence, special consideration only in poor-responding patients if not eligible for the randomizations
- Pts with t(17:19) will be stratified for Blina and will receive BZM in consolidation
- DS-ALL pts with HR-ALL will be stratified for Blina and for the no-BZM arm in consolidation

AIEOP-BFM ALL 2017: Treatment Overview

Randomizations



Blinatumomab 15 µg/m²/d × 28 d p.i.

or immunophenotype unknown

pCRT 12 Gy in T-ALL and WBC ≥100T, or CNS-3, if age ≥4 yrs *
All other T-ALL, HR-pB-ALL and CNS 3-if age <4 yrs: no CRT + 6× IT MTX in MT

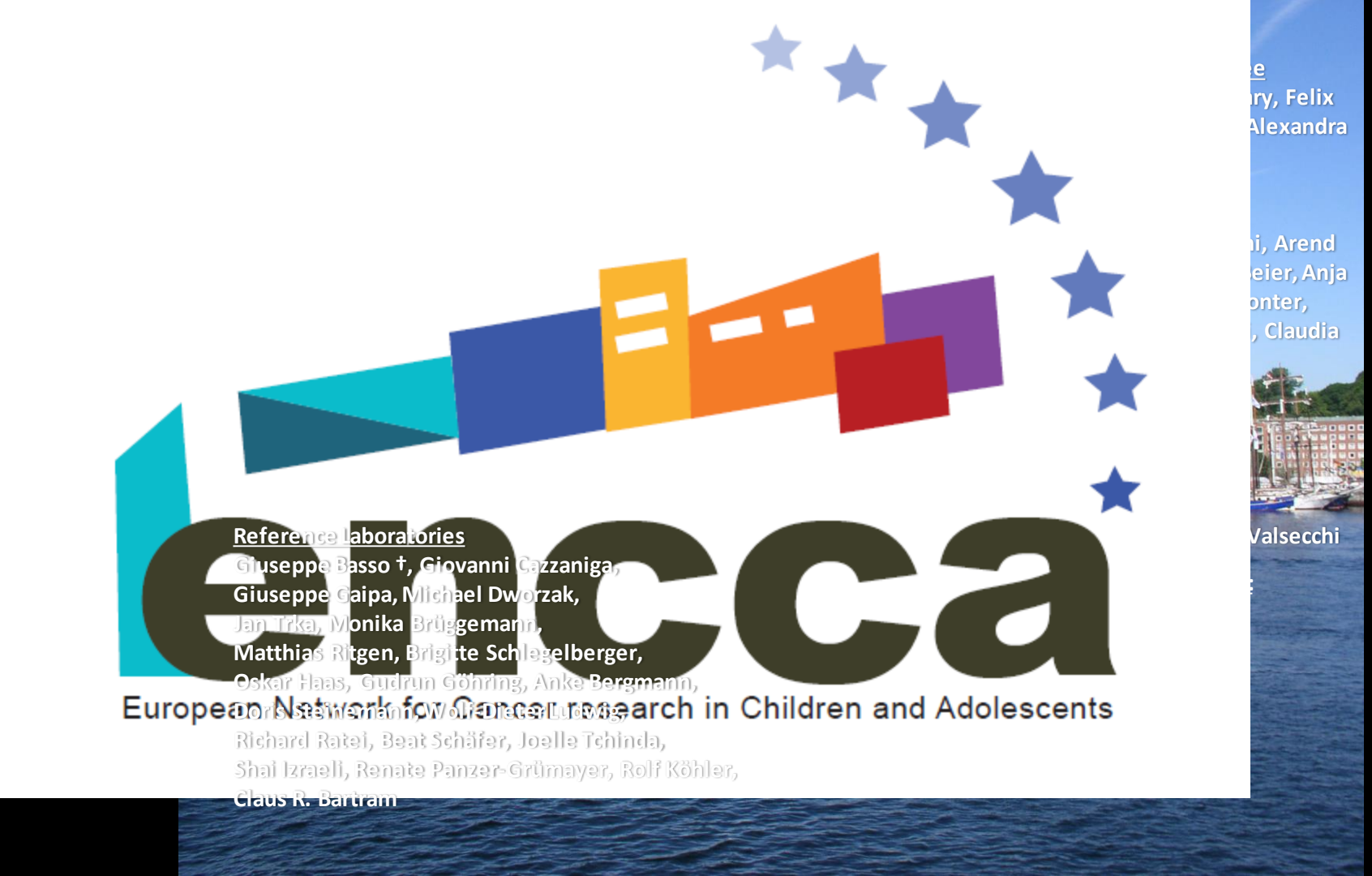
Summary and Outlook

- Clinically relevant diagnostic subgroups of ALL can be defined more precisely
- Novel definitions for diagnostics and disease response are now available and accepted
- Contemporary trials for pediatric ALL in Europe will provide novel insights into treatment modulation and explore new strategies
- Future aims
  - Safe treatment reduction to avoid critical late effects
  - Well-balanced treatment intensity of frontline and second-line therapy

Thank you

ALL-BFM Clinical Trial Center

ALL-BFM Diagnostic Laboratory (Kiel)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Reference Laboratories
Giuseppe Basso †, Giovanni Cazzaniga,
Giuseppe Gaipa, Michael Dworzak,
Jan Trka, Monika Brüggemann,
Matthias Ritgen, Brigitte Schlegelberger,
Oskar Haas, Gudrun Göhring, Anke Bergmann,
Horst Stefanowicz, Wolf-Dieter Ludwig,
Richard Ratei, Beat Schäfer, Joelle Tchinda,
Shai Izraeli, Renate Panzer-Grümayer, Rolf Köhler,
Claus R. Bartram
ercca
European Network for Cancer research in Children and Adolescents

[repeated question] Question 1

Genetic subgroups in pediatric ALL have been well described. Can you pick the most appropriate definition for a novel entity, called *IKZF1*-plus?

A. Novel mutation in the *bcr/abl* fusion gene
B. Simultaneous deletions in *IKZF1* and *PAX5* and/or *CDKN2A* and/or *CDKN2B* and/or *CRLF2 (PAR),* and negativity for *ERG* deletion
C. Gain of function in *IKZF1*
D. Novel term for hypodiploidy
E. Mutation in drug resistant patients with *ETV6/RUNX1* positivity

[repeated question] Question 2

Please indicate which of the following statements for positive testing of MRD at a level of 0.1% is most appropriate:

A. At the end of induction therapy for ALL, such a level of MRD equals induction failure
B. MRD at this level at the end of consolidation (approx. 12 weeks after start of treatment) can be considered a very favorable response
C. MRD at this level after allogeneic hSCT is a normal observation when measured at day +100
D. MRD at this level at any time of ALL therapy equals disease recurrence (relapse)
E. MRD at this level at the end of induction may indicate a more resistant leukemia, as compared to others with no detectable MRD at the end of induction

Global Leukemia Academy

Q&A session

APTITUDE HEALTH

Global Leukemia Academy

Current treatment options for relapsed ALL in children, including HSCT considerations

Franco Locatelli

APTITUDE HEALTH

Current treatment options for relapsed ALL in children, including HSCT considerations

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	Speakers' 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]

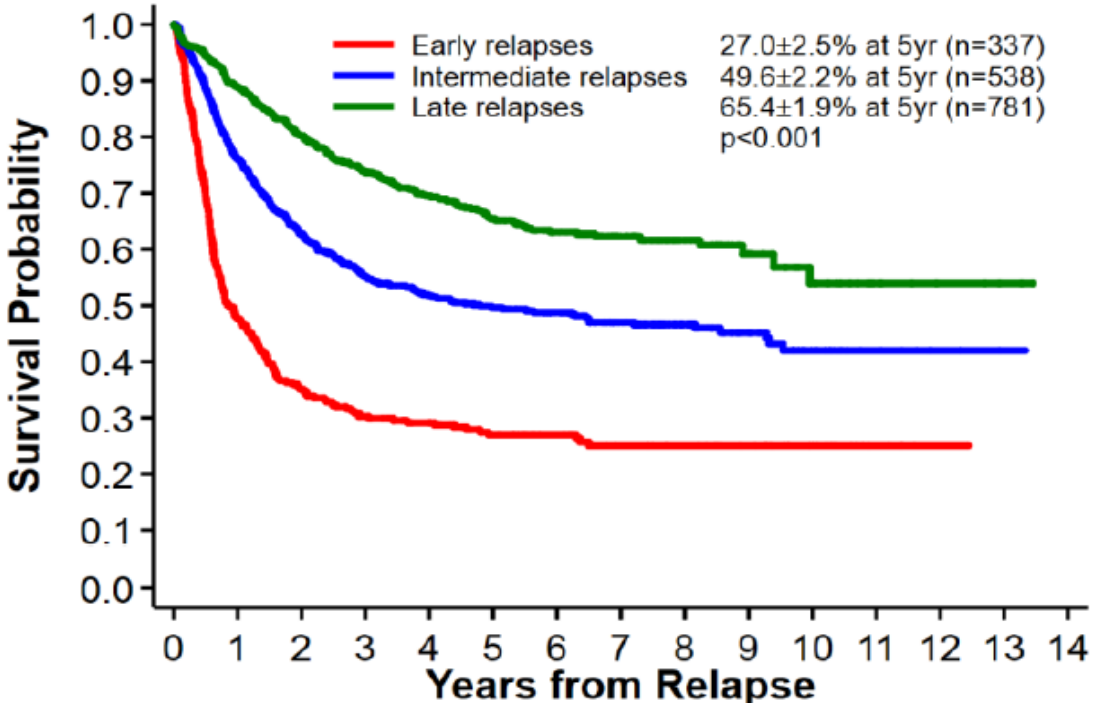
BCP-ALL, B-cell precursor acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplant.

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

Immunophenotype	B-cell precursor			(pre) T		
Time Point/Site	Extramed isolated	Bone marrow combined	Bone marrow isolated	Extramed 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



We need innovative therapies for improving the outcome of patients experiencing leukemia relapse

Rheingold SR, et al. ASCO 2019. Abstract 10008.

IntReALL-BCP 2020: New risk-stratification

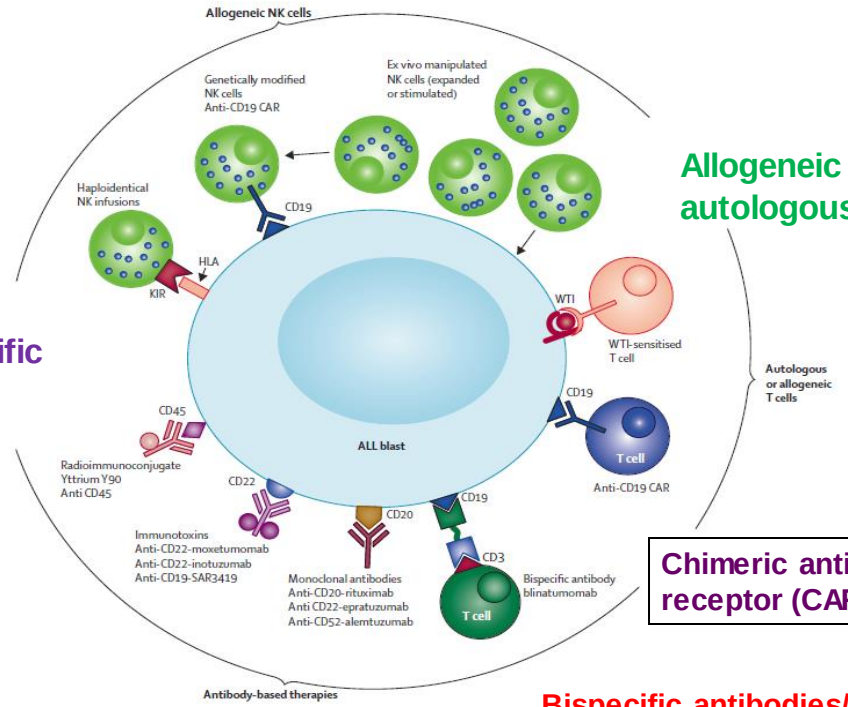
VHR (15%) Eligible for allo-HSCT or consolidation therapy

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

SR (60%) Late isolated or combined medullary/extramedullary relapse (alloHSCT 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 alloHSCT as final consolidation)

New immunologic approaches under investigation in childhood ALL



Allogeneic and autologous NK cells

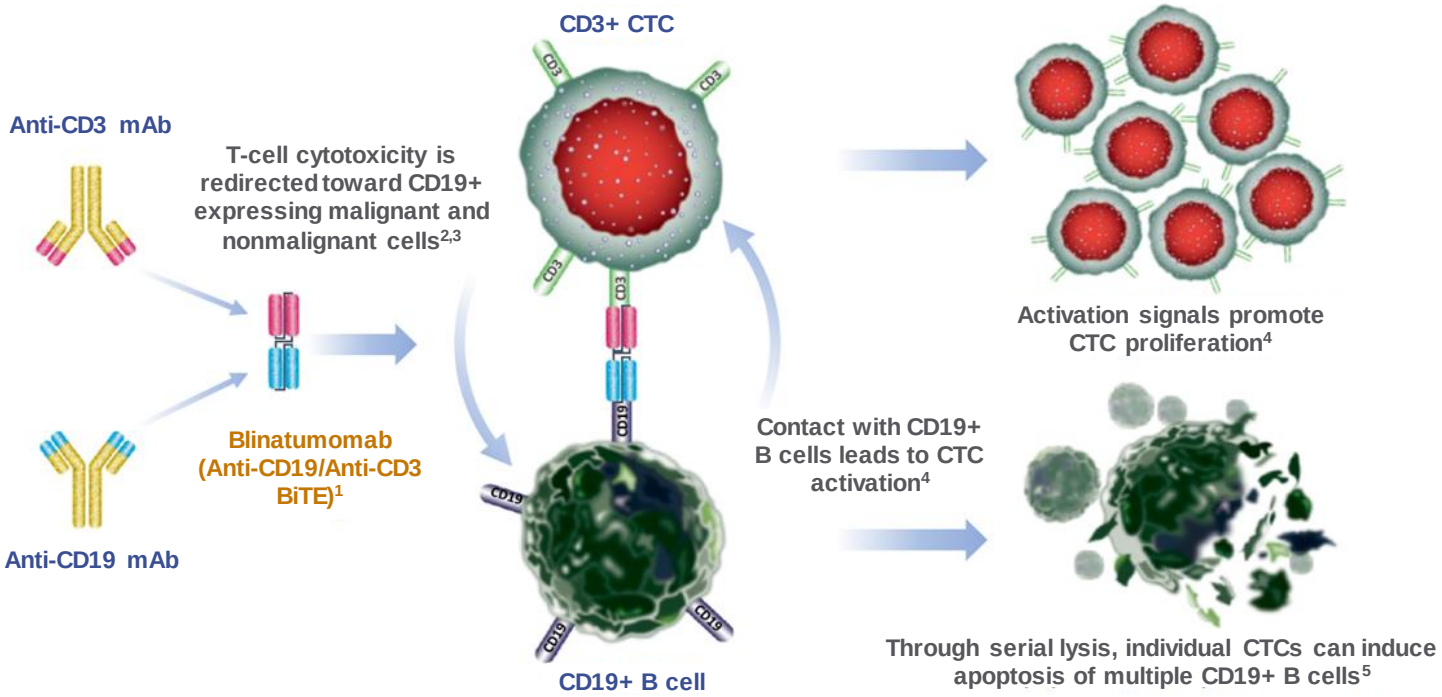
Immunotoxin-specific antibodies

Chimeric antigen receptor (CAR) T cells

Bispecific antibodies/antibody constructs

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

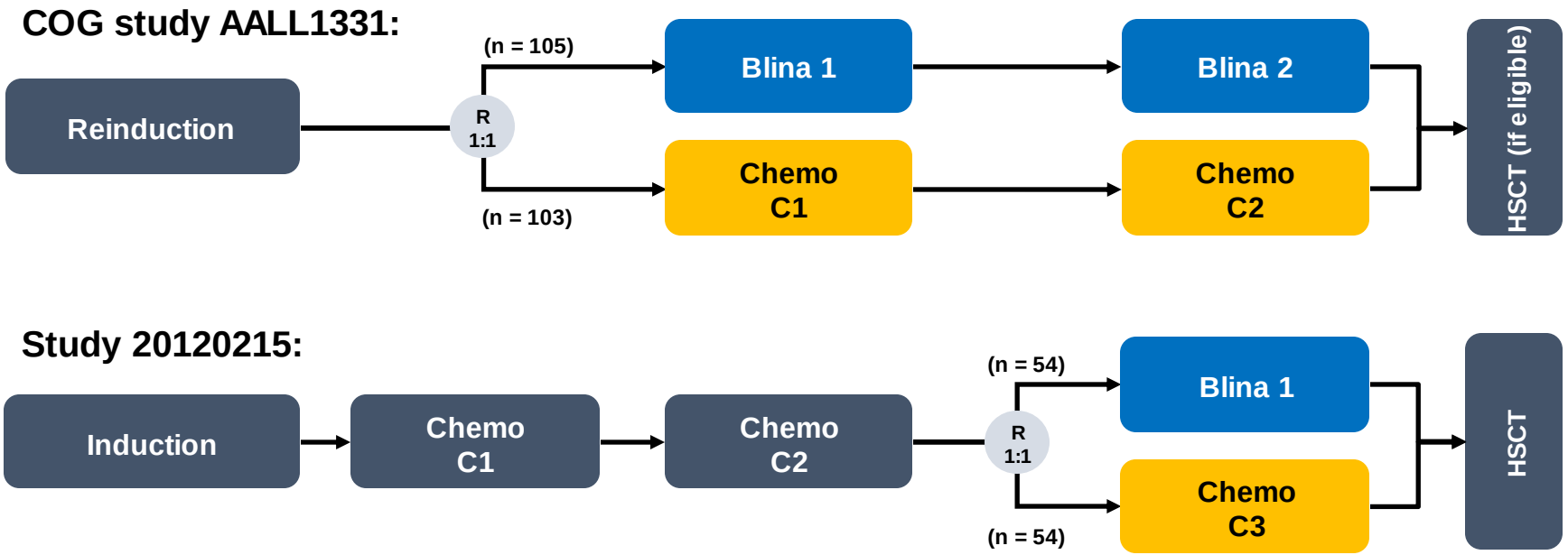
Blinatumomab (CD19 BiTE® molecule)



BiTE®, bispecific T cell engager; CD, cluster of differentiation; CTC, cytotoxic T cell; mAb, monoclonal antibody.

1. Baeuerle PA, et al. *Cancer Res*. 2009;69:4941-4944; 2. Bargou R, et al. *Science*. 2008;321:974-977; 3.Topp MS, et al. *Lancet Oncol*. 2015;16:57-66; 4. Klinger M, et al. *Blood*. 2012;119:6226-6233; 5. Hoffmann P, et al. *Int J Cancer*. 2005;115:98-104.

Design of the phase III studies

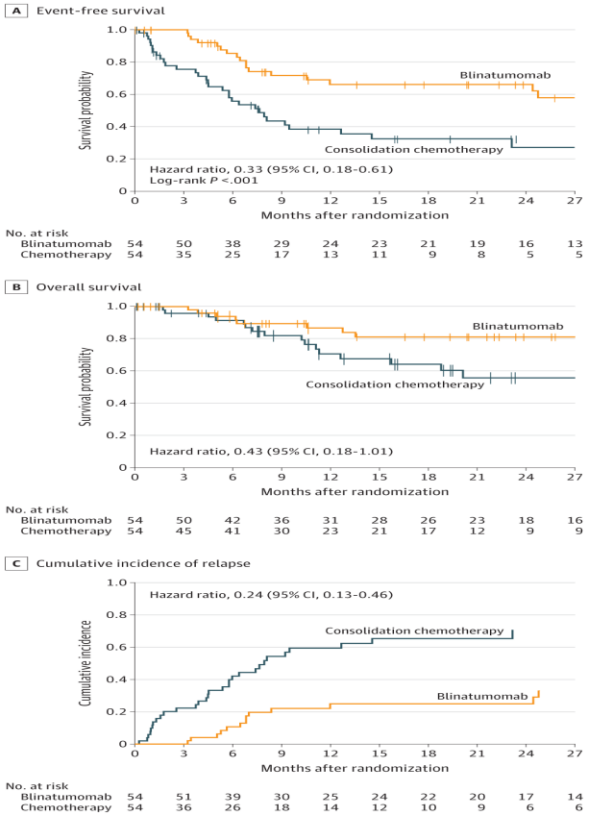


Brown PA, et al. *JAMA*. 2021;325:888-842; Locatelli F, et al. *JAMA*. 2021;325:843-854.

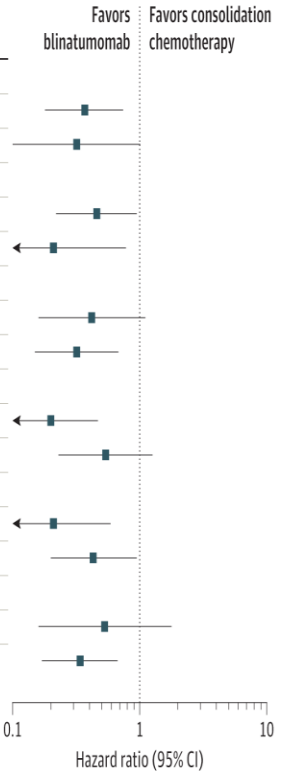
JAMA Network™

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**

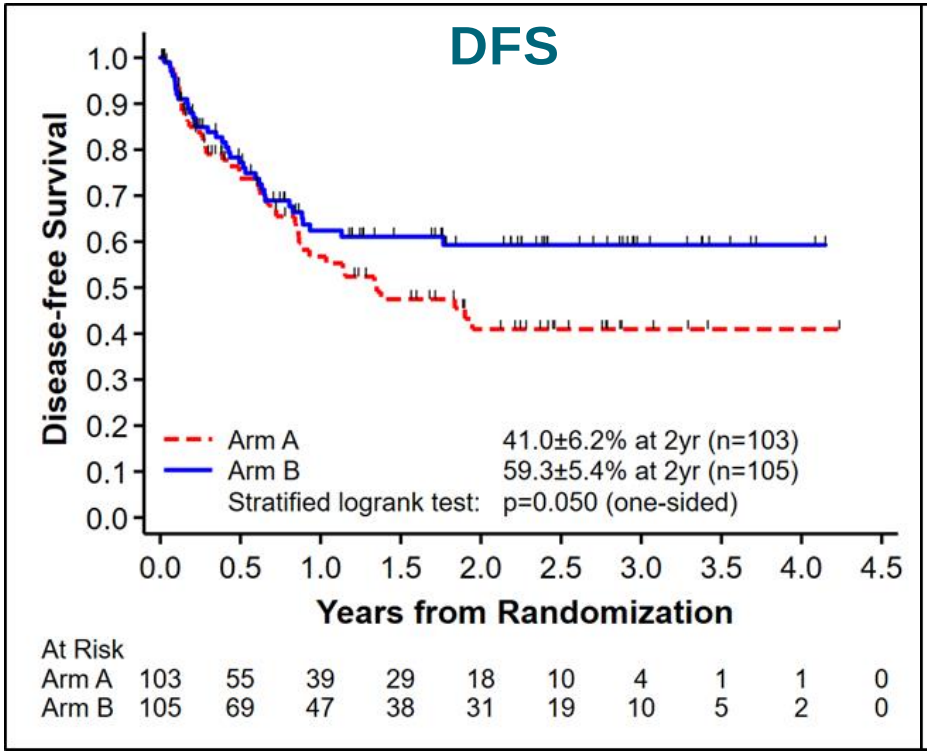
JAMA. 2021;325:843-854. doi:10.1001/jama.2021.0987

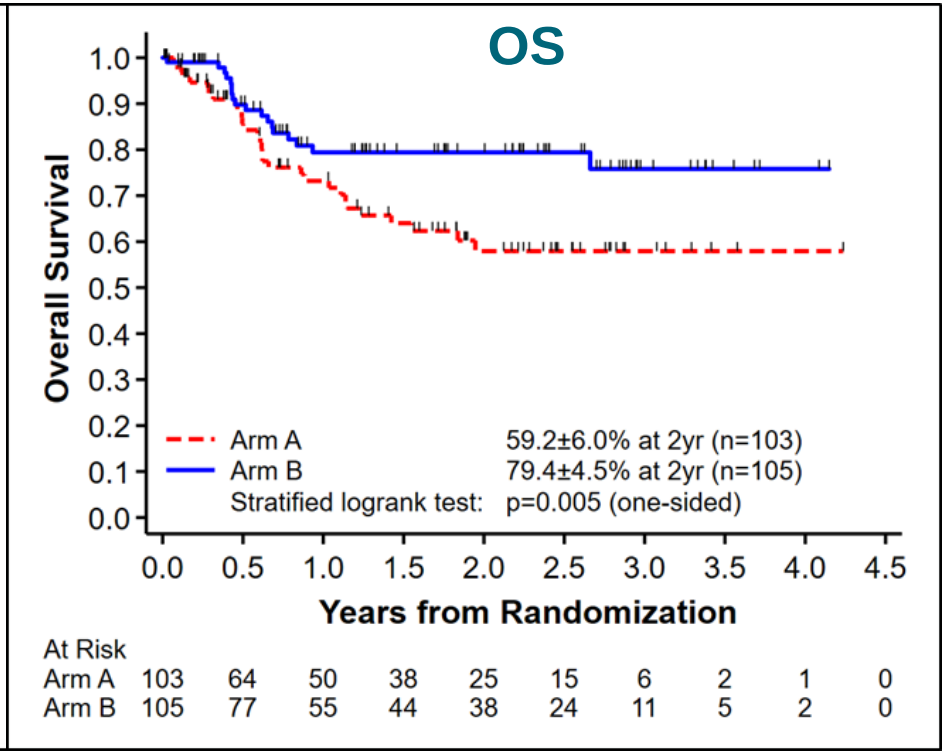


Subgroup	No. of events/No. treated (%) Blinatumomab	Consolidation chemotherapy	Hazard ratio (95% CI)
Age, y			
1-9	12/39 (30.8)	23/38 (60.5)	0.37 (0.18-0.74)
>9	5/15 (33.3)	8/16 (50.0)	0.32 (0.10-1.01)
Minimal residual disease at end of induction			
$<10^{-3}$ Blast cells	12/35 (34.3)	19/34 (55.9)	0.46 (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)

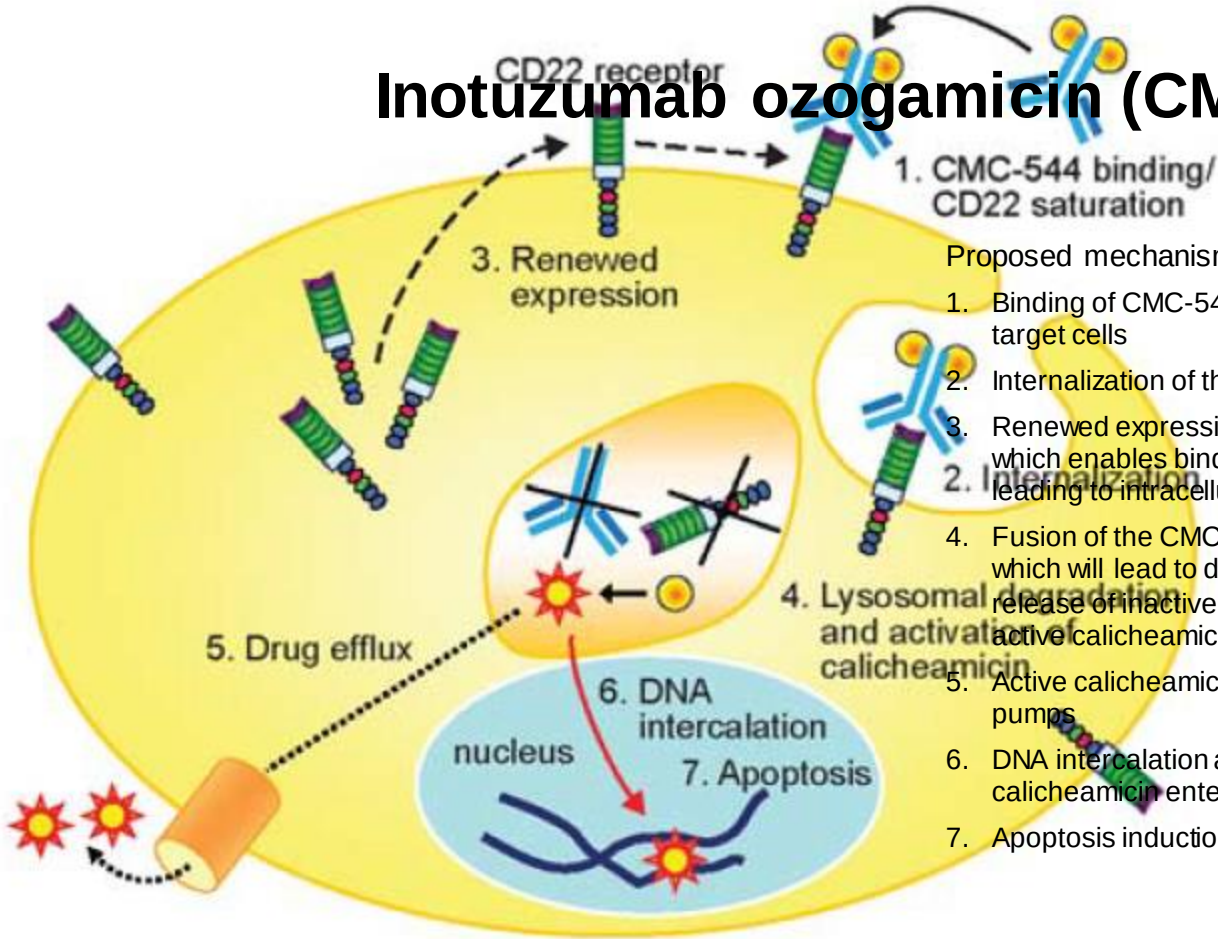




Median follow-up 1.4 years

Brown PA, et al. *JAMA*. 2021;325:888-842.

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.

A phase 1 study of inotuzumab ozogamici relapsed/refractory acute lymphoblastic leu (ITCC-059 study)

Erica Brivio,[1,2] Franco Locatelli,[3] Marta Lopez-Yurc Bel
Vincent H. J. van der Velden,[9] Anneke C. J. Amme Mo
Barbara Sleight,[12] Benoit Brethon,[13] Karsten Nyso ti,[3]
and Christian Michel Zwaan[1,2]

Phase I Study of Single-Agent Inotuzumab Ozogamicin in Pediatric Relapsed/Refractory ALL

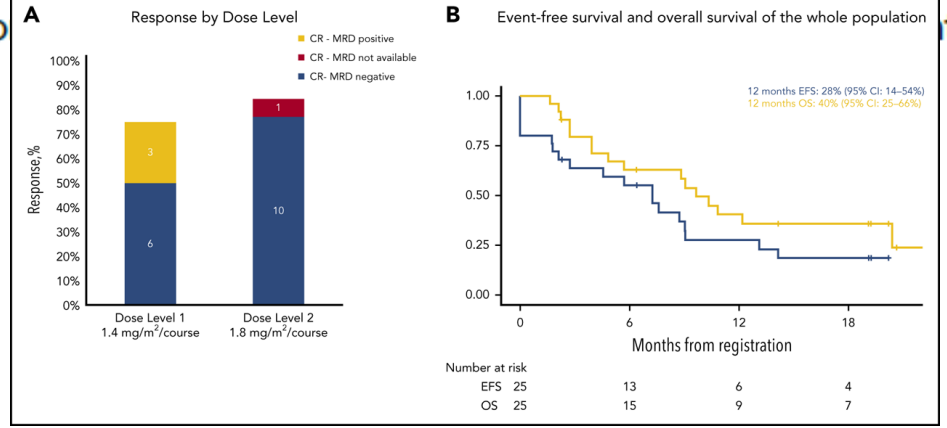
Safety
- Similar toxicity at DL1 and DL2 (1.4 and 1.8 mg/m^2/course)
- Gr 3/4 neutropenia and thrombocytopenia in almost all patients
- 2 SOS cases after additional chemotherapy (1 DL1, 1 DL2)

Efficacy
- Higher CR rate (*p-value 0.6*) and MRD negativity rate (*p-value 0.1*) at DL2
- Longer median duration of response (*p-value 0.1*) and OS (*p-value 0.06*) at DL2

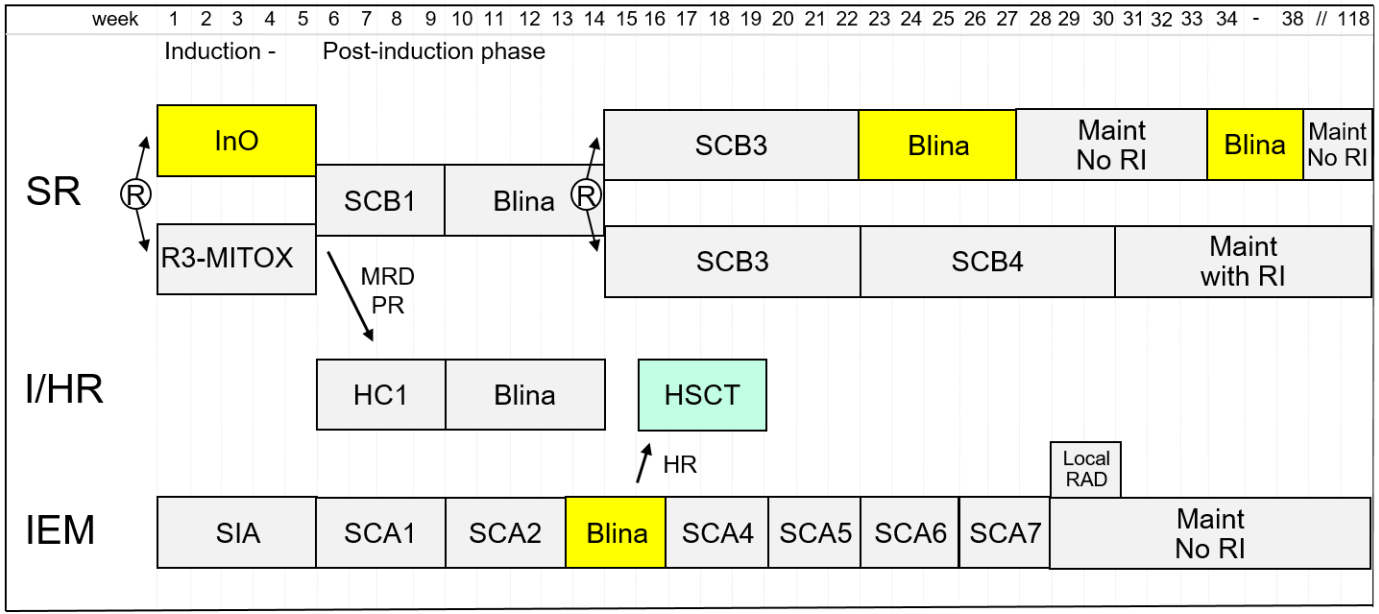
Differences not statistically significant (small sample size)

Pharmacokinetics
- Comparable plasma PK at DL1 and DL2

RP2D = DL2 (1.8 mg/m2/course)

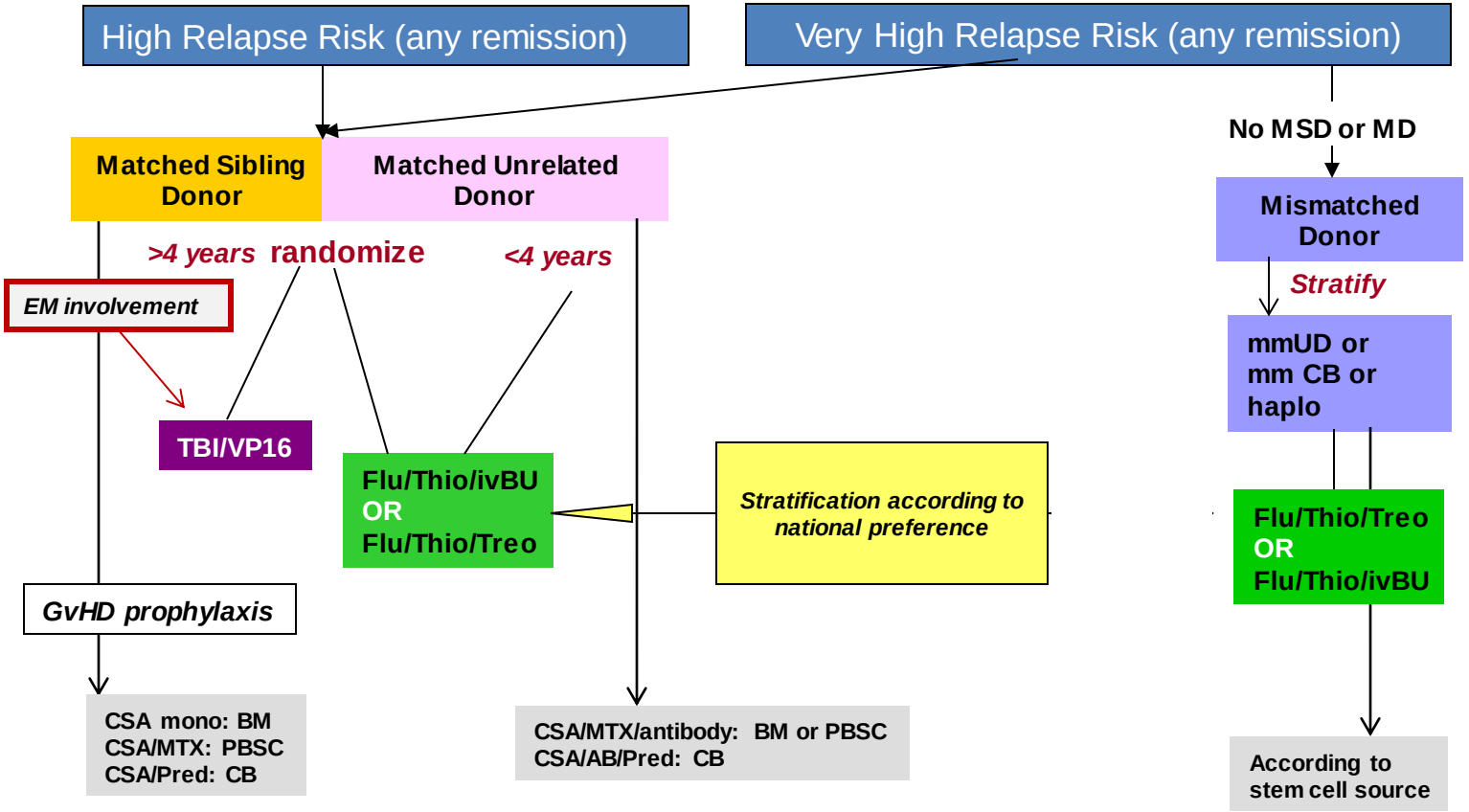


Treatment schedule – IntReALL BCP 2020



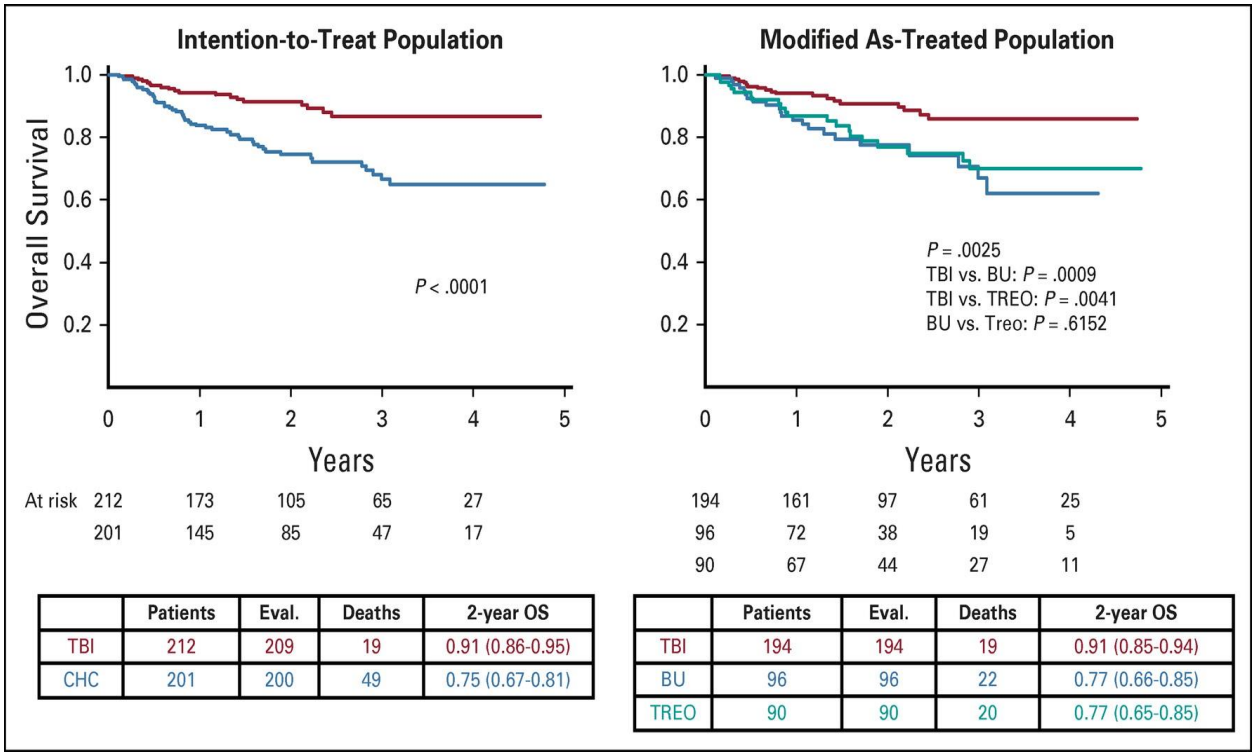
Arrow down (↓), bone marrow puncture with CR/MRD assessment.
Blina, blinatumomab; HC1, HR consolidation 1; HR, high-risk group; MRD, minimal residual disease; R, randomization; R3BB, ALL R3 backbone; Maint, maintenance therapy; MITOX, mitoxantrone; RI, reinduction pulses; S, stratification; SCB1-4, standard consolidation arm B 1-4; SCT, stem cell transplantation.

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

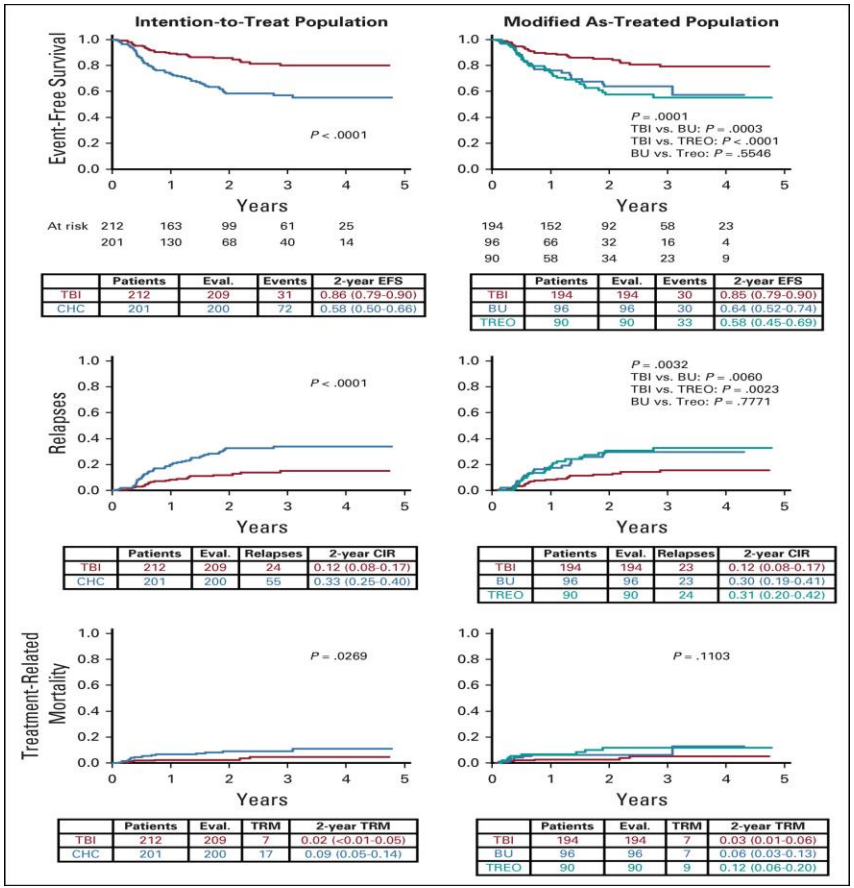


	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

	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.

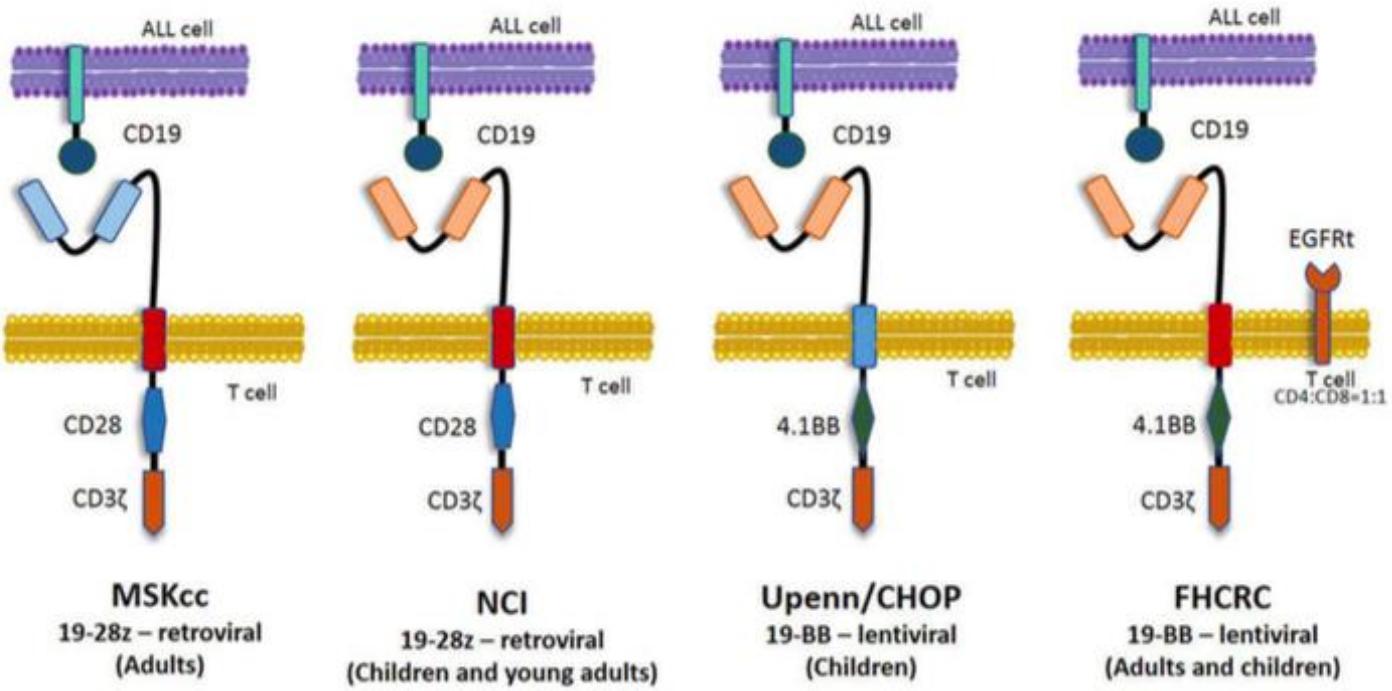
Secondary endpoints



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.

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.

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)

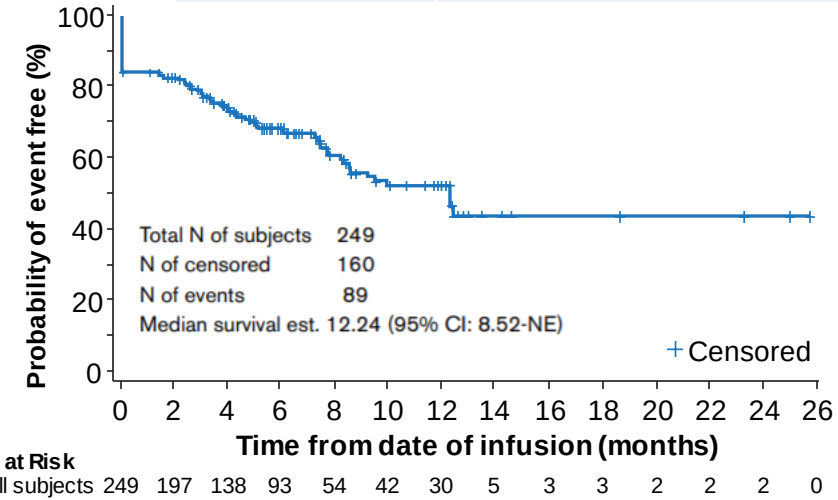
Baseline Characteristic	Pediatric ALL (N = 255)
Prior CNS involvement, n (%)	24 (9.4)
Number of prior therapies, median (range)	3 (0-15)
Prior alloSCT, n (%)	71 (27.8)
Prior blinatumomab, n (%)	38 (14.9)
Prior inotuzumab, n (%)	27 (10.6)
Down syndrome, n (%)	12 (4.7)

- 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

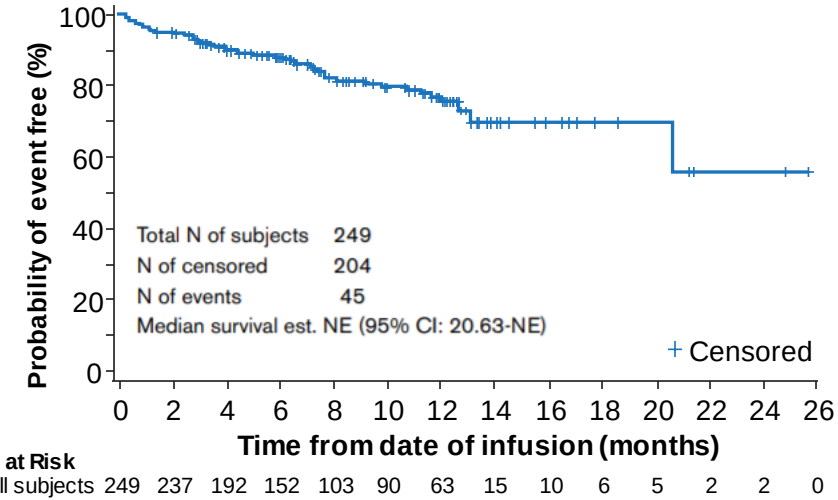
Pasquini MC, et al. *Blood Adv*. 2020;4:5414-5424.

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)



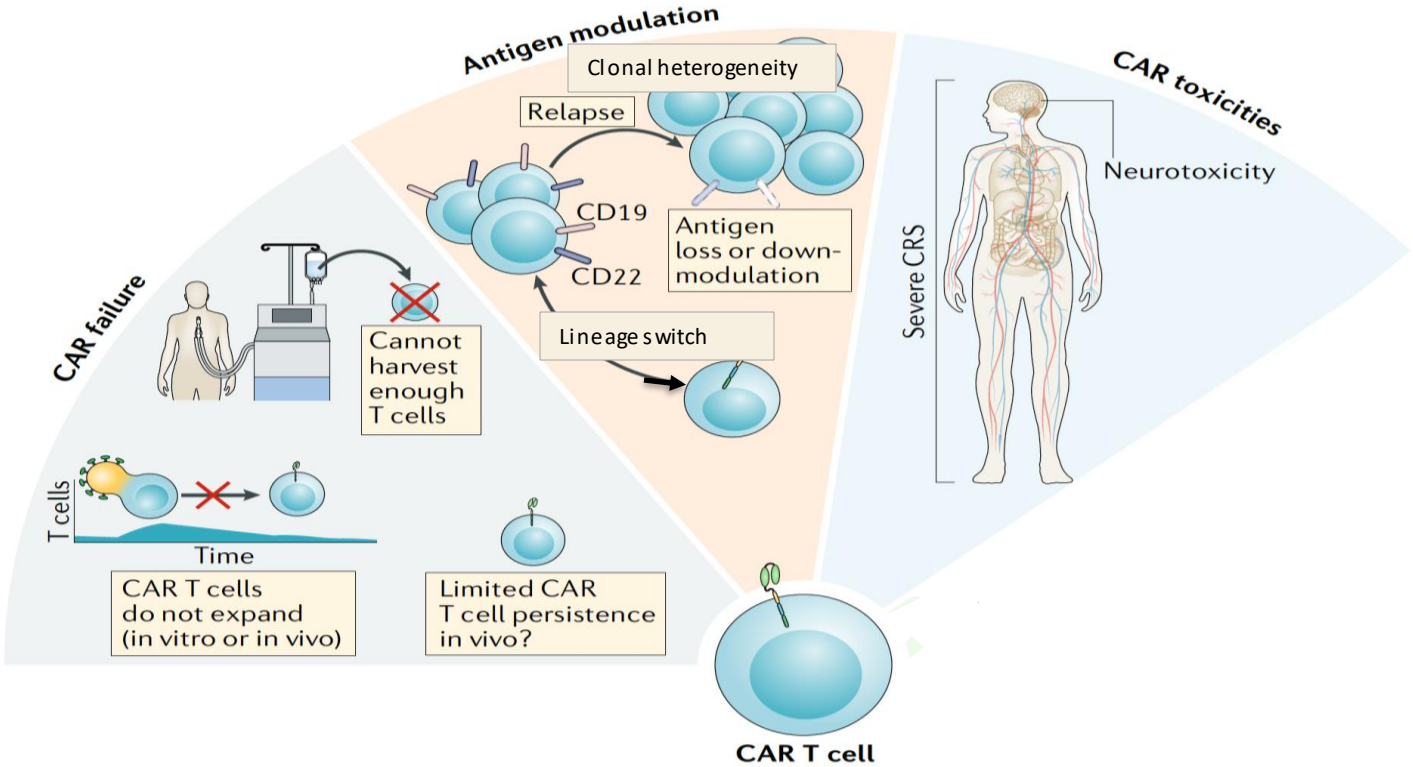
OS Rates Among All Infused Patients, % (95% CI) N = 249	
6 months	88.5 (83.6-92.0)
12 months	77.2 (69.8-83.1)



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

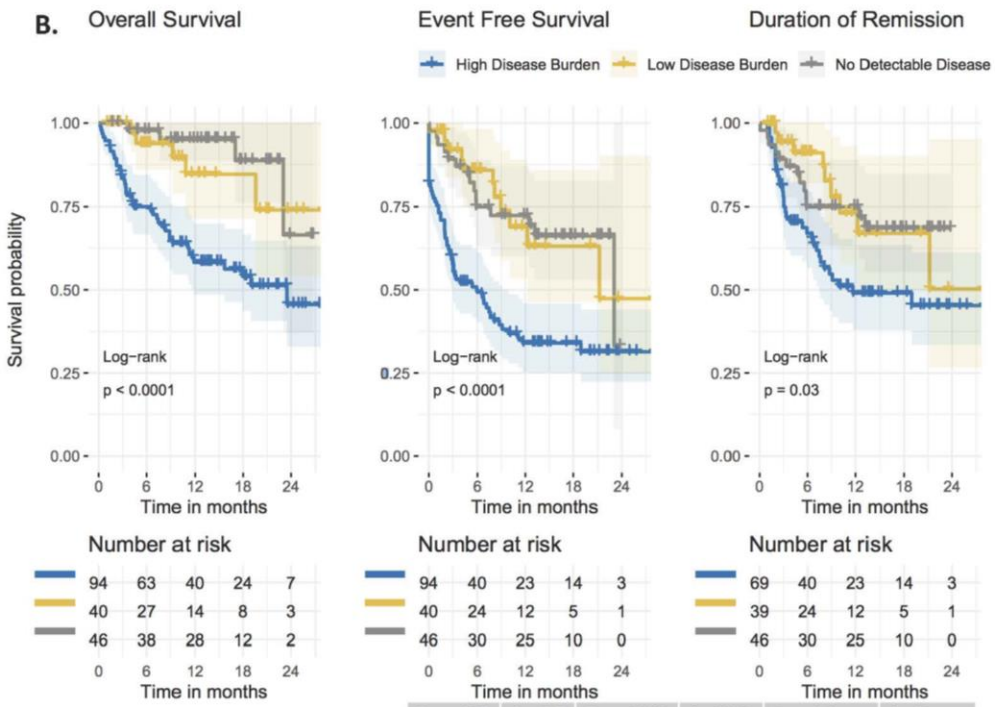
EFS, event-free survival; HSCT, hematopoietic stem cell transplant; OS, overall survival.
Pasquini MC, et al. *Blood Adv*. 2020;4:5414-5424.

Current limitations of CAR T cells



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

Real-world experience with tisagenlecleucel



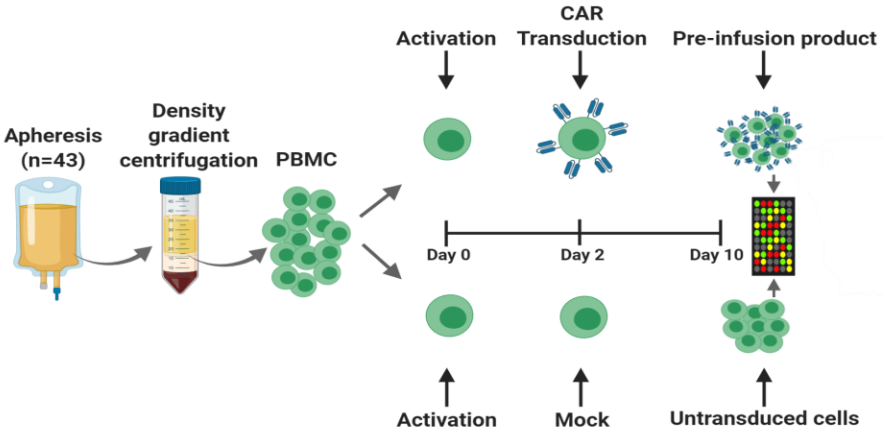
	6mo OS	1y OS	6mo EFS	1y EFS	6mo Drem	1y Drem
High Disease Burden	0.75	0.58	0.50	0.34	0.67	0.49
Low Disease Burden	0.94	0.85	0.86	0.69	0.91	0.73
No Detectable Disease	0.98	0.95	0.75	0.72	0.75	0.75

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

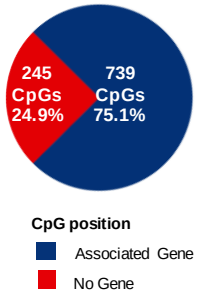
Schultz LM, et al. ASH 2020. Abstract 468.

A specific methylation pattern is identified in CAR-transduced vs untransduced T cells of the patients

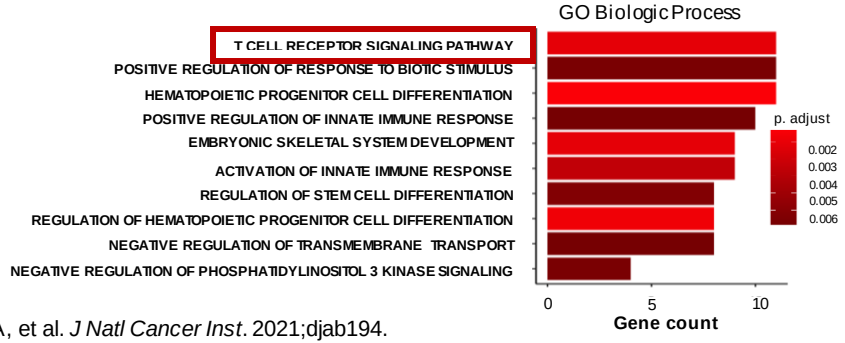
Initial study of the methylation landscape

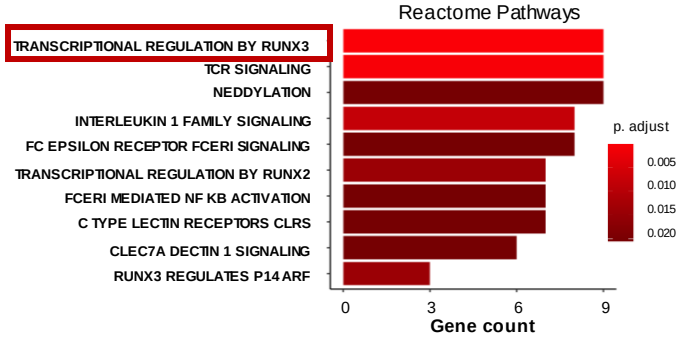


Distribution of CpG sites in the genome



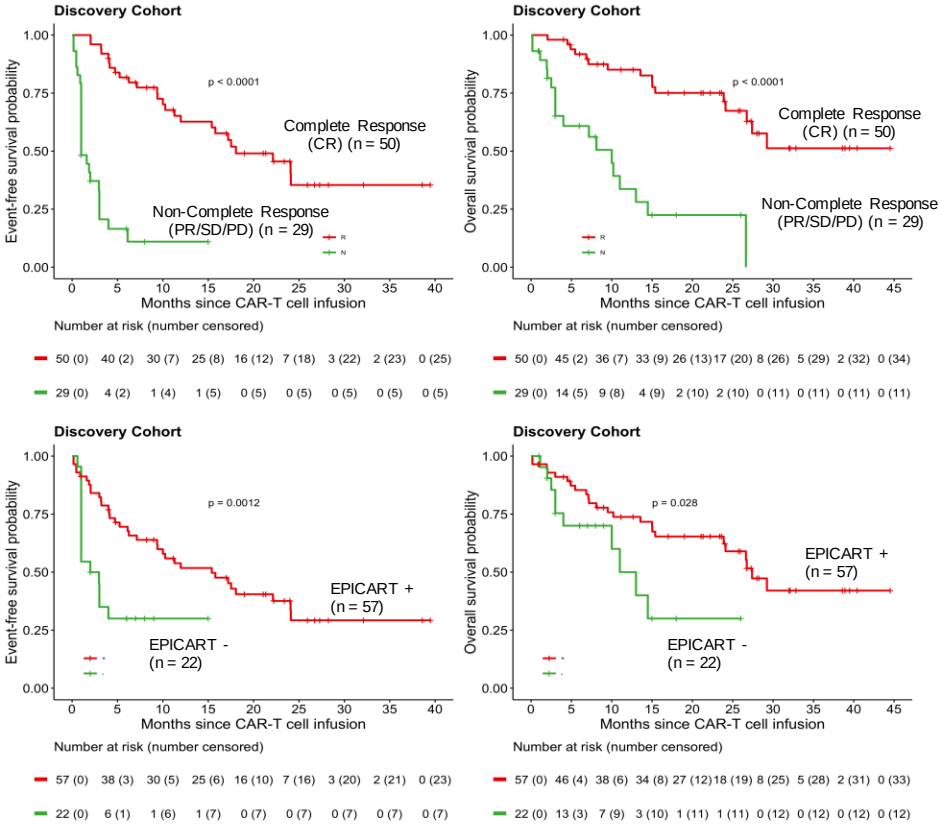
Gene ontology analysis

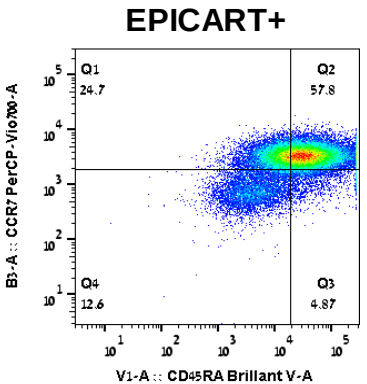


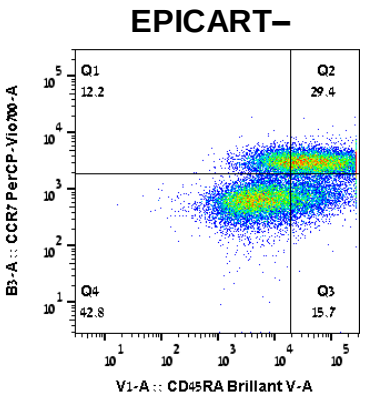


Garcia-Prieto CA, et al. *J Natl Cancer Inst*. 2021;djab194.

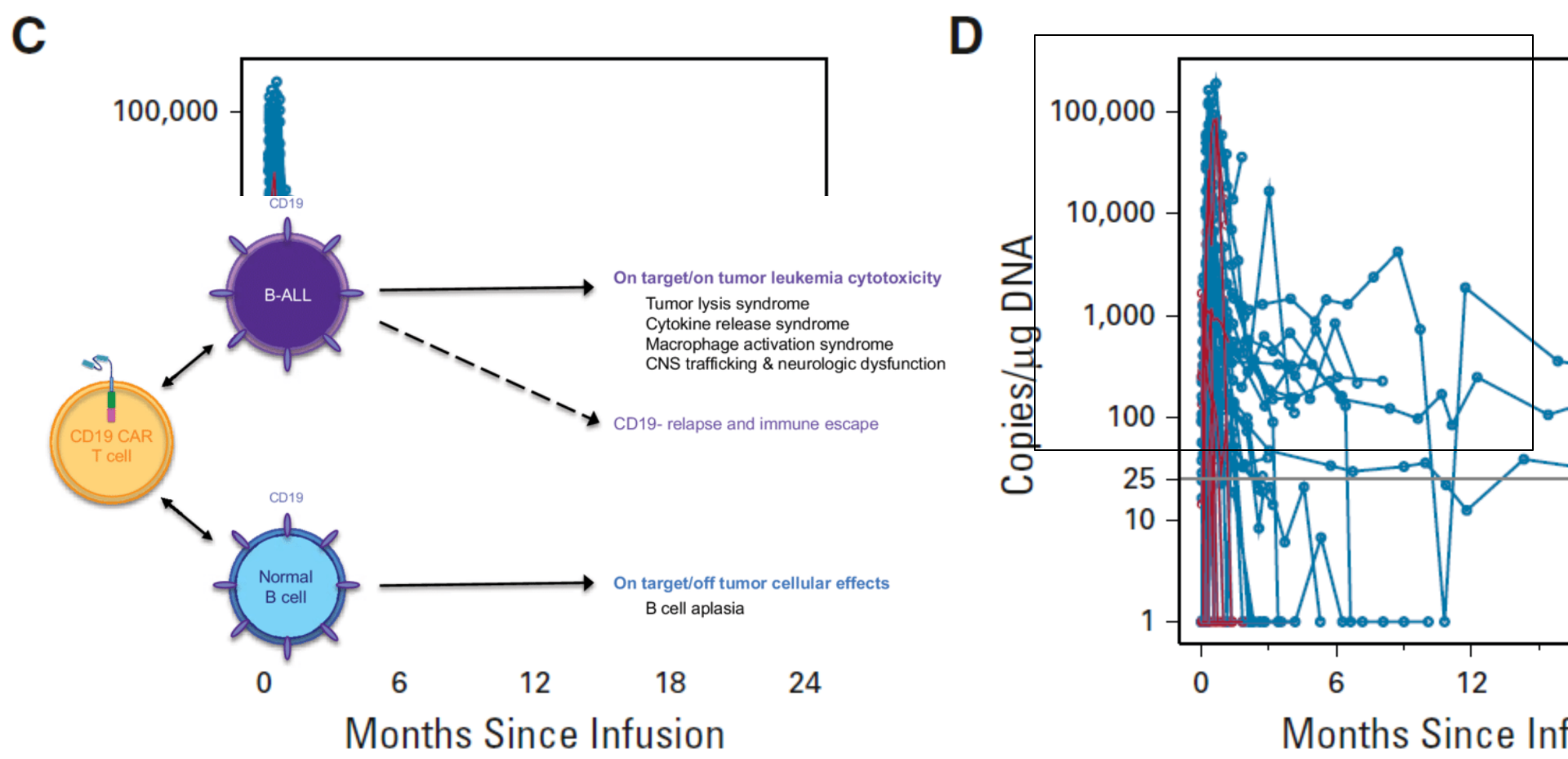
18 specific methylation sites that independently correlate with survival outcomes and a naive-like/early memory phenotype was identified (EPICART signature)







Villaneuva et al. *J Natl Cancer Inst*. 2021. In press.


C
100,000
CD19
B-ALL
On target/on tumor leukemia cytotoxicity
Tumor lysis syndrome
Cytokine release syndrome
Macrophage activation syndrome
CNS trafficking & neurologic dysfunction
CD19- relapse and immune escape
CD19 CAR T cell
CD19
Normal B cell
On target/off tumor cellular effects
B cell aplasia
0
6
12
18
24
Months Since Infusion
D
Copies/µg DNA
100,000
10,000
1,000
100
25
10
1
0
6
12
Months Since Inf


E
1.00
F
1.00

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 × 10^9 total WBC)
	CD4/CD8 enriched cells (20-200 × 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

Patient 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%
	004	M	4	None	ALL 2nd relapse (combined BM+CNS)	Yes	0.6%
DL2	005	M	12	t(1;19)	ALL 1st refractory relapse (combined BM + bone)	No	2.3%
	006	F	13	None	ALL 1st very early relapse (combined BM + bone + lymph nodes)	Yes	10%

Bambino Gesù
OSPEDALE PEDIATRICO

Feasibility and toxicity

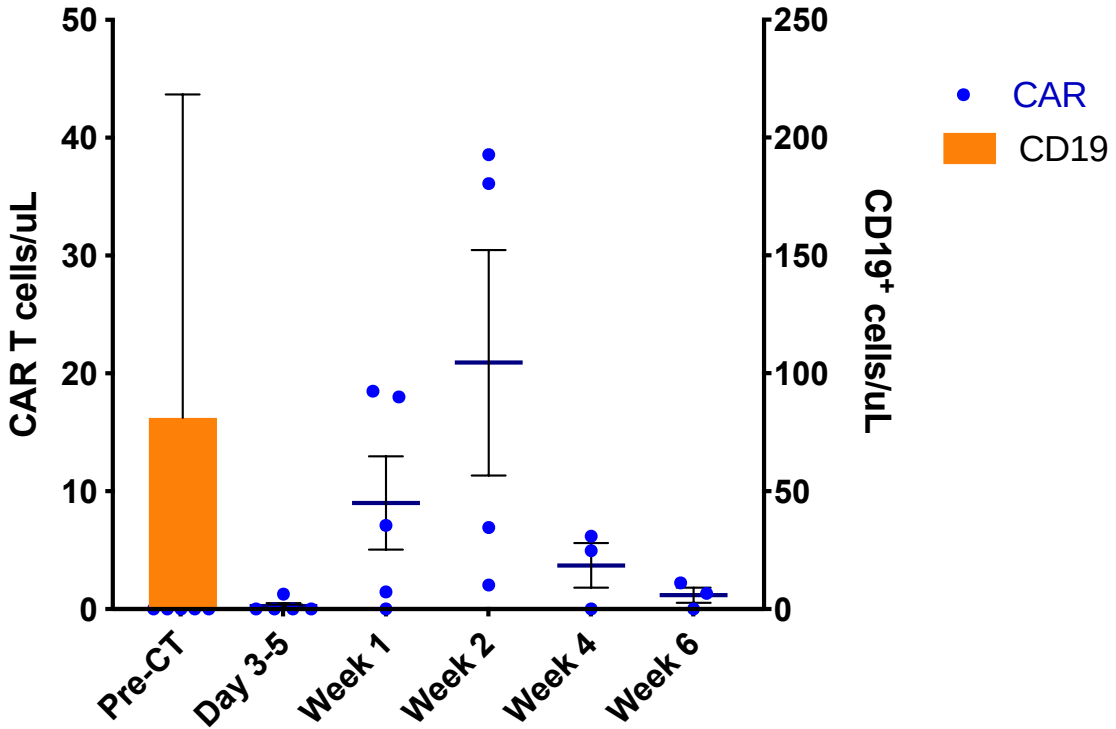
ID	Total Cell End-Production ($\times 10^9$)	Viability	CAR, %
CD19_Lenti-OPBG-001	1.39	89.1 %	55.4%
CD19_Lenti-OPBG-002	4.05	93.8 %	27.4%
CD19_Lenti-OPBG-003	4.62	97.3%	17.5%
CD19_Lenti-OPBG-004	5.36	95.1%	35%
CD19_Lenti-OPBG-005	4.99	97.4%	39%
CD19_Lenti-OPBG-006	4.83	94%	54.8%
AVERAGE	**3.37**	**94.5%**	**38.2%**

Pre-collection counts
- WBC: 200/µL
- Lymphocytes: 150/µL
- $CD3^+$ cells: 120/µL

CRS	4/6
- Grade 1-2	4
- Grade 3	0
- Grade 4	0
Neutropenia	6/6
- Grade 1-2	0
- Grade 3-4	6
Thrombocytopenia	6/6
Anemia	6/6
B-cell aplasia	6/6
Neurotoxicity	2/6

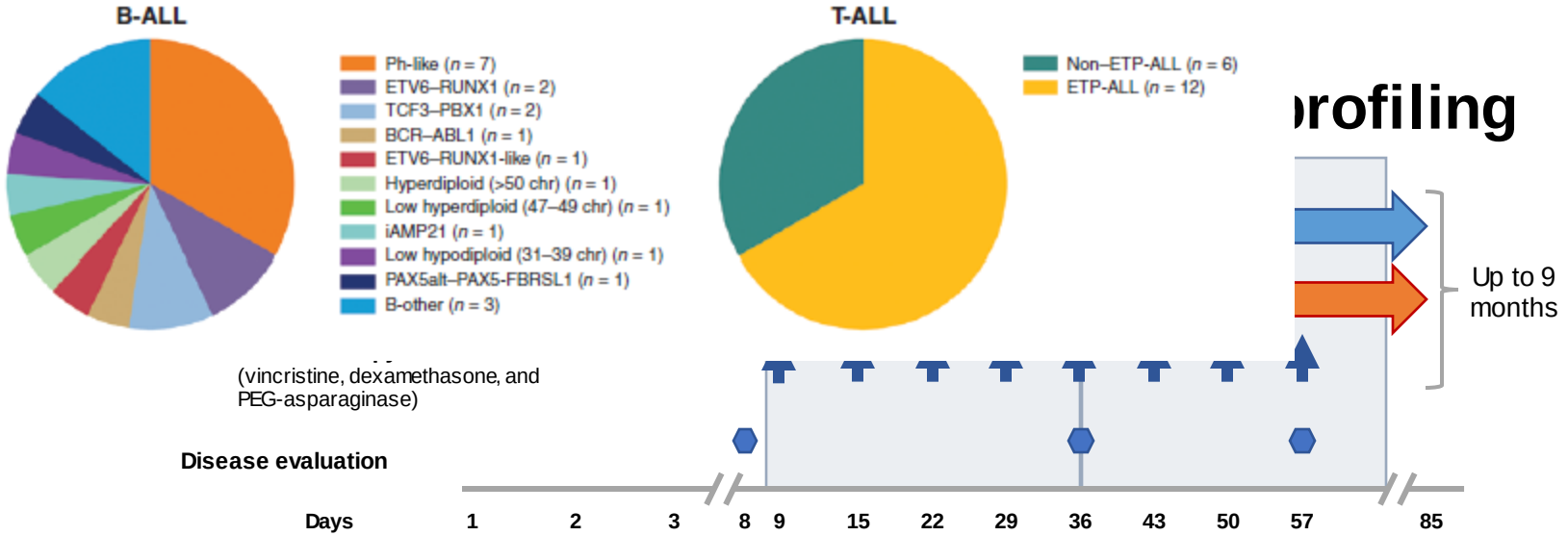
Bambino Gesù
OSPEDALE PEDIATRICO

CAR_Lenti expansion and outcome



All patients obtained CR 2 weeks after infusion

Bambino Gesù
OSPEDALE PEDIATRICO



Outcomes

Primary: safety assessments (including incidence of DLTs and AEs) and pharmacokinetics of venetoclax and navitoclax

Secondary: efficacy assessments (CR rate, PFS, OS) and proportion of patients proceeding to SCT or CAR T-cell therapy

Pullarkat VA, et al. *Cancer Discov.* 2021;11:1440-1453.

Parameter	B-ALL ($n=25$)	T-ALL ($n=19$)	LL ($n=3$)	All patients[a] (N = 47)	Pediatric[a] ($n=12$)
Response[b], *n* (%)					
CR rate (CR/CR_i/CR_p)	16 (64.0)	10 (52.6)	2 (66.7)	28 (59.6)	9 (75.0)
PR	3 (12.0)	0	0	3 (6.4)	1 (8.3)
SD	2 (8.0)	6 (31.6)	0	8 (17.0)	0
PD	4 (16.0)	3 (15.8)	1 (33.3)	8 (17.0)	2 (16.7)
Patients with ALL and morphologic CR at baseline, *n*	*n* = 1	*n* = 4	NA	*n* = 5	*n* = 1
Response, *n* (%)					
CR rate (CR/CR_i/CR_p)	0	3 (75.0)		3 (60.0)	1 (100)
SD	0	1 (25.0)		1 (20.0)	0
NE[c]	1 (100)	0		1 (20.0)	0
DOR[d] in all responders					
n	19	10	2	31	10
Median (95% CI), mo	9.1 (1.4–14.6)	4.2 (0.8–12.3)	NE (NE–NE)	4.2 (2.3–11.5)	3.5 (0.7–3.5)
OS					
Median (95% CI), mo	9.7 (4.0–15.7)	6.6 (3.2–12.5)	NE (2.0–NE)	7.8 (4.0–12.5)	NE (2.0–NE)
12-month (95% CI), %	33.8 (13.7–55.2)	29.7 (10.4–52.2)	66.7 (5.4–94.5)	35.6 (20.9–50.7)	60.8 (25.0–83.6)
Bone marrow MRD, *n* (%)					
MRD negative ($<10^{-4}$)	9 (36.0)	6 (31.6)	1 (33.3)	16 (34.0)	6 (50.0)
MRD positive	10 (40.0)	3 (15.8)	1 (33.3)	14 (29.8)	5 (41.7)
Other[e]	6 (24.0)	10 (52.6)	1 (33.3)	17 (36.2)	1 (8.3)
Proceeded to CAR T-cell therapy or HCT, *n* (%)[f]	8 (32.0)	3 (15.8)	2 (66.7)	13 (27.7)	7 (58.3)

Pullarkat VA, et al. *Cancer Discov.* 2021;11:1440-1453.

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 B-ALL**
- **BiTE, ADC, and CAR T cells were shown to be effective in inducing, consolidating, and maintaining remission in children with B-ALL**
- **Future studies are warranted to more precisely define the role of different immunotherapy options with the respective pros and limitations, also in comparison with the standard of care, still represented by allogeneic HSCT**
- **Patients with T-ALL have much more limited benefit from immunotherapy, and rescue strategy for relapsed patients still represents an unmet medical need**
- **Targeted therapy may represent a valuable option for both BCP-ALL after immunotherapy and for T-ALL**

Global Leukemia Academy

Bispecific T-cell engagers for pediatric ALL

Christina Peters

APTITUDE HEALTH

Question 1

A 2-year-old boy (CD19-ALL/MLL-rearrangement) presents with MRD 10^{-2} 28 days after 3 high-risk blocks and bone marrow hypoplasia.

Would you

a) Give another intensive chemo-block
b) Proceed with allogeneic HSCT with a TBI-containing regimen
c) Start blinatumomab continuous infusion
d) Proceed with allogeneic HSCT with a myeloablative chemo-conditioning regimen
e) Produce CD19 CAR T cells

Question 2

What severe side effect in children is unlikely to be associated with blinatumomab?

a) Hypotension
b) Fever
c) Cytokine release syndrome
d) Encephalopathy
e) Seizures
f) Irreversible bone marrow aplasia

Bispecific T-Cell Engagers for Pediatric ALL

Christina Peters, Medical University Vienna, Vienna, Austria

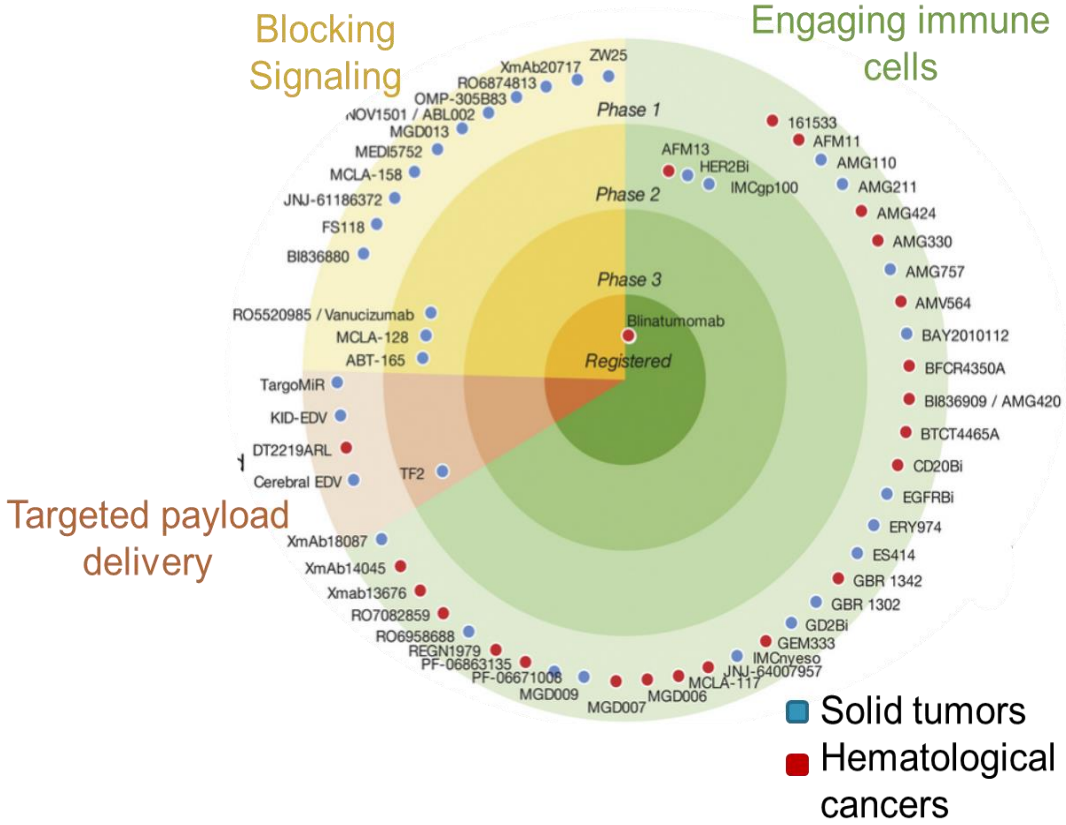
Global Leukemia Academy
27-28 October 2021

Company name	Disclosure
Amgen	Consultancy, honoraria and travel support
Novartis	Consultancy
Jazz	Speakers bureau
Pfizer	Consultancy
Medac	Consultancy
Neovii	Speakers bureau

Bispecific Antibodies in children and AYA: Topics

- Treatment options prior to HSCT
- Special pediatric populations
  - Down Syndrome
  - Infant ALL
  - Patients with risk for severe organ toxicities and/or opportunistic infections
- Treatment options post HSCT

Bispecific Antibodies Today



Frans Suurs, et al. *Pharmacology & Therapeutics*. 2019.

Summary of Blinatumomab Pharmacodynamics

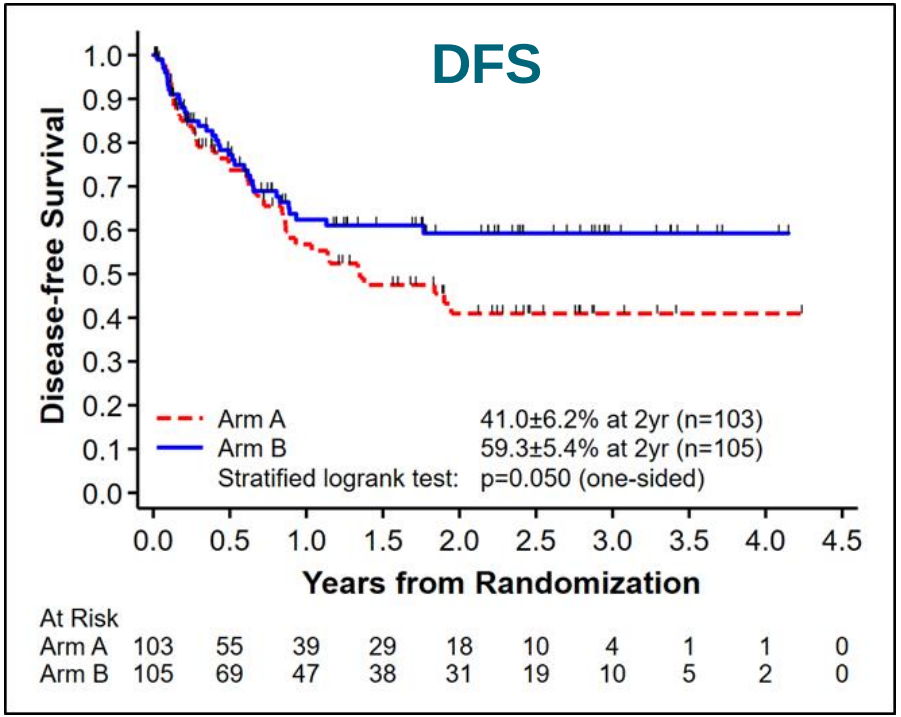
- Blinatumomab cIV infusion leads to rapid depletion of B-cells during Cycle 1, which is associated with decrease in serum immunoglobulin levels[1–3]
- Blinatumomab leads to a transient decrease in T-cell counts, followed by an accelerated recovery[1,3–5]
  - May induce peripheral expansion of T-cell compartment, predominantly effector memory T-cell subsets, above baseline levels
- Blinatumomab induces T-cell activation[1,3,4,6]
  - Associated with cytokine release, mainly in Cycle 1
  - Risk of severe CRS managed by stepped dosing and pre-phase DEX

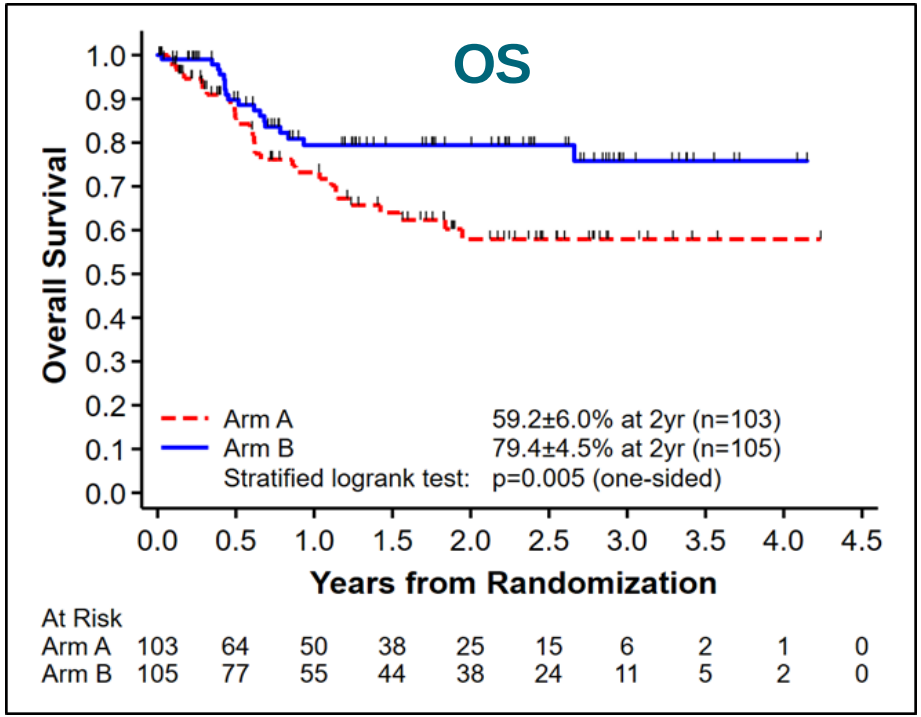
1. Zhu M, et al. *Clin Pharmacokinet.* 2016; 2. Zugmaier G, et al. *Blood Cancer J*. 2014;4:244; 3. Schub A, et al. ASCO 2013. Abstract 7020 and poster presentation; 4. Klinger M, et al. *Blood*. 2012;119:6226-6233; 5. Topp MS, et al. *J Clin Oncol*. 2011;29:2493-2498; 6. Topp MS, et al. *Lancet Oncol*. 2015;16:57-66.

Safety and Adverse Reactions

- **Cytokine release syndrome**
- **Neurological toxicities**
- Infections
- Tumor lysis syndrome
- Neutropenia and febrile neutropenia
- Effects on ability to drive and use machines
- Elevated liver enzymes
- Pancreatitis
- Leukoencephalopathy
- Preparation and administration errors
- Immunization
- **Risk of serious adverse reactions in pediatric patients due to benzyl alcohol (C7H8O) preservative**

ALL 1st Relapse:
Survival: Arm A (Chemotherapy) vs Arm B (Blinatumomab)



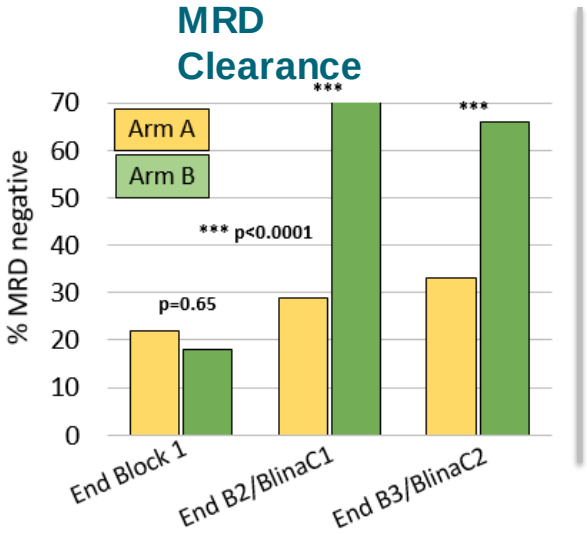


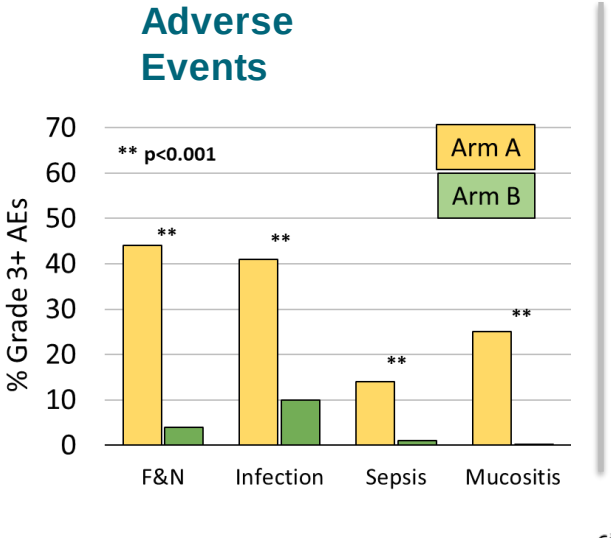
CHILDREN'S ONCOLOGY GROUP

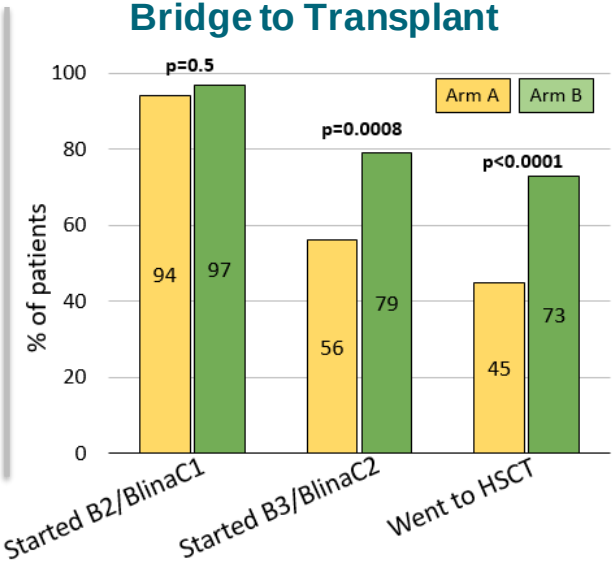
Median follow-up 2.9 years

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

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

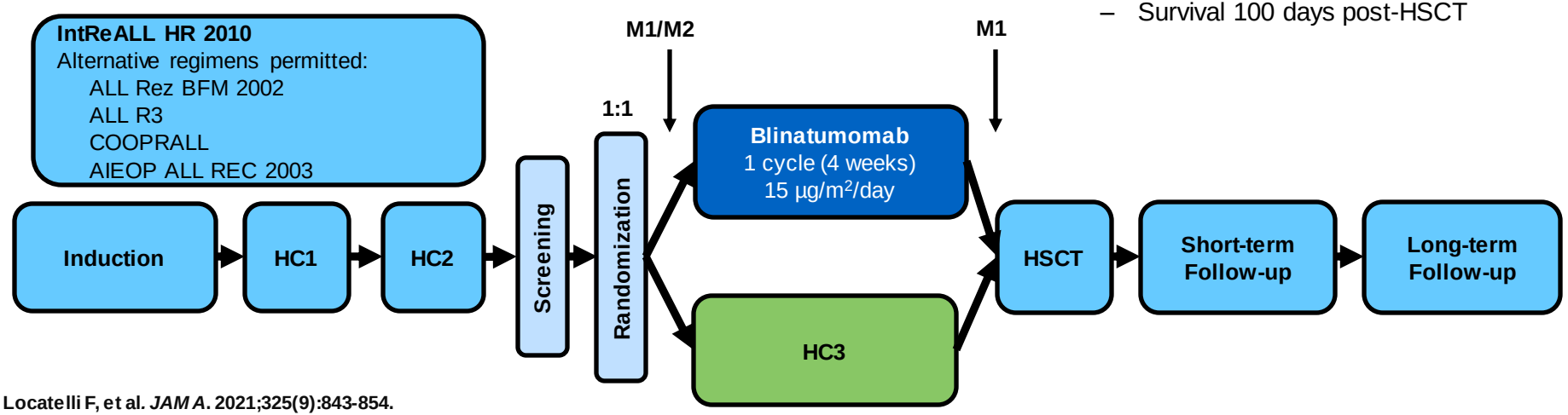
Brown P, et al. *JAMA*. 2021;325(9):833-842.

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 enrolment
- 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

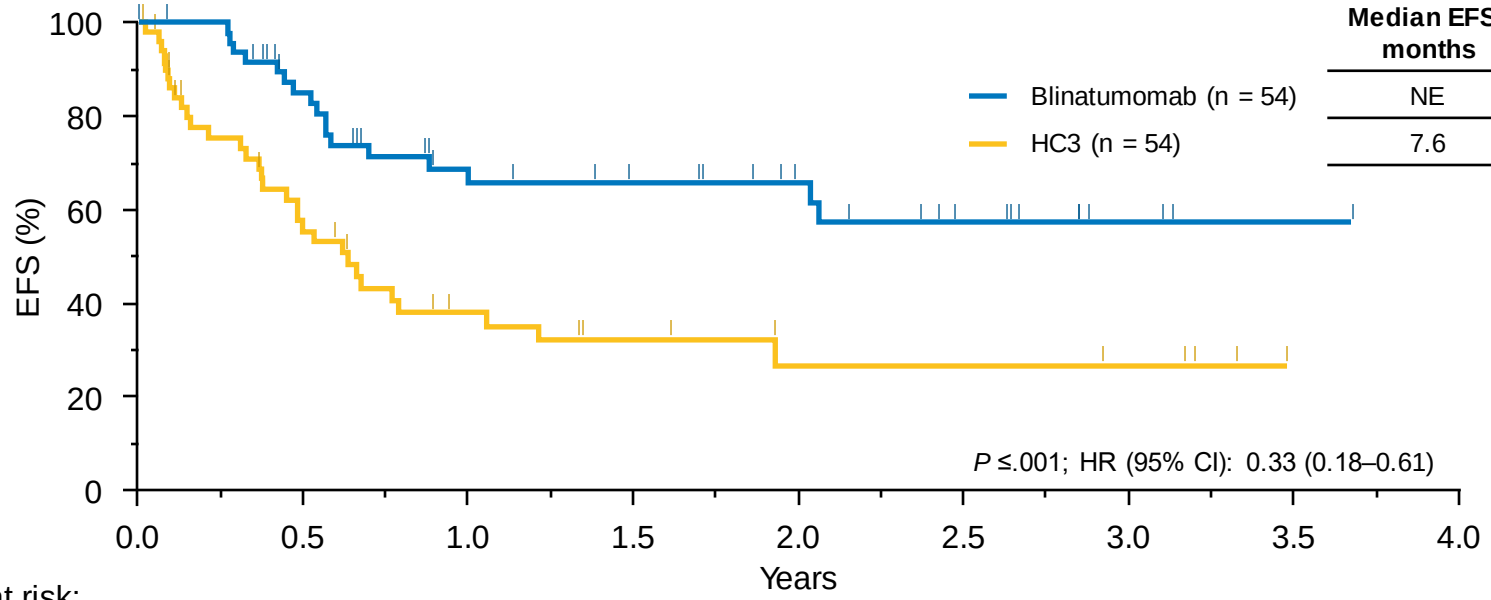
Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post-HSCT



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

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

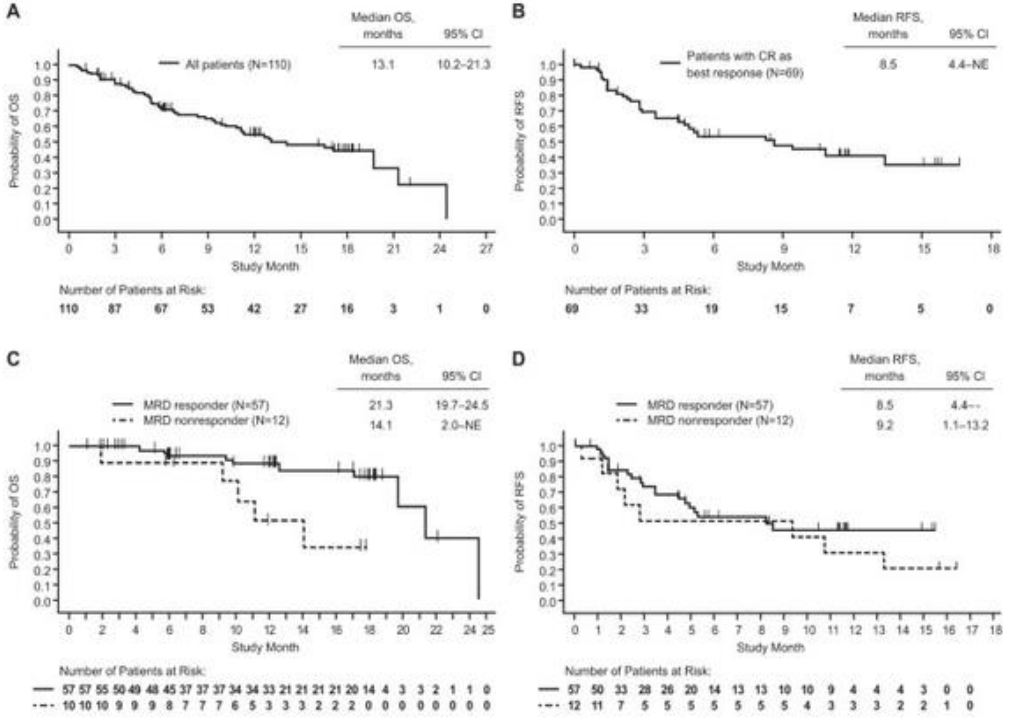
Patients at risk:

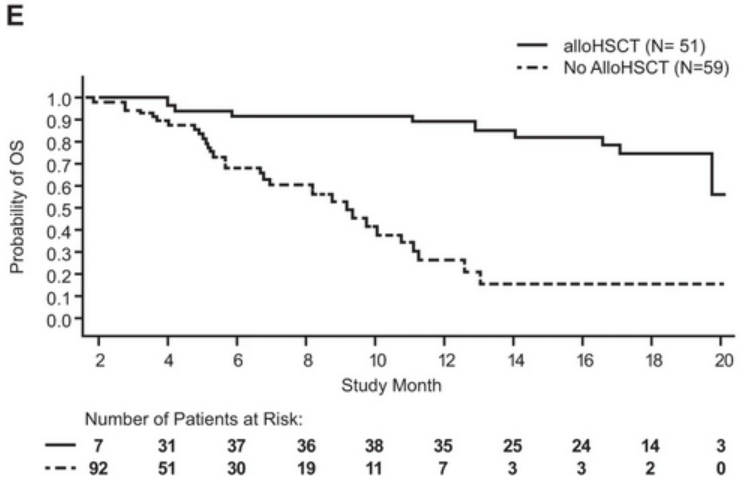
Blinatumomab	54	50	38	29	24	23	21	19	16	13	10	7	4	1	1	0
HC3	54	35	25	17	13	11	9	8	5	5	5	5	4	2	0	

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

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

Blinatumomab Use in Pediatric Patients With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia From an Open-Label, Multicenter, Expanded Access Study (RIALTO)





Locatelli F, et al. *Blood Cancer.* 2020.

Children With Down Syndrome (DS)[1-6]

- Have a greater risk for developing leukemia
- Experience significant adverse effects of chemotherapy
- Increased risk for infection-associated TRM

- Buitenkamp TD, Izraeli S, Zimmermann M, Forestier E, Heerema NA, van den Heuvel-Eibrink MM, Pieters R, Korbijn CM, Silverman LB, Schmiegelow K, Liang DC, Horibe K, Arico M, Biondi A, Basso G, Rabin KR, Schrappe M, Cario G, Mann G, Morak M, Panzer-Grümayer R, Mondelaers V, Lammens T, Cavé H, Stark B, Ganmore I, Moorman AV, Vora A, Hunger SP, Pui CH, Mullighan CG, Manabe A, Escherich G, Kowalczyk JR, Whitlock JA, Zwaan CM. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood.* 2014;123(1):70-77.

- Meissner B, Borkhardt A, Dilloo D, Fuchs D, Friedrich W, Handgretinger R, Peters C, Schrauder A, Schuster FR, Vormoor J, Maecker B, Sykora KW, Zintl F, Welte K, Sauer M. Relapse, not regimen-related toxicity, was the major cause of treatment failure in 11 children with Down syndrome undergoing haematopoietic stem cell transplantation for acute leukaemia. *Bone Marrow Transplant.* 2007;40(10):945-949.

- Hitzler JK, He W, Doyle J, Cairo M, Camitta BM, Chan KW, Diaz Perez MA, Fraser C, Gross TG, Horan JT, Kennedy-Nasser AA, Kitko C, Kurtzberg J, Lehmann L, O'Brien T, Pulsipher MA, Smith FO, Zhang MJ, Eapen M, Carpenter PA; CIBMTR Pediatric Cancer Working Committee. Outcome of transplantation for acute lymphoblastic leukemia in children with Down syndrome. *Pediatr Blood Cancer.* 2014;61(6):1126-1128.
- Wadhwa, A, Kutny, MA, Xavier, AC. Blinatumomab activity in a patient with Down syndrome B-precursor acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2018;65:e26824..

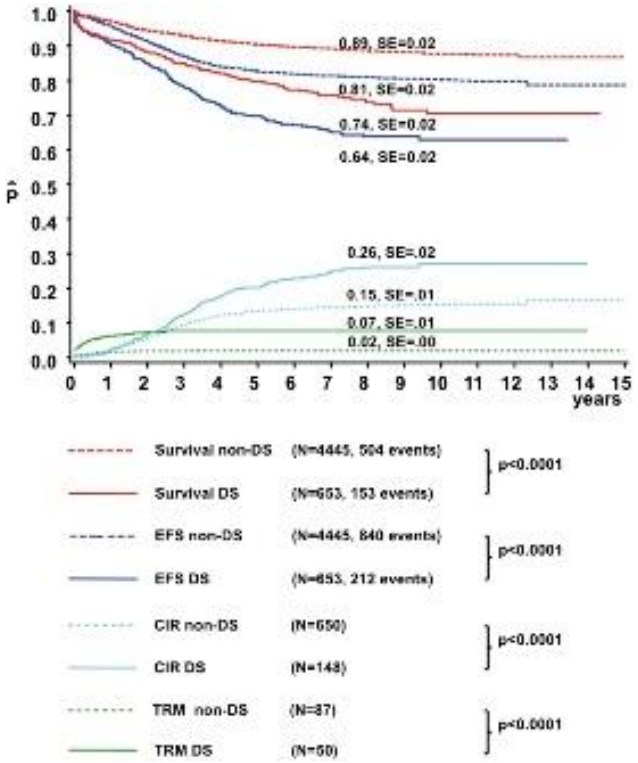


Image: Buitenkamp TD, et al. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood.* 2014;123(1):70-77.

New Trials for Patient With DS and ALL

- A Phase III Trial Investigating Blinatumomab in Combination With Chemotherapy in Patients With Newly Diagnosed Standard Risk or Down Syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients With Localized B-Lymphoblastic Lymphoma (B-LLy): *NCT03914625 (NCI)*
  - Primary Outcome Measure: DFS in randomization eligible patients with higher risk features (SR-High) or standard risk average (SR-Avg) B-ALL patients based on randomization with addition of Blinatumomab
  - Secondary: TRM, Neurocognitive functions, QOL, Caregiver burden, MRD

- Some frontline trials are now enabling DS-patients with high-risk features access to upfront-access with Blinatumomab: NCT03643276 (AIEOP 2017) , NCT04307576 (AllTogether1) and NCT03117751 (TOTAL St. Jude).

Infant ALL: Poorer Outcome Compared With Older Children

- Biology: 80% KMT2A-rearrangement
- Treatment related toxicity: 18.4% in prospective INTERFANT-trial

- Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, Hovi L, LeBlanc T, Szczepanski T, Ferster A, Janka G, Rubnitz J, Silverman L, Stary J, Campbell M, Li CK, Mann G, Suppiah R, Biondi A, Vora A, Valsecchi MG. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet.* 2007;370(9583):240-250.
- Pieters R, De Lorenzo P, Ancliffe P, Aversa LA, Brethon B, Biondi A, Campbell M, Escherich G, Ferster A, Gardner RA, Kotecha RS, Lausen B, Li CK, Locatelli F, Attarbaschi A, Peters C, Rubnitz JE, Silverman LB, Stary J, Szczepanski T, Vora A, Schrappe M, Valsecchi MG. Outcome of Infants Younger Than 1 Year With Acute Lymphoblastic Leukemia Treated With the Interfant-06 Protocol: Results From an International Phase III Randomized Study. *J Clin Oncol.* 2019;37(25):2246-2256

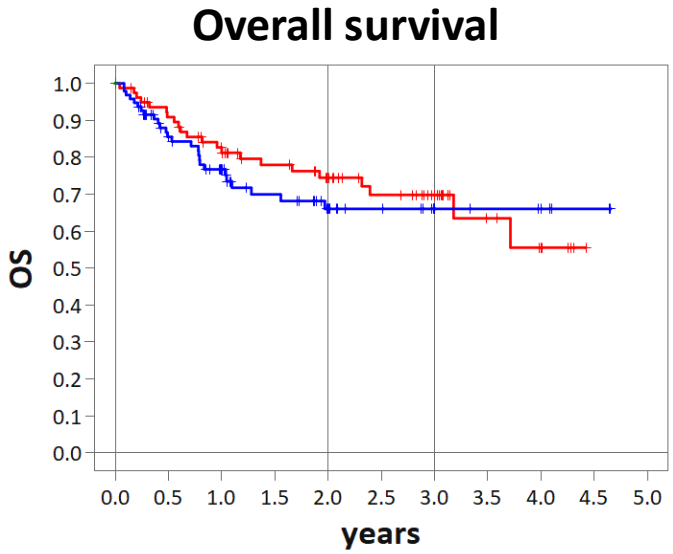
- HSCT with TBI associated with several late effects

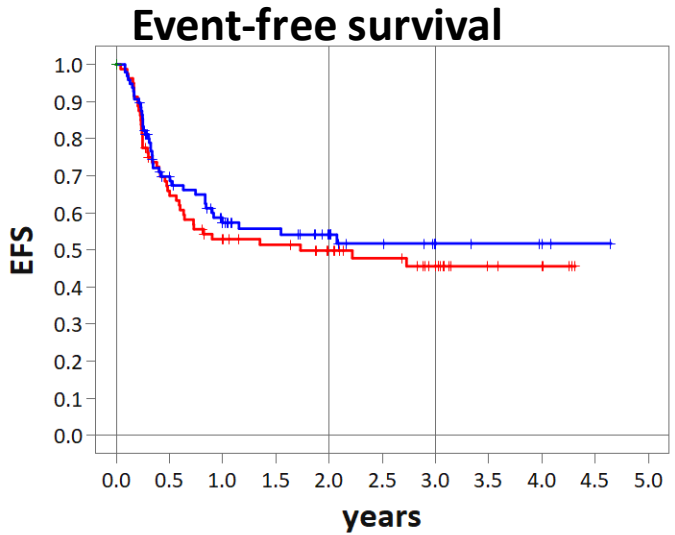
- Sanders JE, Im HJ, Hoffmeister PA, Gooley TA, Woolfrey AE, Carpenter PA, Andrews RG, Bryant EM, Appelbaum FR. Allogeneic hematopoietic cell transplantation for infants with acute lymphoblastic leukemia. *Blood.* 2005;105(9):3749-3756.

- HSCT with chemo-conditioning is associated with higher relapse incidence

- Peters C, Schrappe M, von Stackelberg A, Schrauder A, Bader P, Ebell W, Lang P, Sykora KW, Schrum J, Kremens B, Ehlert K, Albert MH, Meisel R, Matthes-Martin S, Gungor T, Holter W, Strahm B, Gruhn B, Schulz A, Woessmann W, Poetschger U, Zimmermann M, Klingebiel T. Stem-cell transplantation in children with acute lymphoblastic leukemia: A prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. *J Clin Oncol.* 2015;33(11):1265-1274.
- Willasch AM, Peters C, Sedláček P, Dalle JH, Kitra-Roussou V, Yesilipek A, Wachowiak J, Lankester A, Prete A, Hamidieh AA, Ifversen M, Buechner J, Kriván G, Hamladji RM, Diaz-de-Heredia C, Skorobogatova E, Michel G, Locatelli F, Bertaina A, Veys P, Dupont S, Or R, Güngör T, Aleinikova O, Sufliarska S, Sundin M, Rascon J, Kaare A, Nemet D, Fagioli F, Klingebiel TE, Styczynski J, Bierings M, Nagy K, Abecasis M, Afanasyev B, Ansari M, Vettenranta K, Alseraihy A, Chybicka A, Robinson S, Bertrand Y, Kupesiz A, Ghavamzadeh A, Campos A, Pichler H, Dalissier A, Labopin M, Corbacioglu S, Balduzzi A, Galimard JE, Bader P; EBMT Paediatric Diseases Working Party. Myeloablative conditioning for allo-HSCT in pediatric ALL: FTBI or chemotherapy?-A multicenter EBMT-PDWP study. *Bone Marrow Transplant*. 2020;55(8):1540-1551.

MSD/MD<4 yrs.

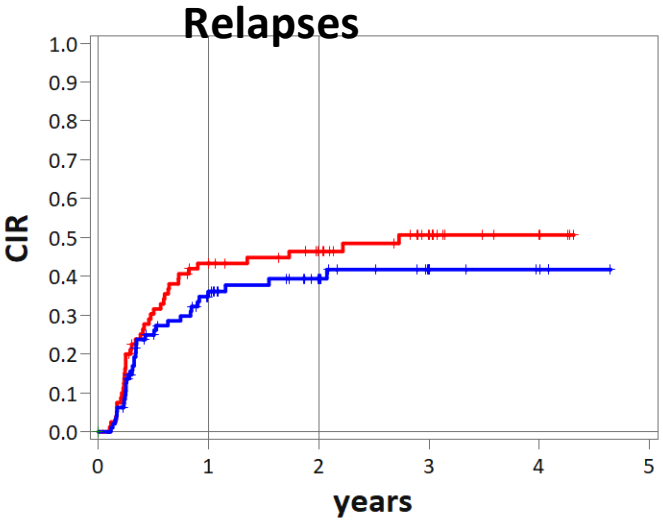


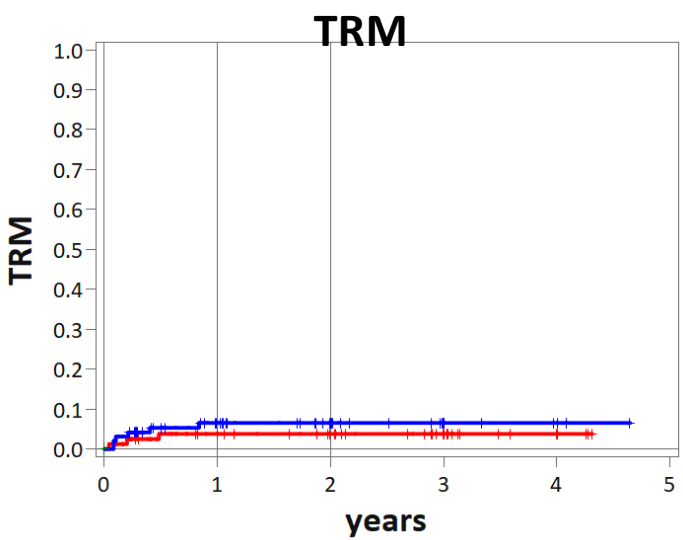


age2	Patients	Events	2-yrs OS	3-yrs. OS	p-value
0-2	86	22	0.74±0.05	0.70±0.06	0.612
2-4	101	26	0.66±0.06	0.66±0.06	.

Events	2-yrs EFS	3-yrs. EFS	p-value
41	0.50±0.06	0.46±0.06	0.472
41	0.54±0.05	0.52±0.06	.

MSD/MD<4 yrs. Flu/Thio/Bu; Flu/Thio/Treo





age2	Patients	n(CIR)	2 years CIR	n(TRM)	2 years TRM	n(Sec. mal)	2 years EFS
0-2	86	38	0.46±0.06	3	0.04±0.02	0	0.50±0.06
2-4	101	35	0.39±0.05	6	0.07±0.03	0	0.54±0.05
P-value	.	.	0.255	.	0.442	.	0.472

Blinatumomab for Infants

- Clesham K, Rao V, Bartram J, Ancliff P, Ghorashian S, O'Connor D, Pavasovic V, Rao A, Samarasinghe S, Cummins M, Malone A, Patrick K, Bonney D, James B, Gibson B, Vora A. Blinatumomab for infant acute lymphoblastic leukemia. *Blood*. 2020;135(17):1501-1504..

- Sutton R, Pozza LD, Khaw SL, Fraser C, Revesz T, Chamberlain J, Mitchell R, Trahair TN, Bateman CM, Venn NC, Law T, Ong E, Heatley SL, McClure BJ, Meyer C, Marschalek R, Henderson MJ, Cross S, White DL, Kotecha RS. Outcomes for Australian children with relapsed/refractory acute lymphoblastic leukaemia treated with blinatumomab. *Pediatr Blood Cancer.* 2021;68(5):e28922.

- Popov A, Fominikh V, Mikhailova E, Shelikhova L, Tsaur G, Abugova Y, Zerkalenkova E, Olshanskaya Y, Balashov D, Novichkova G, Maschan A, Miakova N. Blinatumomab following haematopoietic stem cell transplantation - a novel approach for the treatment of acute lymphoblastic leukaemia in infants. *Br J Haematol.* 2021;194(1):174-178.

- Interfant network: Blinfant protocol: Pilot study - the addition of Blinatumomab to the Interfant-06 backbone in infants with MLL-rearranged acute lymphoblastic leukaemia. EudraCT: 2016-00467417

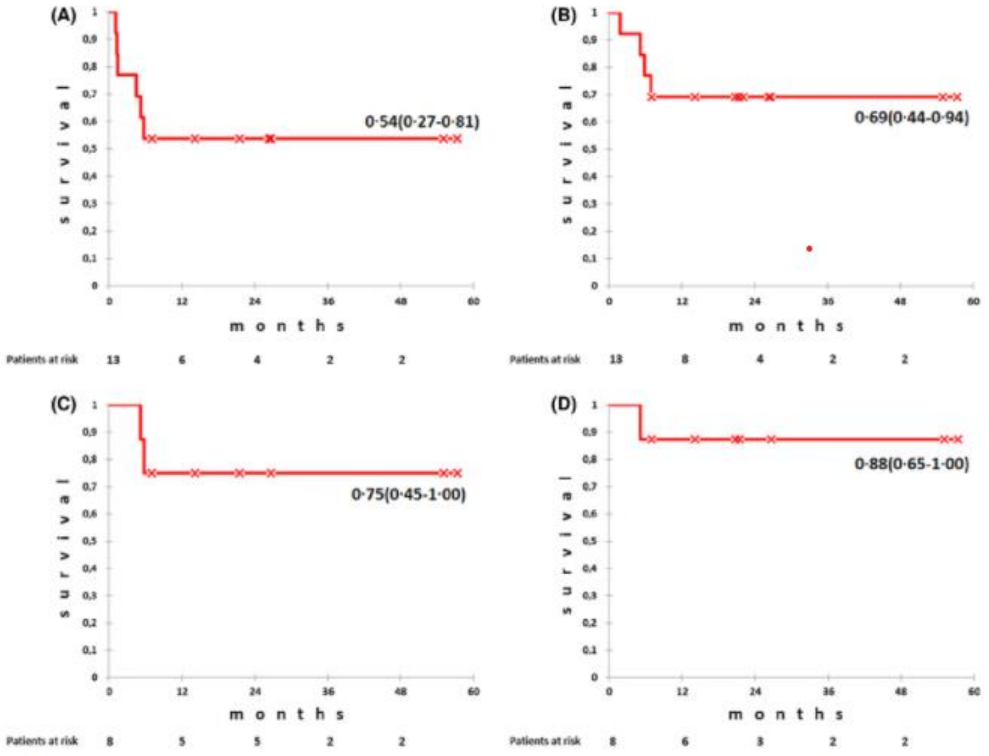


Fig 1. Disease-free survival (panels A and C) and overall survival (panels B and D) of all studied patients (n = 13, panels A and B), as well as of eight infants, who were treated with blinatumomab with subsequent haematopoietic stem cell transplantation in first complete remission because of slow clearance or persistence of multicolour flow cytometry minimal residual disease (MRD) or fusion-gene transcript MRD (panels C and D). The 95% confidential intervals are indicated in parenthesis. Censored patients are marked with ×sign. [Colour figure can be viewed at wiley onlinelibrary.com]

Other Rare Pediatric Conditions

- Minson KA, Prasad P, Vear S, Borinstein S, Ho R, Domm J, Frangoul H. **t(17;19) in Children** with Acute Lymphocytic Leukemia: A Report of 3 Cases and a Review of the Literature. *Case Rep Hematol.* 2013;2013:563291. doi: 10.1155/2013/563291. PMID: 23346431; PMCID: PMC3549381.
- Tambaro FP, Khazal S, Nunez C, Ragoonanan D, Tewari P, Petropoulos D, Kebriaei P, Wierda WG, Mahadeo KM. Complete remission in refractory acute lymphoblastic leukemia using blinatumomab after **failure of response to CD-19 chimeric antigen receptor T-cell therapy**. *Clin Case Rep.* 2020;8(9):1678-1681. doi: 10.1002/ccr3.2918. PMID: 32983475; PMCID: PMC7495807.
- Borriello A, Locasciulli A, Bianco AM, Criscuolo M, Conti V, Grammatico P, Cappellacci S, Zatterale A, Morgese F, Cucciolla V, Delia D, Della Ragione F, Savoia A. A novel Leu153Ser mutation of the **Fanconi anemia** FANCD2 gene is associated with severe chemotherapy toxicity in a pediatric T-cell acute lymphoblastic leukemia. *Leukemia.* 2007;21(1):72-78. doi: 10.1038/sj.leu.2404468. PMID: 17096012.

Blinatumomab After HSCT

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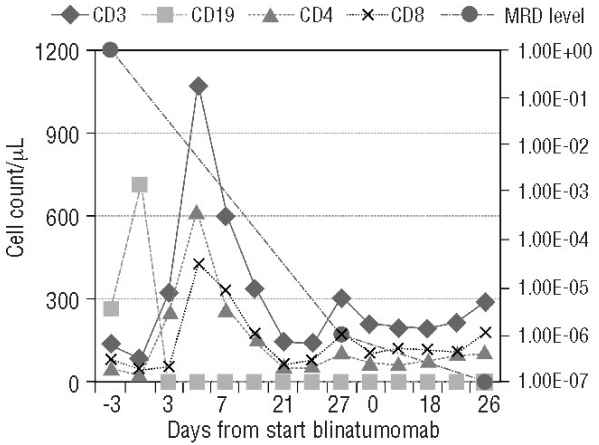
- Schlegel P, Lang P, Zugmaier G, Ebinger M, Kreyenberg H, Witte KE, Feucht J, Pfeiffer M, Teltschik HM, Kyzirakos C, Feuchtinger T, Handgretinger R. Pediatric posttransplant relapsed/refractory B-precursor acute lymphoblastic leukemia shows durable remission by therapy with the T-cell engaging bispecific antibody blinatumomab. *Haematologica.* 2014;99(7):1212-1219.
- Wu H, Cai Z, Shi J, Luo Y, Huang H, Zhao Y. Blinatumomab for HLA loss relapse after haploidentical hematopoietic stem cell transplantation. *Am J Cancer Res.* 2021;11(6):3111-3122.
- Stein AS, Kantarjian H, Gökbuget N, Bargou R, Litzow MR, Rambaldi A, Ribera JM, Zhang A, Zimmerman Z, Zugmaier G, Topp MS. Blinatumomab for Acute Lymphoblastic Leukemia Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2019;25(8):1498-1504.
- Alcharakh M, Yun S, Dong Y, Vincelette ND, Daud M, Manzoor S, Riaz IB, Anwer F. Blinatumomab-induced donor T-cell activation for post-stem cell transplant-relapsed acute CD19-positive biphenotypic leukemia. *Immunotherapy.* 2016;8(8):847-852.
- **Blinatumomab Maintenance Following Allogeneic Hematopoietic Cell Transplantation for Patients With Acute Lymphoblastic Leukemia: (NCT02807883)**
- **Blinatumomab after T-cell receptor (TCR) alpha/beta-depleted HSCT (NCT04746209)**
- **Blinatumomab for MRD in pre-B-ALL patients following HSCT (NCT04044560)**



Allogeneic Stem Cell Transplantation for Children and Adolescents with Acute Lymphoblastic Leukaemia: ALL SCTped FORUM

(For Omitting Radiation Under Majority age)

Christina Peters, Peter Bader, Franco Locatelli
for the Study Group

Multicentre phase II study

Add-on study to ALL SCTped 2012 FORUM (EudraCT number: 2012-003032-22)

A Phase II Study of Blincyto in Children with CD19+ precursor B-lineage ALL and MRD-Positivity before and/or following first allogeneic HSCT in second remission

International treatment protocol

Investigator-Sponsored Study Proposal: Synopsis

- Indication for first allogeneic HSCT: CD19+ ALL in first, second, > second remission
- Inclusion criteria
  - Age: ≥0.5 years and ≤21 years of age
  - Confirmed CD19+ disease prior to enrollment on study
- Exclusion criteria
  - Patients with recent episode of seizures or posterior reversible encephalopathy syndrome in the past 30 days
- Patients must be at least ≥60 days post-SCT without evidence of grade 2 or higher acute GVHD and no steroid use. Withdrawal of immunosuppression will be allowed. The dose of blinatumomab used in this trial will be 15 mcg/m^2/day for 28 days (starting with 5 mcg/m^2/day)
- The study drug will be provided by AMGEN and will be directly distributed to the European study sites. Decentral study visits and lab investigations if study site is experienced with Blincyto-treatment
- Documentation, data collection, and central monitoring vial FORUM-Marvin
- Study aims: (to be amended?)
  - To assess the feasibility of administering blinatumomab post SCT
  - To define and describe the toxicities of blinatumomab when given in the peri-SCT setting
  - To estimate the 6-month event-free survival (EFS) rate
  - To evaluate the 1-year overall survival rate

Conclusions

- Blinatumomab is approved in Europe for pediatric patients >1 year or older with R/R Ph-negative CD19-positive B-precursor ALL
- Prospective randomized trials show superior survival compared with intensive chemotherapy
- The toxicity profile is less severe than that observed with contemporary chemotherapy
- Extremely vulnerable ALL patients such as patients with Down syndrome and infants and patients with chromosomal breakage syndromes might benefit from bispecific antibody treatment
- Pre-emptive therapy might reduce relapse-risk after hematopoietic stem-cell transplantation without increasing graft-vs-host disease
- Bispecific monoclonal antibodies might replace toxic chemotherapy for different conditions in pediatric leukemia

Repeated Question 1

A 2-year-old boy (CD19-ALL/MLL-rearrangement) presents with MRD 10^{-2} 28 days after 3 high-risk blocks and bone marrow hypoplasia.

Would you

a) Give another intensive chemo-block
b) Proceed with allogeneic HSCT with a TBI-containing regimen
c) Start blinatumomab continuous infusion
d) Proceed with allogeneic HSCT with a myeloablative chemo-conditioning regimen
e) Produce CD19 CAR T cells

Repeated Question 2

What severe side effect in children is unlikely to be associated with blinatumomab?

a) Hypotension
b) Fever
c) Cytokine release syndrome
d) Encephalopathy
e) Seizures
f) Irreversible bone marrow aplasia

Global Leukemia Academy

Q&A session

APTITUDE HEALTH

Global Leukemia Academy

Case-based panel discussion – management of long- and short-term toxicities in pediatric ALL patients

Presenters: Francesca Del Bufalo, Natalia Zubarovskaya

Faculty panel: Rob Pieters, Franco Locatelli, Patrick Brown, Christina Peters, Martin Schrappe

APTITUDE HEALTH

Global Leukemia Academy

Management of long- and short-term toxicities in pediatric ALL patients – case 1

Francesca Del Bufalo

APTITUDE HEALTH

CRS management in pediatric ALL

Case presentation

Francesca del Bufalo, MD
IRCCS Bambino Gesù Children's Hospital, Rome, Italy

Bambino Gesù
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DISCLOSURES

No relevant disclosures

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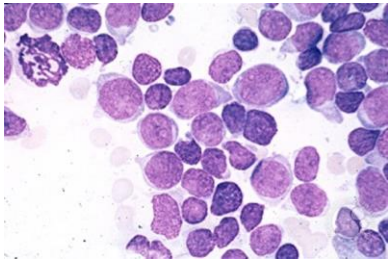
Medical history



- 5-year-old boy
- Diagnosis of BCP-LLA, t(12;21) in December 2013
- First-line treatment according to the AIEOP-BFM ALL 2009 international protocol – intermediate risk (TP1 and TP2 response)
- Stop therapy: December 2015
- First combined relapse (BM + testicles + CNS): February 2016
- Bilateral orchiectomy + enrollment in the first-relapse protocol IntReALL SR 2010, arm B

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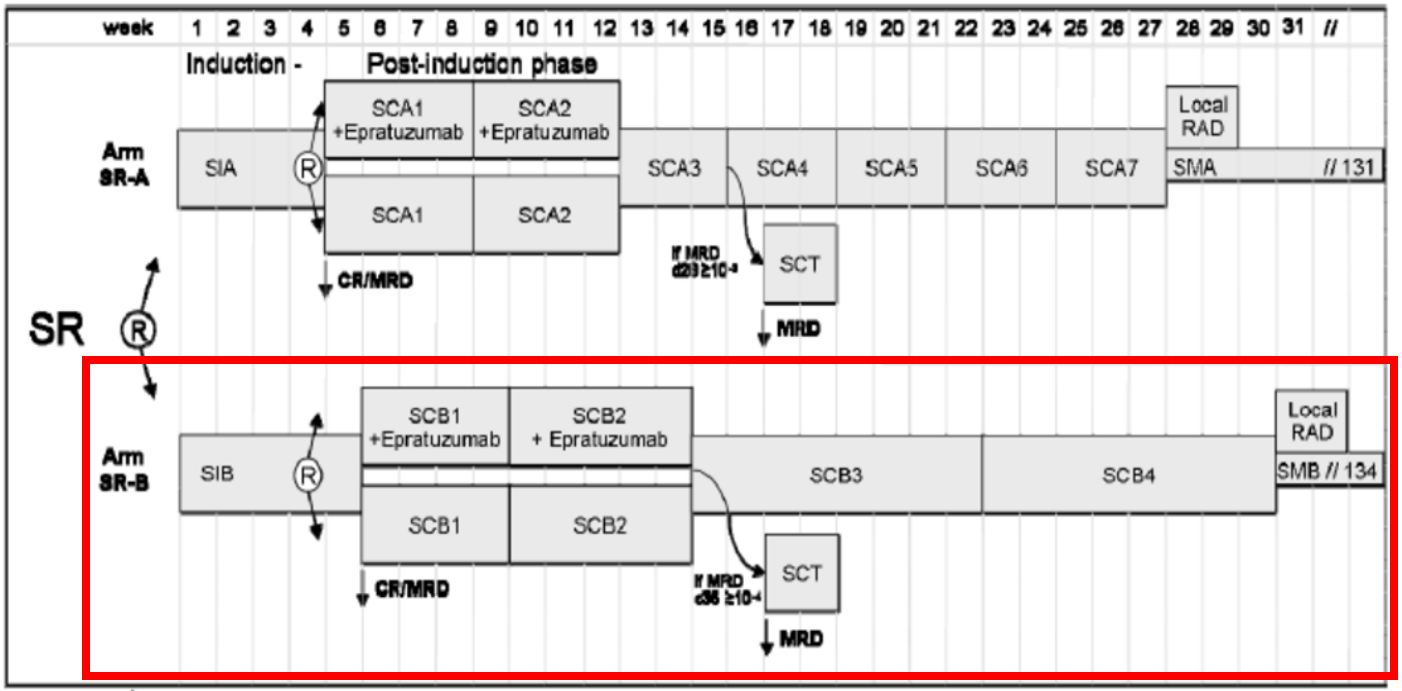
IntReALL SR 2010, Arm B

2 TREATMENT SCHEDULE INTREALL SR 2010



.Arrow down (↓), bone marrow puncture with CR/MRD assessment; CNS-RAD, irradiation of the central nervous system, if indicated; CR, cytological remission; MRD, minimal residual disease; SIA ALL-REZ BFM induction course; SCA 1-7 ALL-REZ BFM consolidation courses; ®, randomization; SIB, UK-R3 induction courses; SCB 1-4 UK-R3 consolidation / intensification courses; SCT, stem-cell transplantation; SR, standard risk group.

Medical history

- Second, CNS-isolated relapse → rescue chemotherapy (intratecal and systemic) + allogeneic HSCT (June 2017)
- Subsequently, third CNS and bone marrow relapse

→ Enrollment in the academic clinical trial CD19-CAR01 (phase I, DL3: 3 × 10^6 CAR+ cells/kg patient body weight)

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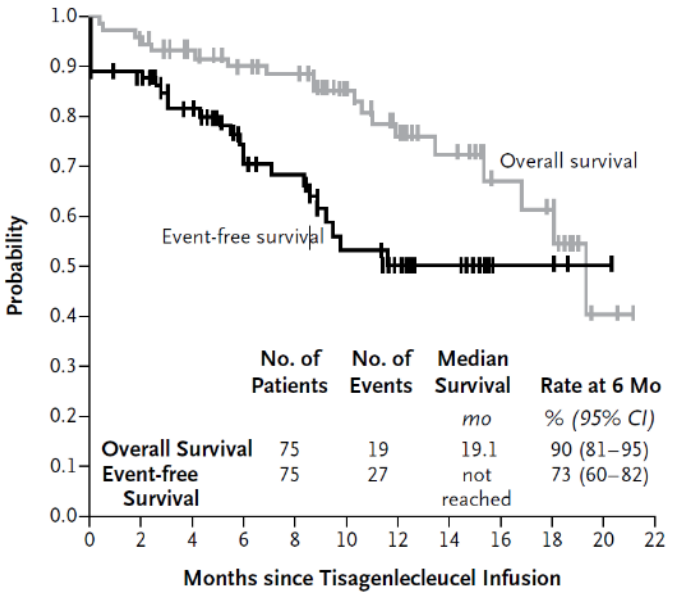
CAR T cells for R/R ALL: Summary of ELIANA study

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%
- Demonstrates feasibility of delivery in multiple centers
- **FDA approval for R/R pediatric ALL: August 2017**



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

Monitoring after CAR T-cell infusion

- From day 0: Severe cytopenia
- D +3: Persistent fever (T >39°C)

10-year-old boy with R/R ALL, fever, and severe cytopenia on day +3 after CAR T-cell infusion

Question

What is the approriate initial management for this case?

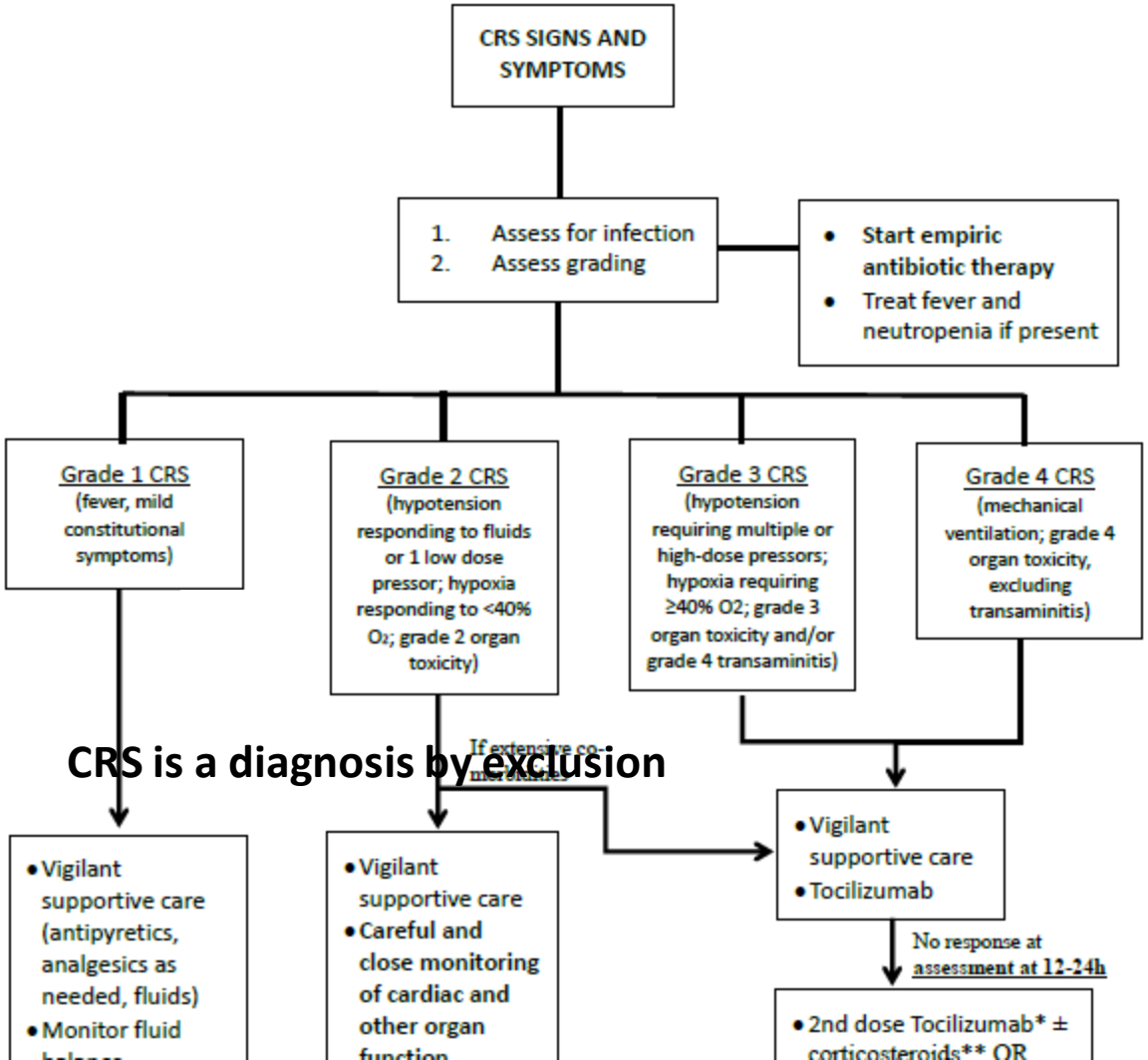
a) Administer steroids

b) Close observation, wide microbiologic screening, empiric antibiotic therapy, management of symptoms (paracetamol, fluids . . .); keep tocilizumab available in the unit

c) Administer tocilizumab

d) Transfer to ICU

ent guidelines

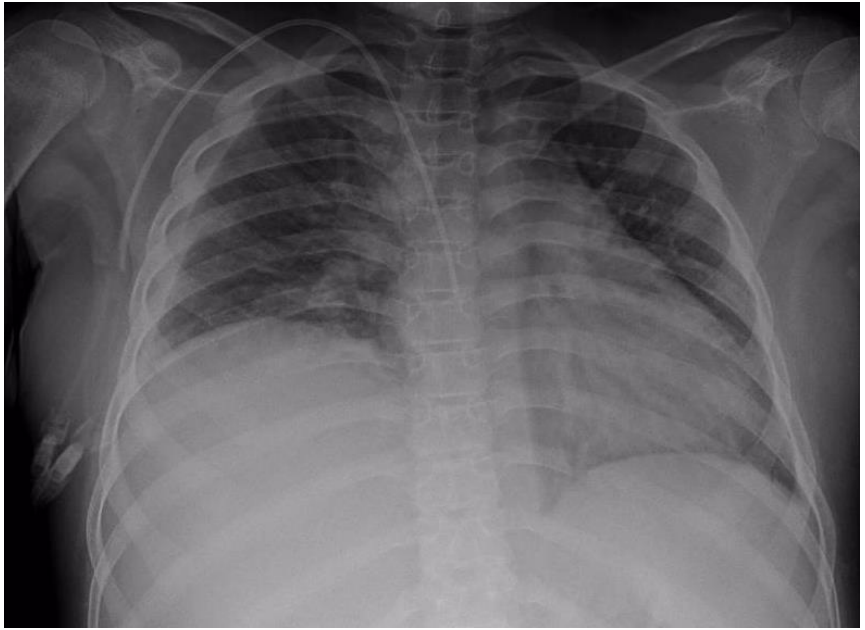


CRS is a diagnosis by exclusion

Lee DW et al. Blood 2014

Monitoring after CAR T-cell infusion

- From day 0: Severe cytopenia
- D +3: Persistent fever (T >39°C)
  → Empiric antibiotic therapy
  →Negative wide microbiologic screening
  →**Grade 1 CRS**
- D +5: Hypotension despite IV fluids, initial dyspnea



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10-year-old boy with R/R ALL, CRS on day +5 after CAR T-cell infusion, and development of hypotension and low oxygen saturation

Question

What is the grade of CRS and the relative management at this point?

a) Grade 2; administer steroids

b) Grade 1; close observation, wide microbiologic screening, empiric antibiotic therapy, management of symptoms (paracetamol, fluids...)

c) Grade 4; administer tocilizumab

d) Grade 2; start of vasopressors, administration of oxygen, and evaluation with the ICU team, administer tocilizumab

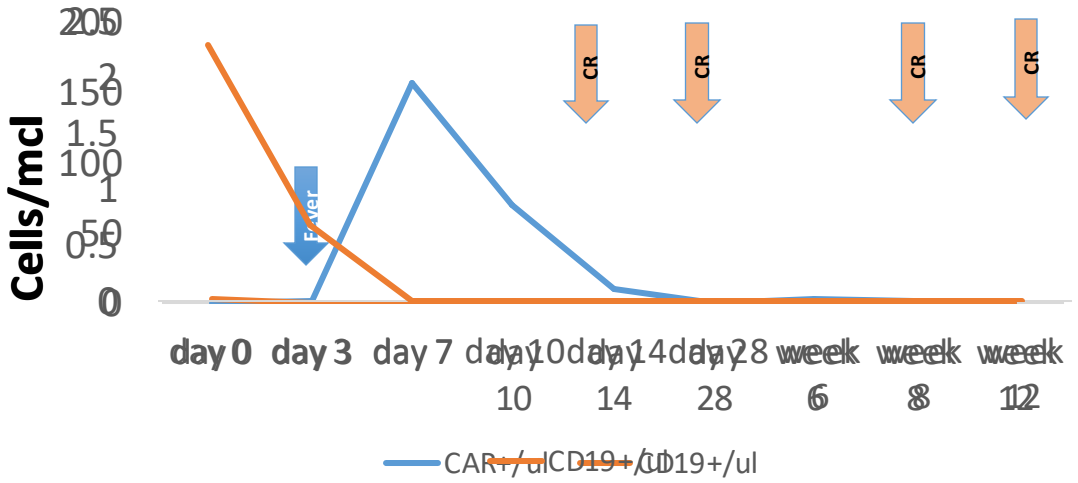
Table 2 | **Cytokine-release syndrome grading and management**

Grade 1 CRS	Grade 2 CRS	Grade 3 CRS	Grade 4 CRS
Signs and symptoms			
• Temperature ≥38 °C • No hypotension • No hypoxia • Grade ≤1 organ toxicity[a]	Any temperature and any of the following: • Hypotension that responds to i.v. fluids or low-dose vasopressor treatment • SpO_2 <90% on room air: FiO_2 requirement <40% to keep SpO_2 >88% • Grade 2 organ toxicity[a]	Any temperature and any of the following: • Hypotension (age 1–10 years: SBP <(70 + (2 × age in years)) mmHg; age >10 years: SBP <90 mmHg) requiring high-dose or multiple vasopressors • FiO_2 requirement ≥40% and/or requiring BiPAP to keep SpO_2 >88% • Grade 3 organ toxicity[a] • Grade 4 transaminitis (>20× ULN)	Any temperature and any of the following: • Persistent hypotension despite fluid resuscitation and treatment with multiple vasopressors • Requirement for invasive mechanical ventilation • Grade 4 organ toxicity[a] (except grade 4 transaminitis)
Paediatric considerations			
• Asymptomatic sinus tachycardia is defined by heart rates above the age-specific normal range or baseline values)	• Hypotension is defined as follows: SBP <(70 + (2 × age in years)) mmHg in patients aged 1–10 years; SBP <90 mmHg in patients aged >10 years	• Oliguria is defined as a urine output of <0.5 ml/kg per hour for 8 hours	• Anuria is defined as a urine output of <0.3 ml/kg per hour for 24 hours or 0 ml/kg per hour for 12 hours
Management			
• Acetaminophen, as needed, for fever • Evaluate for infectious aetiologies (blood and urine cultures and chest radiography) • Consider broad-spectrum antibiotics and filgrastim (if patient is neutropenic) • Assess for adequate hydration • Consider anti-IL-6 therapy for persistent or refractory fever[b]	• Manage according to recommendations for grade 1 CRS (if applicable) • Administer i.v. fluid bolus of 10–20 ml/kg normal saline; repeat as necessary to maintain SBP above baseline or age-specific normal range • For hypotension refractory to fluid boluses or hypoxia, consider anti-IL-6 therapy with i.v. tocilizumab (12 mg/kg for patients weighing <30 kg or 8 mg/kg for those weighing ≥30 kg, to a maximum of 800 mg per dose); repeat dose every 8 hours for up to 3 doses within 24 hours (but titrate frequency according to response)	• Manage according to recommendations for grades 1 and 2 CRS • Transfer patient to PICU and obtain echocardiogram, if not performed already • Administer i.v. dexamethasone 0.5 mg/kg (maximum 10 mg per dose) every 6 hours; can increase dose to maximum of 20 mg every 6 hours if patient is refractory to lower dose (alternatively, methylprednisolone 1–2 mg/kg per day divided	• Administer i.v. fluids, anti-IL-6 therapy, corticosteroids, and vasopressors and perform haemodynamic monitoring as described for grades 1, 2, or 3 CRS • If low doses of corticosteroids do not lead to clinical improvement, consider high-dose methylprednisolone (1 g daily for 3 days followed by rapid taper on the basis of

nes

Monitoring after CAR T-cell infusion

- From day 0: Severe cytopenia
- D +3: Persistent fever (T >39°C)
  - → Empiric antibiotic therapy
  - → Negative wide microbiologic screening
  - → **Grade 1 CRS**
- D +5: Hypotension despite IV fluids
  - → **Grade 2 CRS**
  - → Tocilizumab (8 mg/kg)
  - → Dopamine (6 µg/kg/min)
  - → Low-flow nasal cannulae
  - → Daily monitoring together with ICU team
- D +10: Disappearance of the fever and improvement of BP
  - → Decrease of dopamine (3 µg/kg/min) until withdrwal on d +12



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Thank you!

Global Leukemia Academy

Discussion – case 1

Faculty panel: Rob Pieters, Franco Locatelli, Patrick Brown, Christina Peters, Martin Schrappe

APTITUDE HEALTH

Global Leukemia Academy

Management of long- and short-term toxicities in pediatric ALL patients – case 2

Natalia Zubarovskaya

APTITUDE HEALTH

Patient case

16 y/o female

Diagnosed with B-ALL, CD19+ 46XX; del(9p13); del(21q22) CNSII

MRD+ at TP1 (10^{-2}) and TP2 (10^{-3})

Allogeneic HSCT, MUD (9/10), BM 07/2018

TBI-based conditioning with 12 Gy and Vp-16

GvHD prophylaxis:

ATG 3 × 15 mg/kg, CsA 3 mg/kg (day –1), MTX 10 mg/m^2 (day +1, +3, +6)

Complications

- FUO, BKV viremia, and hemorrhagic cystitis
- aGvHD: skin IV, overall IV

Day +100 after allo-HSCT

Presented with acute kidney disease

- Proximal tubulopathy (Fanconi syndrome)
- Elevated creatinine and cystatin
- GFR 20 mL/min/1.73 m^2
- Normal urine output

Kidney biopsy: glomeruli intact, subacute tubules damage

Patient: Progress

1. Late bone marrow relapse 04/20 (CD19+ and CD19– populations)

Complications: stable chronic kidney disease, asymptomatic CMV reactivation

Treatment: CAR T-cell infusion 06/20

2. Allogeneic HSCT, PBSC (haploidentical donor – mother) 08/20

GvHD prophylaxis: ptCy (day +3, +4), FK-506

End of immunosuppression day +36

Complications: slow hematologic engraftment, HHV-6/7 reactivation

2. Early bone marrow relapse 07/21

Treatment: cytoreductive therapy, CAR T-cell infusion (07/21)

Complications: stable chronic kidney disease (KD), invasive mycoses

Question 1

What would be your strategy in case of ALL – relapse after allo-HSCT in a patient with chronic KD (GFR 20 mL/min/1.73 m^2)?

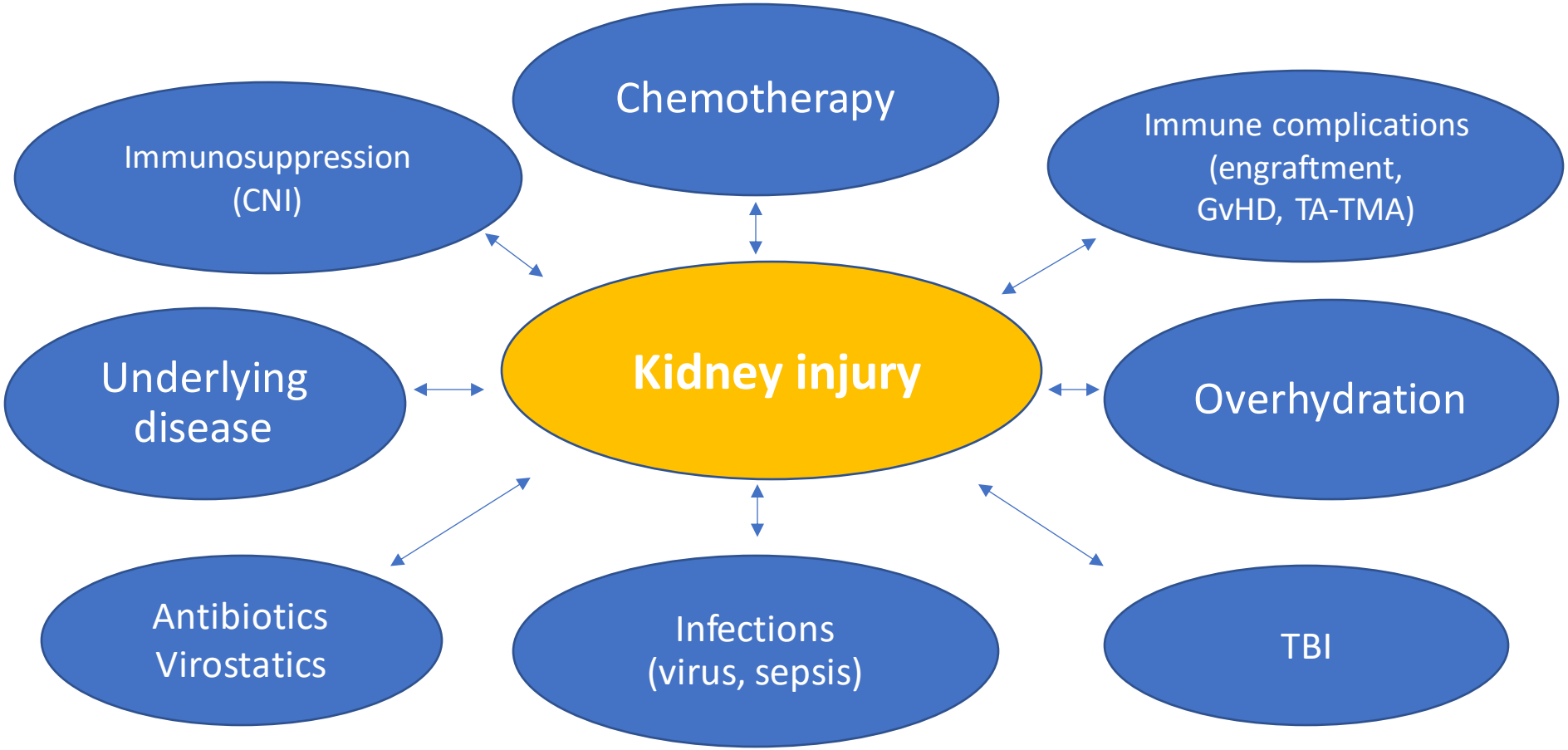
a) Second allo-HSCT with myeloablative conditioning

b) Second allo-HSCT with reduced-intensity conditioning

c) Palliative approach

d) Other treatment

Pathogenesis of acute and chronic KD



How do we screen acute and chronic KD?

- Ultrasound diagnostic
- RR
- Diuresis
- Urine analysis (proteinuria, albuminuria)
- Monitoring of retention parameter (creatinine, BUN, cysC) and electrolytes, GFR
- Monitoring during long-term follow-up

Prevention and treatment of acute and chronic KD

Prevention and monitoring
Optimization of fluid balance
Careful use of nephrotoxic medication and contrast fluid
Monitoring of kidney function
Treatment: General measures
Optimization of fluid balance
Discontinuation of nephrotoxic medications
Aggressive treatment of underlying infections
Treatment: Specific measures
Marrow infusion syndrome: steroids
Hepatic sinusoidal obstruction syndrome: albumin and terlipressin, defibrotide
Thrombotic microangiopathy: treatment of hypertension, cessation of CNI and mTOR inhibitors, complement inhibition

DeMauro Renaghan A, et al. *Clin J Am Soc Nephrol.* 2020;15(2):289-297.

Question 2

What options would you choose during pre- and post-HSCT in a patient with chronic KD?

a) Dose reduction of chemotherapy drugs
b) Drug monitoring
c) Prevention of overhydration
d) Drug application with less nephrotoxicity
e) Aggressive treatment of infections

Discussion

What conditioning would you recommend for second allo-HSCT?

What type of donor would you use in this setting?

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Discussion – case 2

Faculty panel: Rob Pieters, Franco Locatelli, Patrick Brown, Christina Peters, Martin Schrappe

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Final discussion, Q&A, and session close

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Interactive Q&A

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Educational ARS questions

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Educational Questions Pediatric ALL

Repeated Question 1: Which of the following subsets of first-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 hypodiploidy
c) All patients with t(17;19) or t(1;19)
d) Each of the 3 previous subsets

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Educational Questions Pediatric ALL

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

a) Inotuzumab is approved for induction treatment of relapsed B-ALL in childhood

b) Inotuzumab dosage is 3 mg/m^2

c) Blinatumomab is approved for consolidation treatment before HSCT in children with B-ALL

d) None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

Educational Questions Pediatric ALL

Repeated Question 3: Which children with relapsed ALL should be transplanted after a TBI-containing regimen?

a) All children
b) Children above the age of 4 years
c) Children above the age of 10 years
d) Those with T-ALL

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Educational Questions Pediatric ALL

Repeated Question 4: Which of the following statements is incorrect?

a) Leukemia recurrence in patients given CAR T cells is associated with early disappearance of CAR T cells in peripheral blood
b) Leukemia recurrence in patients given CAR T cells is associated with B-cell aplasia
c) Leukemia recurrence in patients given CAR T cells is associated with disease burden at time of infusion
d) Leukemia recurrence in patients given CAR T cells is associated with reappearance of MRD

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Closing remarks

Franco Locatelli

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