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Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

26 March 2022

Virtual Breakout: Pediatric Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

Session open

Franco Locatelli

APTITUDE HEALTH

Meet the Faculty

CHAIR

Franco Locatelli, MD
IRCCS Bambino Gesù Children's Hospital, Rome, Italy

FACULTY

Rob Pieters, MD, PhD
Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands

Christina Peters, MD
St. Anna Children's Hospital, Stem Cell Transplantation Unit, Vienna, Austria

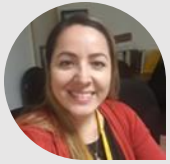
Carlos Andrés Portilla, MD
Centro Médico Imbanaco, Cali, Colombia

Oscar Gonzáles Ramella, MD, PhD
Hospital Civil de Guadalajara, Mexico

Maria Sara Felice, MD, PhD
National Pediatrics Hospital Prof Dr JP Garrahan, Buenos Aires, Argentina

Adriana Seber, MD
GRAACC, Federal University of São Paulo, Brazil

Jorge Buitrago, MD
Centro Médico Imbanaco, Cali, Colombia



Irene Medina Castillo, MD
Hospital Civil de Guadalajara, Mexico

Luisina Perruzo, MD
National Pediatrics Hospital Prof Dr JP Garrahan, Buenos Aires, Argentina

Erica Almeida Viana, MD
GRAACC, Federal University of São Paul, Brazil

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Objectives of the Program

Comprehensively discuss the role of MRD in managing and monitoring pediatric ALL

Understand current treatment patterns for acute leukemias (ALL and AML) including incorporation of new technologies and HSCT

Exchange clinical insights in pediatric leukemia, on the basis of patient case discussions from the LatAm region

Discuss the role of bispecifics for pediatric AYA B-ALL

Virtual Breakout – Pediatric Leukemia Patients (Day 2)

Co-chair: Franco Locatelli

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.10	Session open	Franco Locatelli
10.10 – 10.30	The use of MRD and genetics for risk stratification and therapy guidance in pediatric ALL	Rob Pieters
10.30 – 10.50	First-line treatment of pediatric ALL, including HSCT	Christina Peters
10.50 – 11.10	Current treatment options for relapsed ALL in children, including HSCT	Franco Locatelli
11.10 – 11.25	Bispecifics for pediatric and AYA B-ALL	Christina Peters
11.25 – 11.55	ALL case-based panel discussion • Case 1 (10 min) – Irene Medina (Mex) • Case 2 (10 min) – Jorge Buitrago (Col) • Discussion (10 min) – Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla	All
11.55 – 12.00	Break	
12.00 – 12.20	Current treatment options for pediatric AML	Franco Locatelli
12.20 – 12.50	AML case-based panel discussion • Case 1 (10 min) – Luisina Peruzzo (Arg) • Case 2 (10 min) – Erica Viana (Bra) • Discussion (10 min) – Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla	All
12.50 – 13.00	Session close	Franco Locatelli

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Introduction to the Voting System

Franco Locatelli

APTITUDE HEALTH

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

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

Question 3

Which assertion is correct for children with AML?

a) Treatment of patients is based only on the presence of recurrent molecular alterations

b) Treatment of patients is based only on the level of MRD after induction therapy

c) Both the presence of recurrent molecular alterations and MRD level after induction therapy influence the post-remission treatment choice

d) Neither the presence of recurrent molecular alterations, nor MRD level after induction therapy influence the post-remission treatment choice

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The use of MRD and genetics for risk stratification and therapy guidance in pediatric ALL

Rob Pieters

APTITUDE HEALTH

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

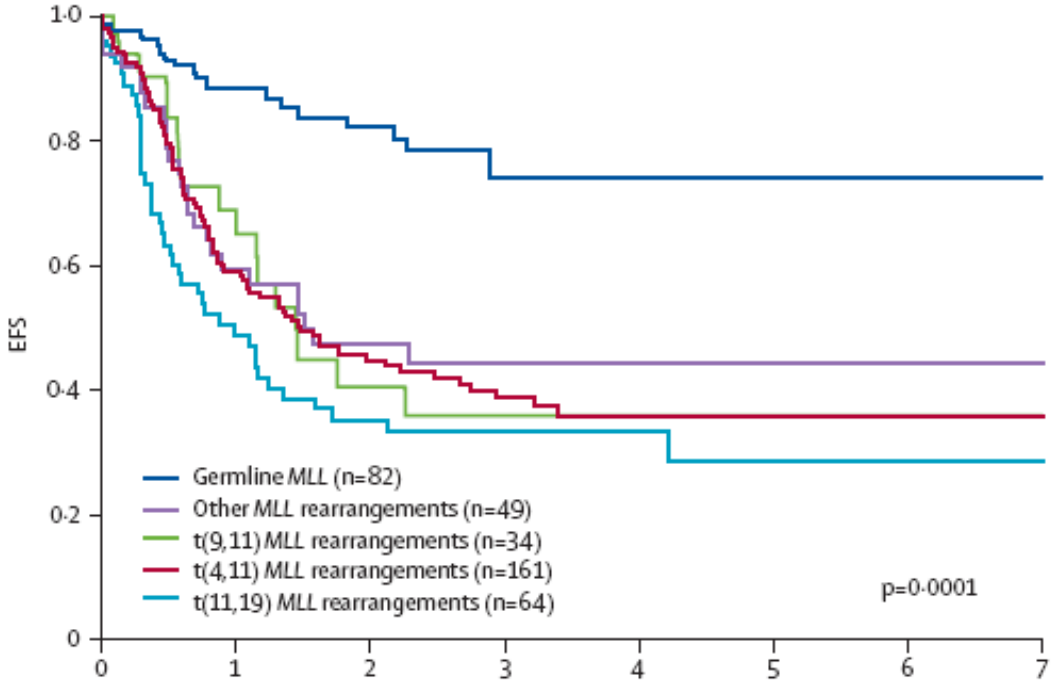
- Specific therapy protocols for high-risk genetic subgroups
- MRD-based choices of specific therapies
- Therapy reduction in MRD low-risk groups
- Therapy intensification in MRD high-risk groups
- Interdependency of MRD and genetics

Question

Which of the following statements is NOT correct?

1. 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
2. MRD at end of induction and consolidation in *BCR-ABL1*–positive ALL is used to select patients who do not need SCT
3. The prognostic relevance of MRD at end of induction depends on the genetic subtype of ALL
4. The majority of relapses occur in patients who remain MRD positive after consolidation

KMT2A (MLL) and infant ALL

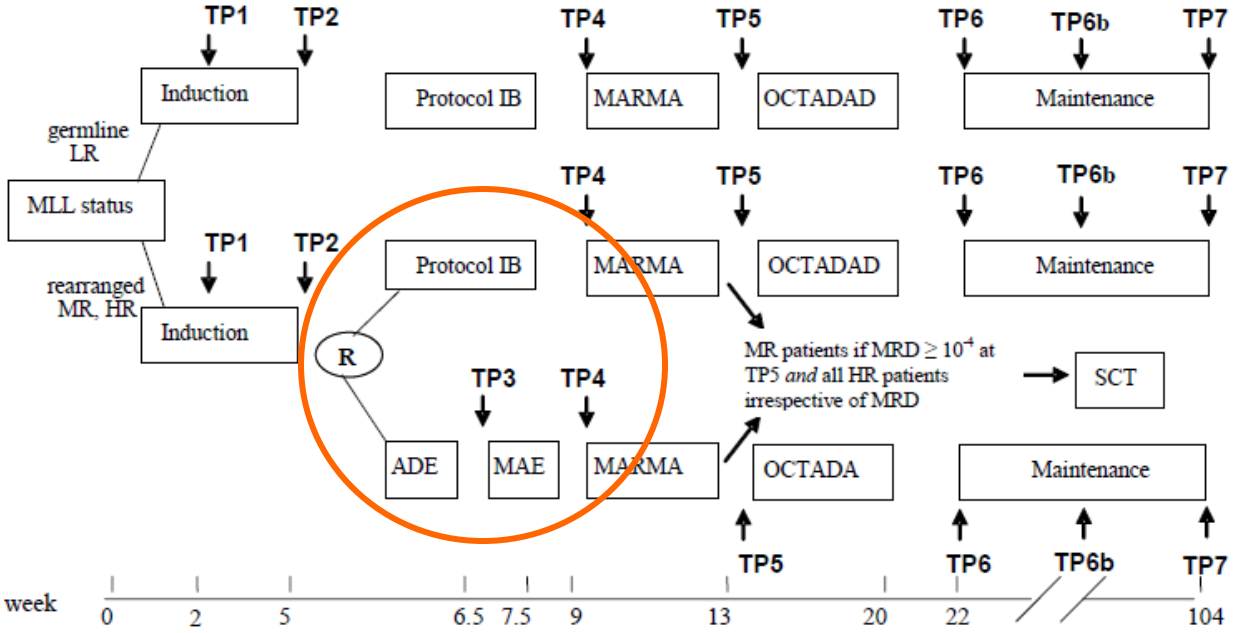


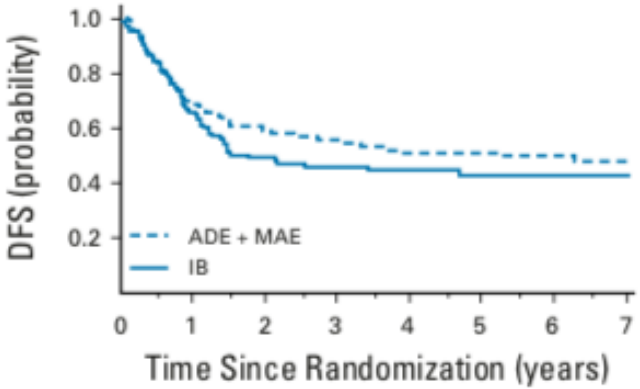
KMT2A germline

KMT2A rearranged

Pieters, Lancet 2007

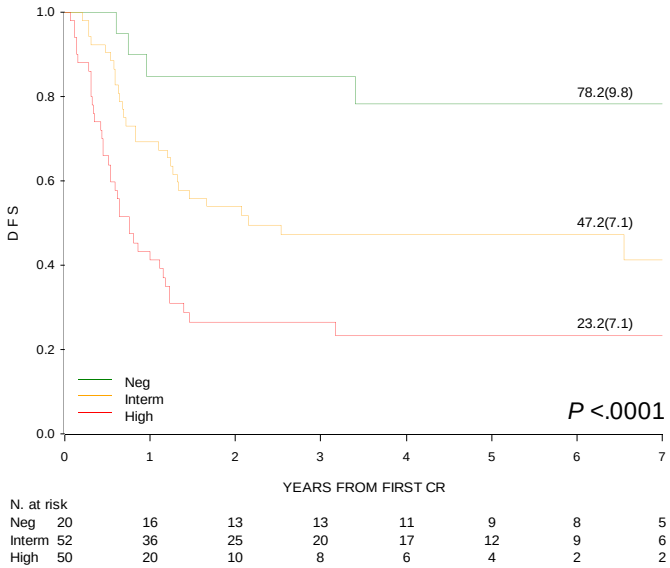
Interfant-06 treatment schedule





Prognostic value of MRD at EOI depends on consolidation treatment given

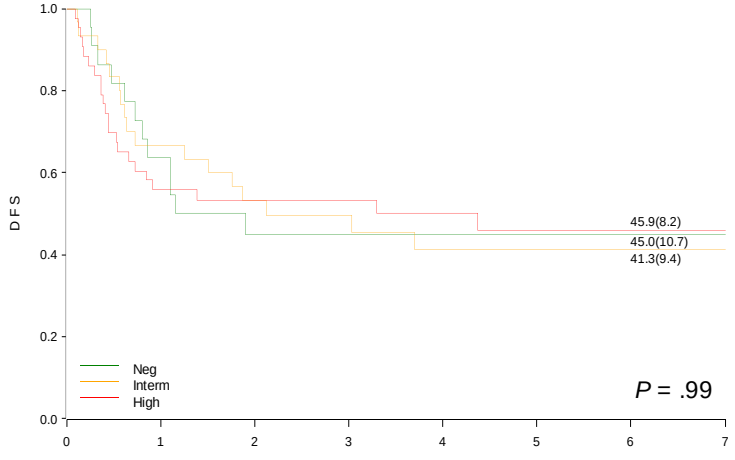
Patients treated with lymphoid IB consolidation



N. at risk

Neg	20	16	13	13	11	9	8	5
Interm	52	36	25	20	17	12	9	6
High	50	20	10	8	6	4	2	2

Patients treated with myeloid ADE/MAE consolidation

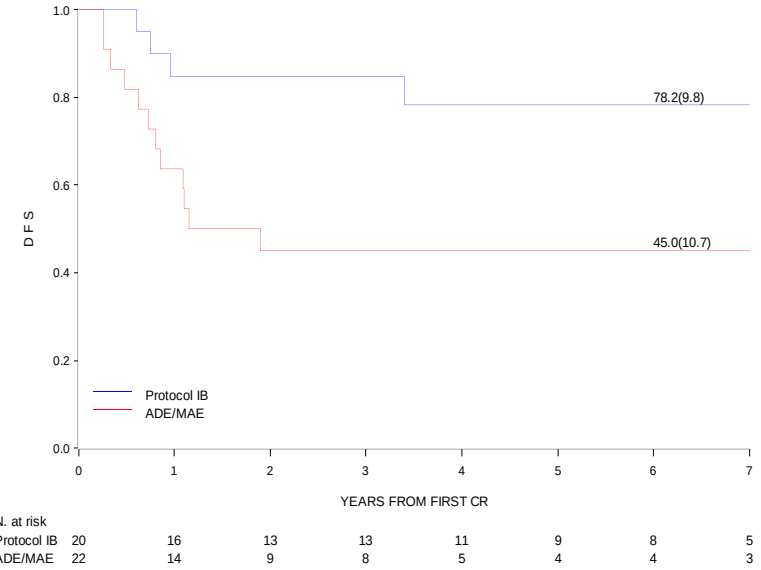


N. at risk

Neg	22	14	9	8	5	4	4	3
Interm	30	20	15	12	8	7	4	2
High	43	24	20	17	13	8	5	3

Patient outcomes by treatment given, according to MRD at EOI

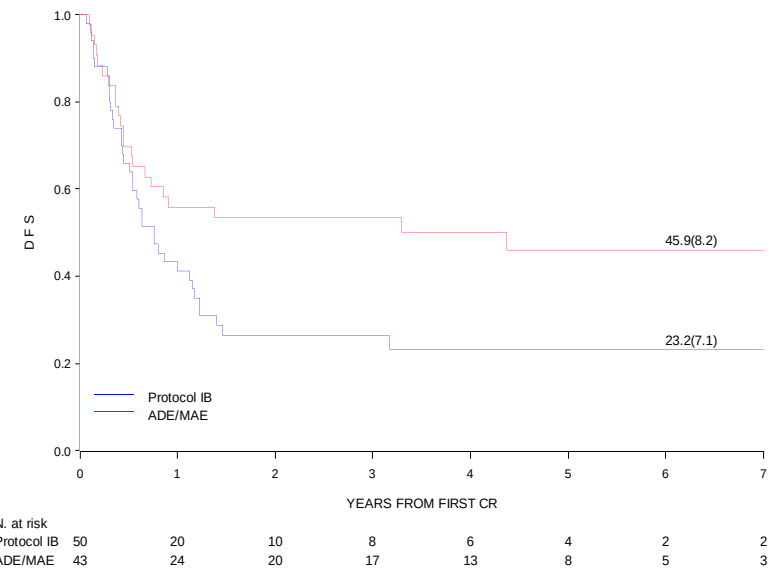
Patients with negative MRD at end of induction



N. at risk

Protocol IB	20	16	13	13	11	9	8	5
ADE/MAE	22	14	9	8	5	4	4	3

Patients with high MRD (≥0.05%) at end of induction



N. at risk

Protocol IB	50	20	10	8	6	4	2	2
ADE/MAE	43	24	20	17	13	8	5	3

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.

TKI in *BCR-ABL1*–positive ALL: Which indication for SCT??

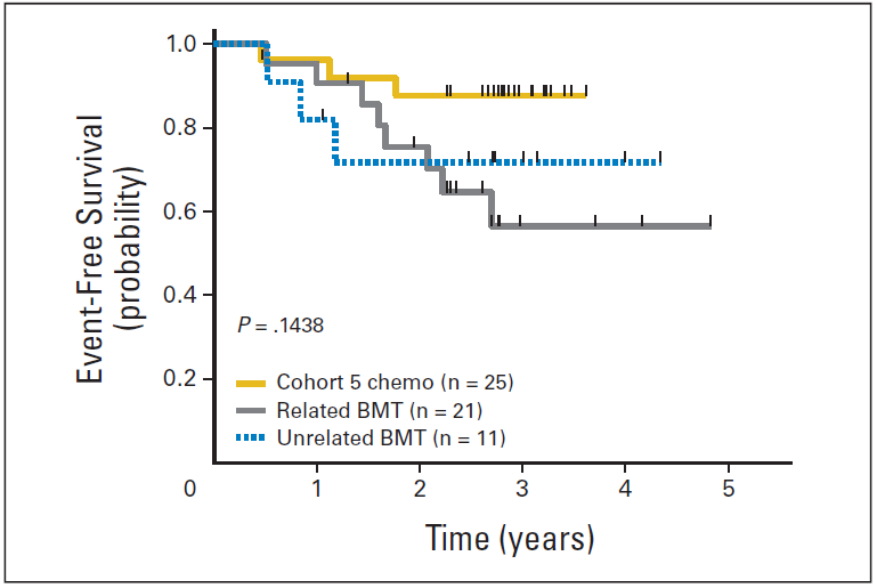
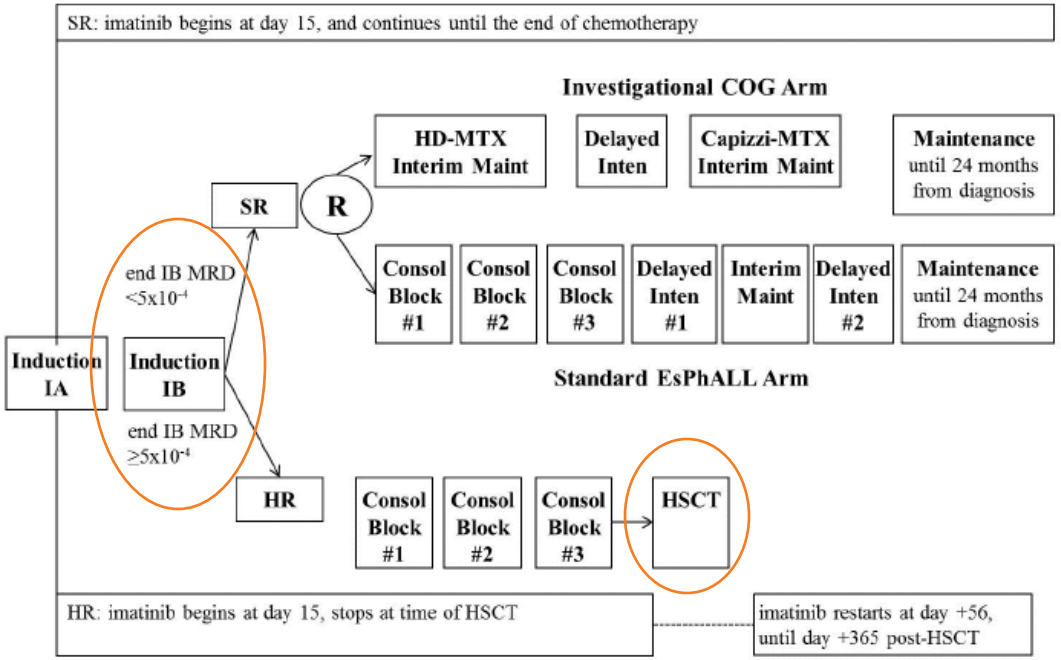


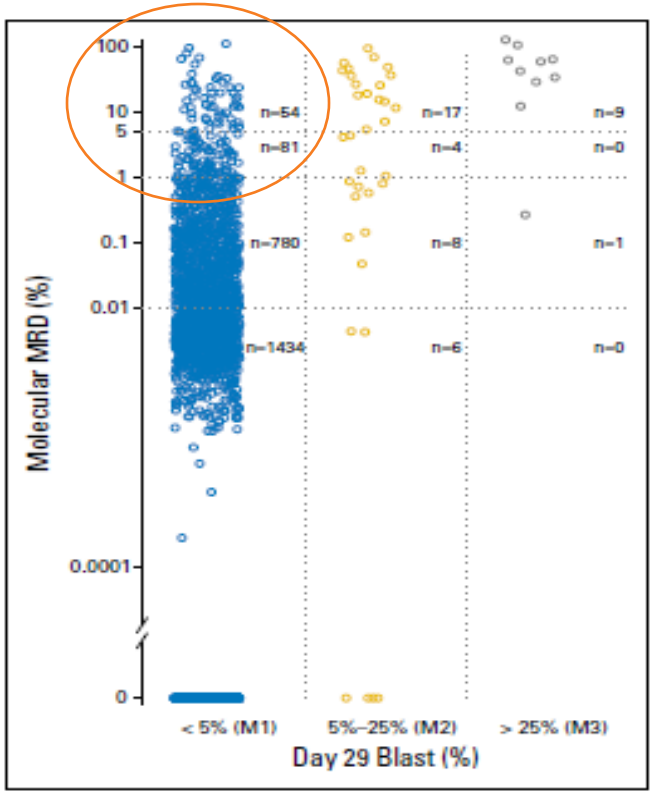
Fig 4. Comparison of event-free survival (EFS) for Cohort 5 chemotherapy only versus related-donor bone marrow transplantation (BMT) versus unrelated-donor BMT. Cohort 5 patients were compared with human leukocyte antigen (HLA) –identical sibling BMT (8 of 39 in cohorts 1-4; 13 of 44 in cohort 5) and 11 of the total 83 patients removed from protocol for an alternative-donor BMT. Patients treated on protocol were given imatinib 340 mg/m^2/d for 6 months starting 4 to 6 months after BMT.

EsPhALL2017/COGAALL1631

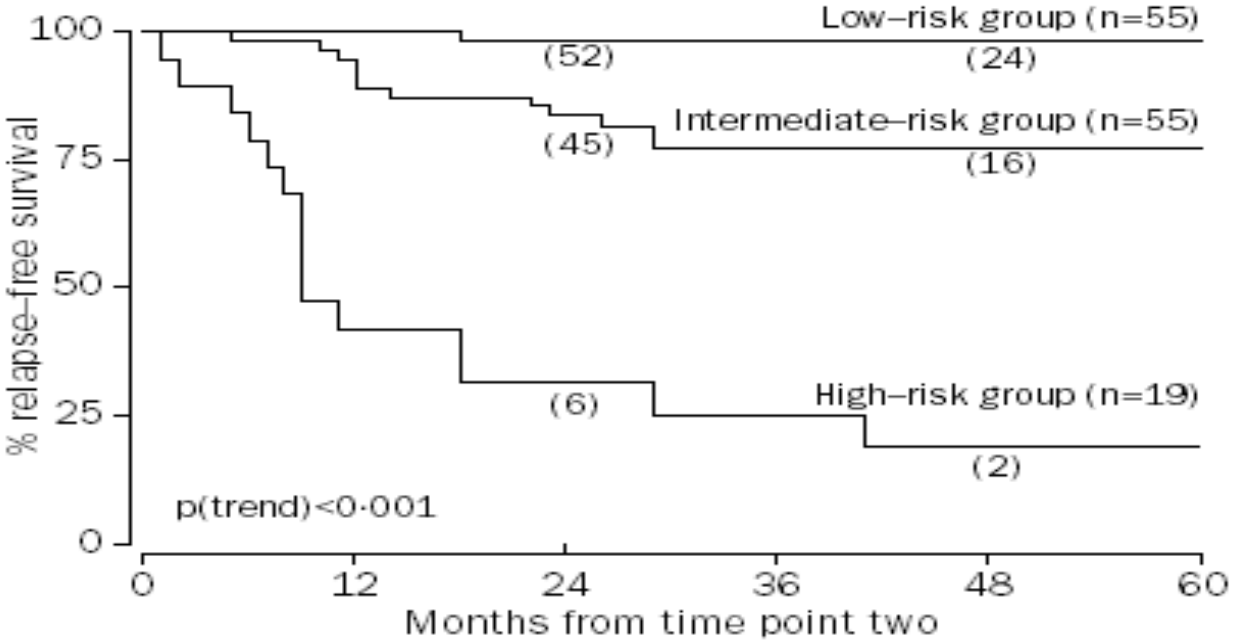


Note. MRD: Minimal Residual Disease, SR:Standard Risk, HR: High Risk, **R**: Randomization, HD-MTX: High Dose Methotrexate, Maint: Maintenance, Inten: Intensification, Consol: Consolidation, HSCT: Hematopoietic Stem Cell Transplant

Morphologic vs molecular detection of MRD at end of induction

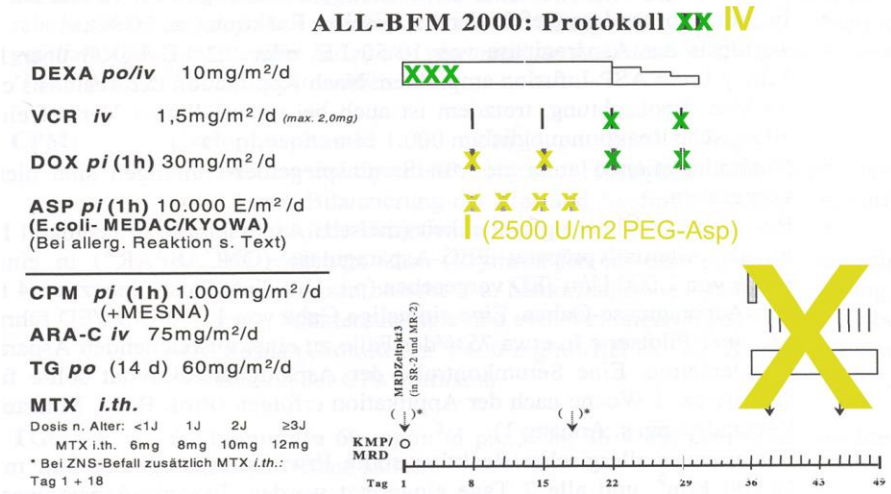


Minimal residual disease and outcome in ALL



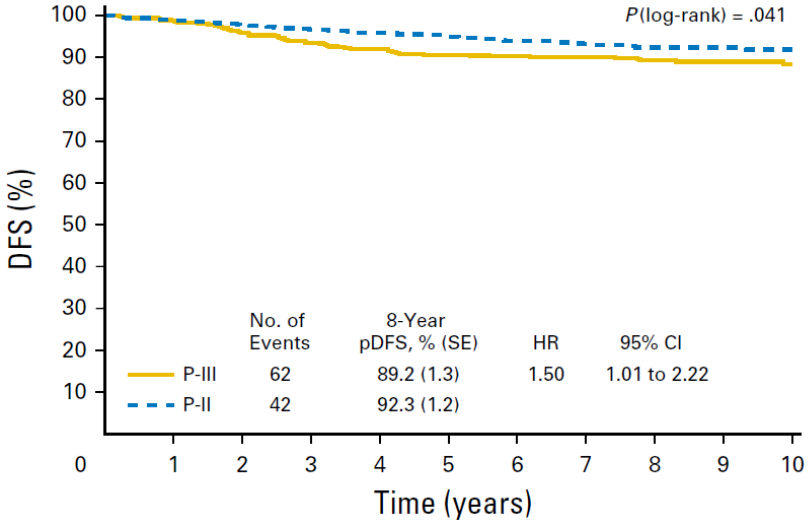
Relapse-free survival of the 3 MRD-based risk groups, as defined by MRD information at time points 1 and 2

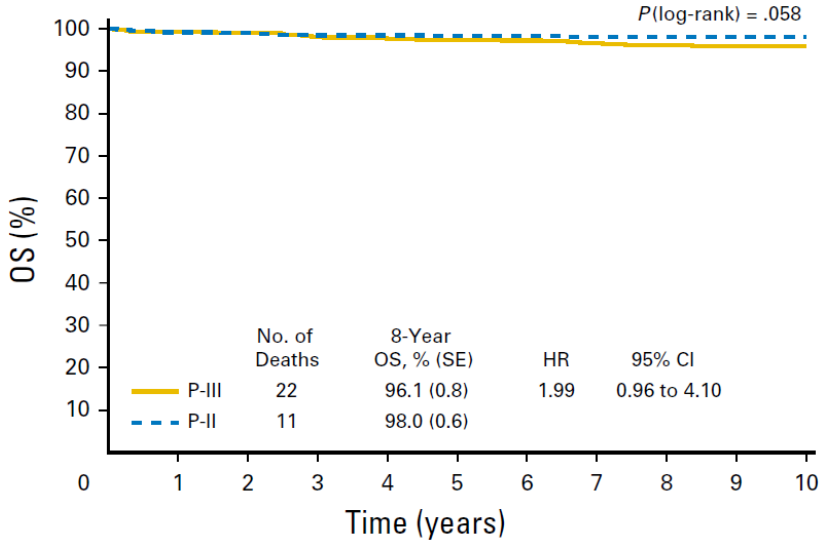
Therapy reduction in MRD-negative patients: BFM-II vs BFM-III vs DCOG-IV



	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





ALL-10 protocol outcome:

1. Therapy reduction in SR is safe; 5-yr survival 99%
2. Intensification in MR: 5-yr EFS from 76% to 88%
3. Intensification in HR: 5-yr EFS from 16% to 78%

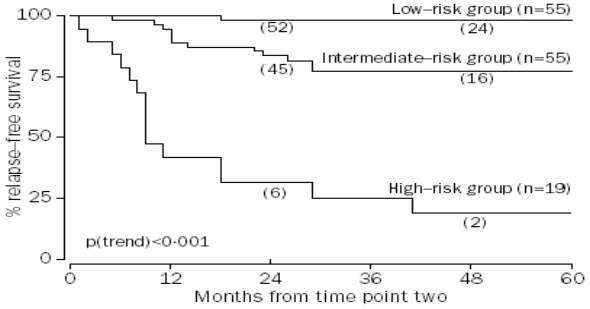
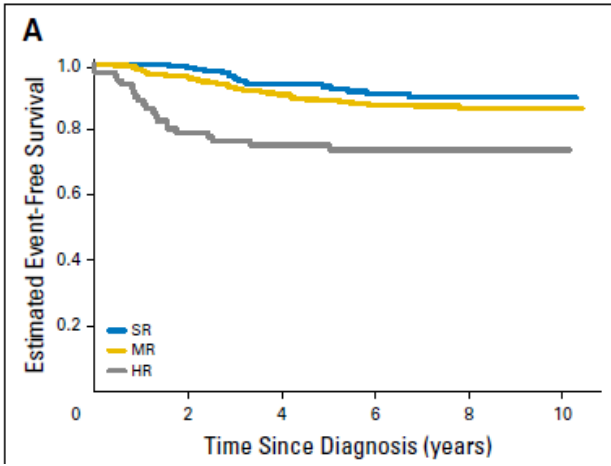
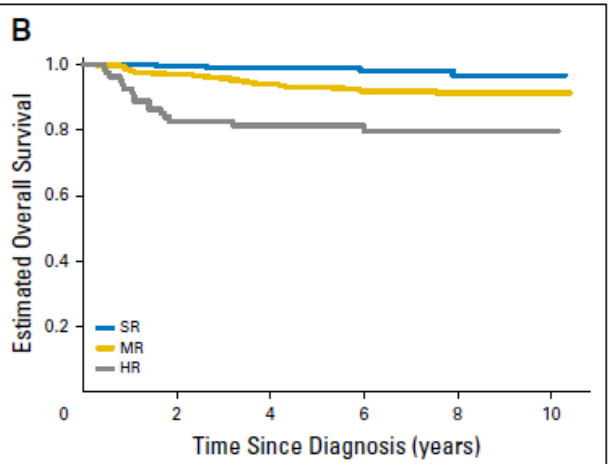


Figure 4: **Relapse-free survival of the three MRD-based risk groups, as defined by MRD information at time points one and two**

Event-free survival



Survival



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

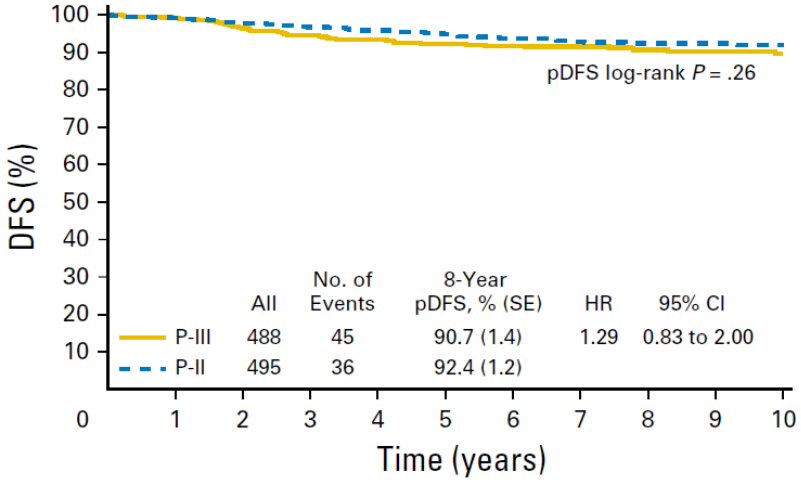
- Decrease of therapy for all MRD low-risk patients: an extra ~4% of them need relapse therapy

OR

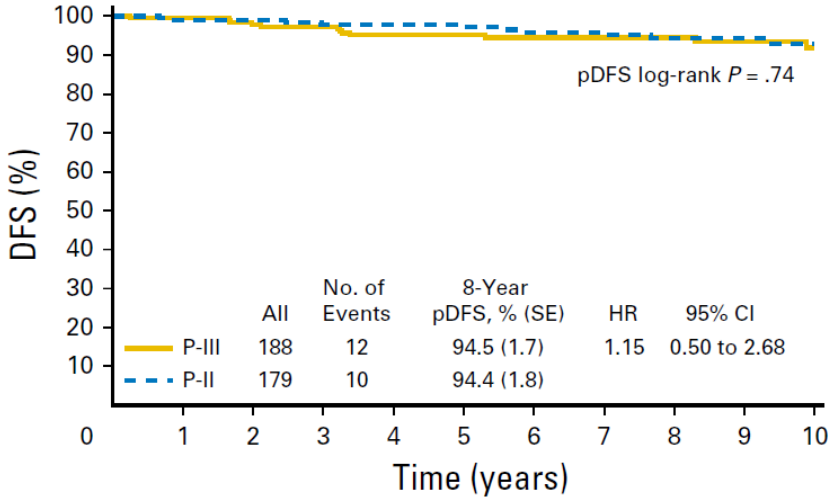
- More intensive therapy for all MRD low-risk patients

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

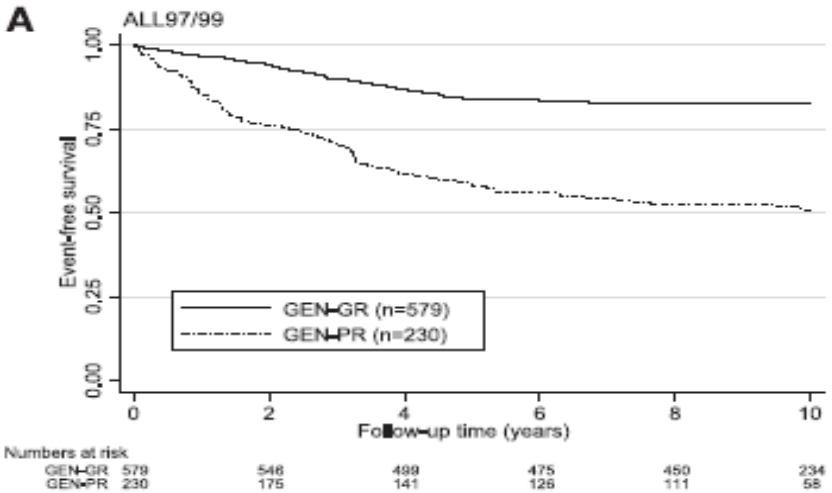
Age 1–9 yr

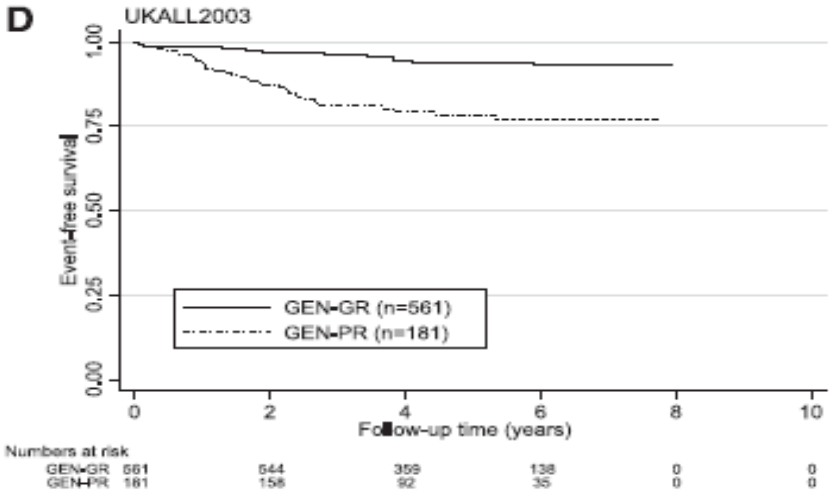


ETV6/RUNX1



EFS ALL97/99 and UKALL2003 by genetic risk group

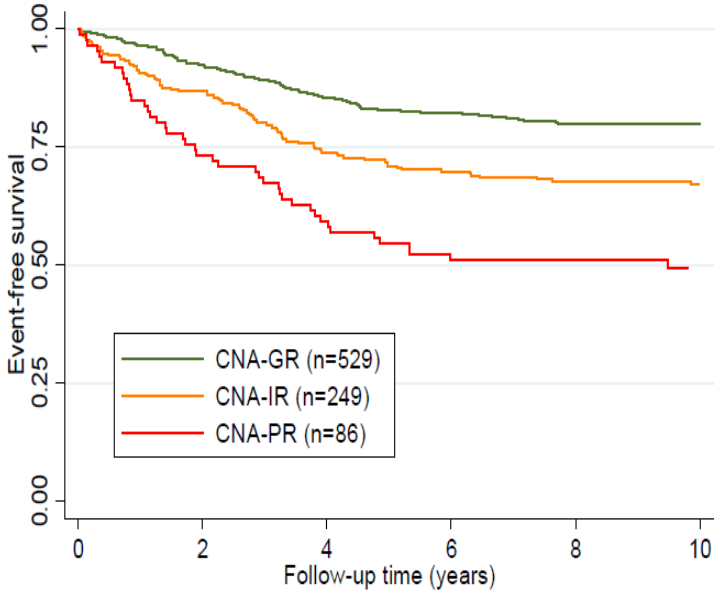




Moorman, Blood 2014

UK copy number alteration (CNA) classifier in UKALL

CNA profile defines risk groups



CNA profiles by MLPA

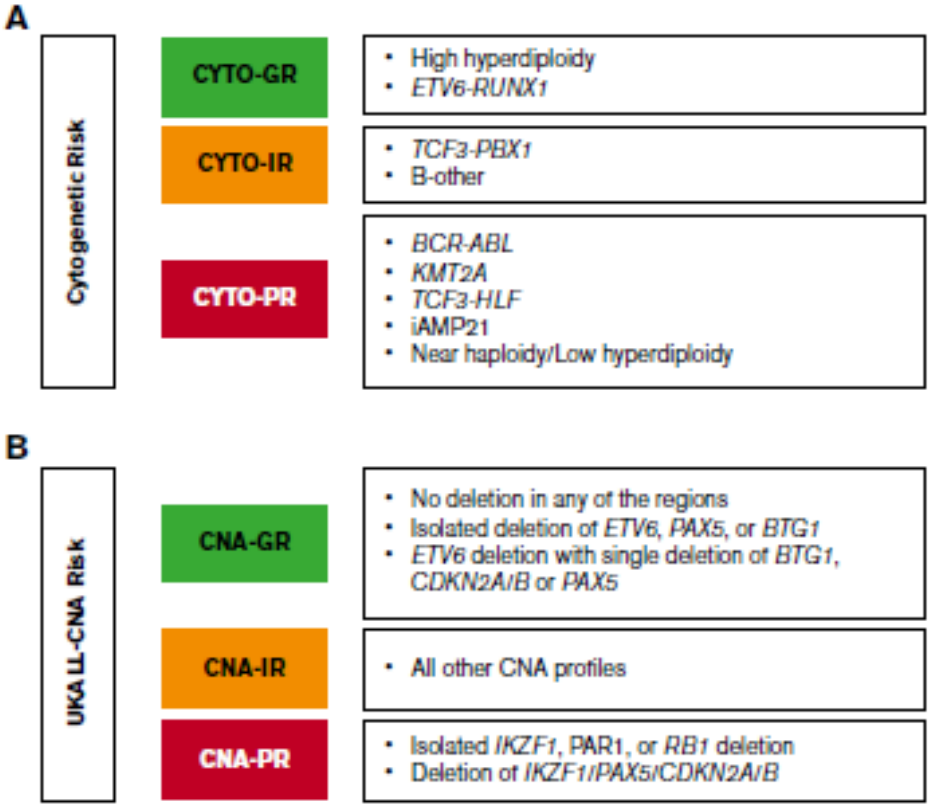
Good risk
- No deletion
- Isolated deletion of *ETV6, PAX5*, or *BTG1*
- *ETV6* deletion + *BTG1, CDKN2A/B* or *PAX5 deletion*

Intermediate risk
- All other CNA profiles

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

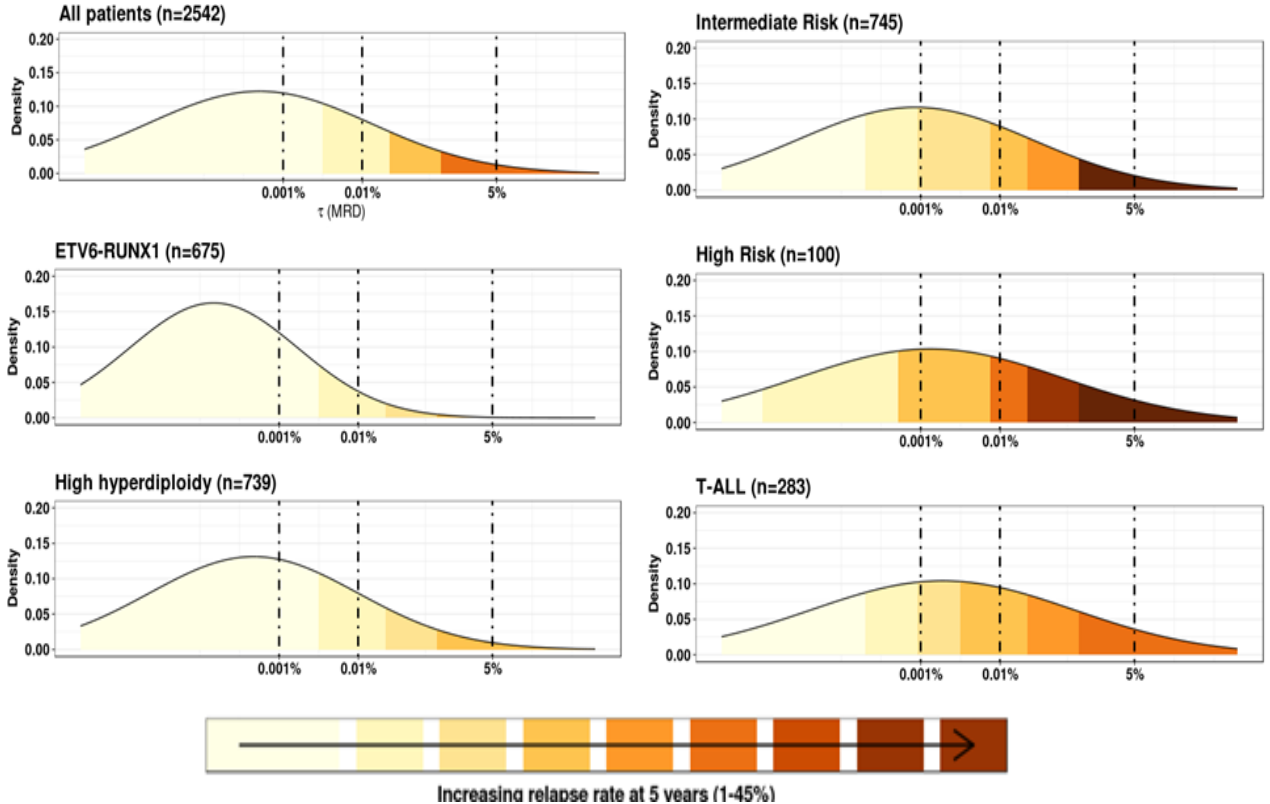
Moorman, Blood 2014

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



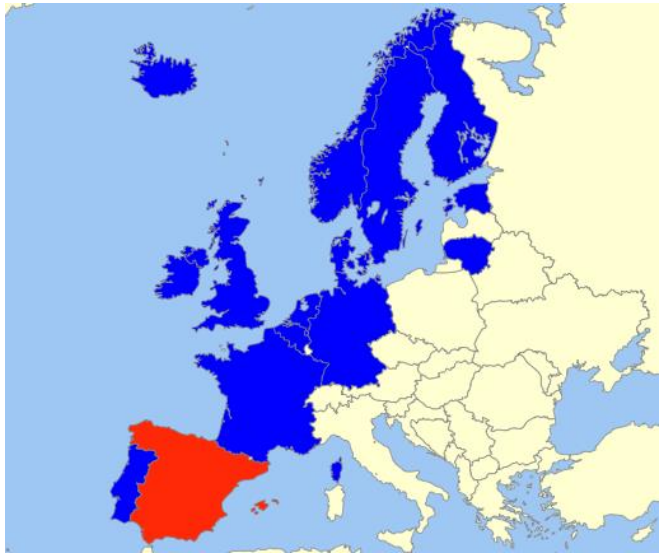
Hamadeh L, et al. *Blood Adv*. 2019;3(2):148-157.

Risk of relapse by MRD value varies by genetic subtype

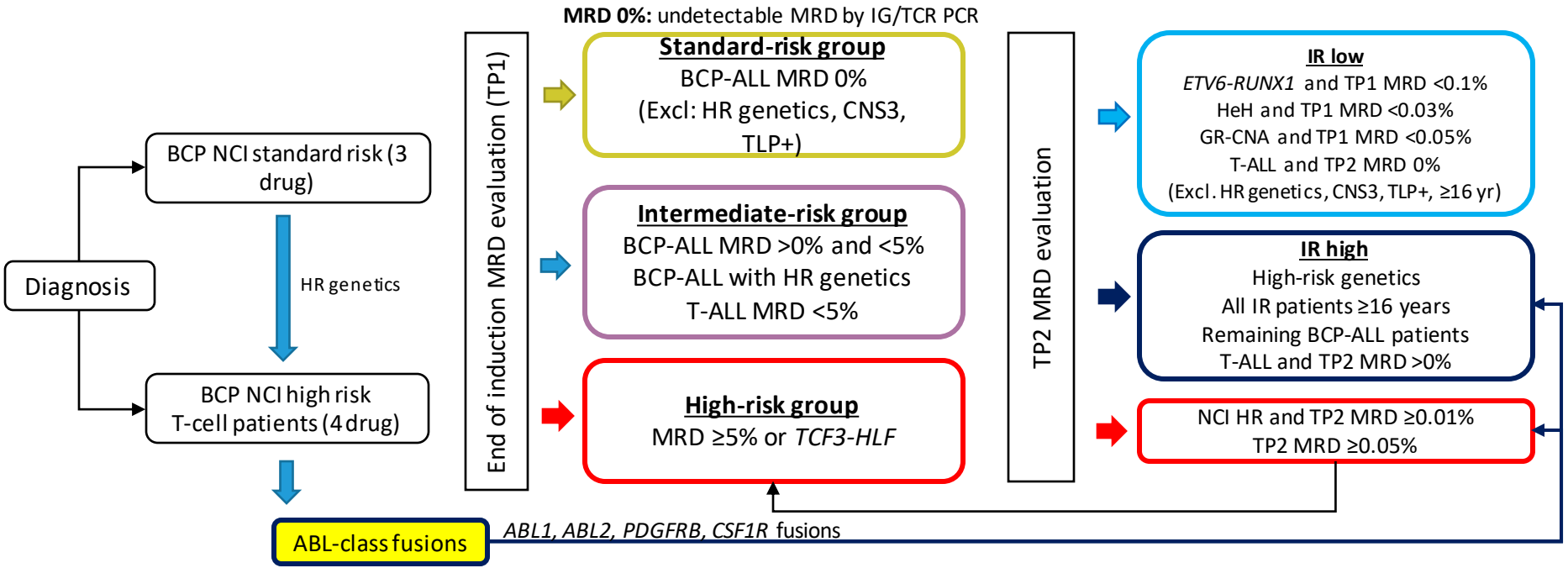


Patient population – ALLTogether

Study Group	Age	Pts/year	Country
DCOG	1–18	106	NL
UKALL	1–24	419	UK
COALL	1–18	90	D
NOPHO	1–45	235	S, DK, N, FIN, IS, EE, LT
BSPHO	1–18	80	B
SHOP	1–18	55	PT
PHOAI	1–24	42	EI
SFCE	1–18	400	F
SEHOP	1–18	?	E – candidate status
Total	1–45	1427 +?	Western Europe



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

Answer to question: Which of the following statements is NOT correct?

1. 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
2. MRD at end of induction and consolidation in *BCR-ABL1*–positive ALL is used to select patients who do not need SCT
3. The prognostic relevance of MRD at end of induction depends on the genetic subtype of ALL
4. The majority of relapses occur in patients who remain MRD positive after consolidation

Thank you!

Global Leukemia Academy

First-line treatment of pediatric ALL, including HSCT

Christina Peters

APTITUDE HEALTH

Global Leukemia Academy 2022

First-Line Treatment of ALL in Childhood and Adolescence Including HSCT

Christina Peters, MD

St. Anna Children‘s Hospital, Children‘s Cancer Research Institute

Vienna, Austria

christina.peters@stanna.at

Question 1

What genetic abnormality in pediatric ALL-patients is known to be a bad prognostic factor?

1. Hyperdiploid
2. *IKFZ1*^{plus}
3. *ETV6-RUNX1*

Question 2

Which pediatric patients are NOT candidates for allogeneic HSCT?

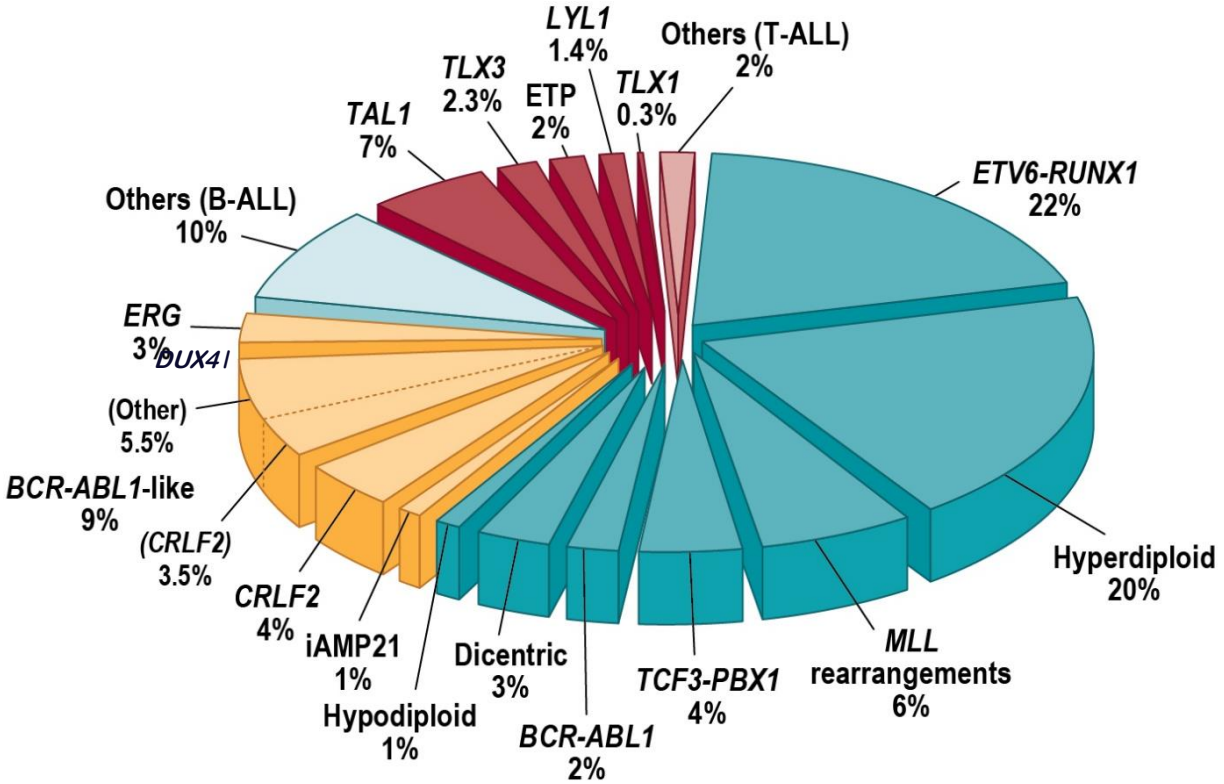
1. Children below 1 year of age and any *KMT2A* rearrangement
2. Patients not in complete morphological remission
3. Patients with hypodiploidy <45 chromosomes
4. Patients with T-ALL in second remission

Topics and Objectives

- Genetic subgroups of ALL – relevance for outcome
- Key components for stratification
- Key components of ALL therapy
- Contemporary first-line trials for pediatric ALL in Europe

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

All Patients Have Specific Leukemic Genetic Abnormalities



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

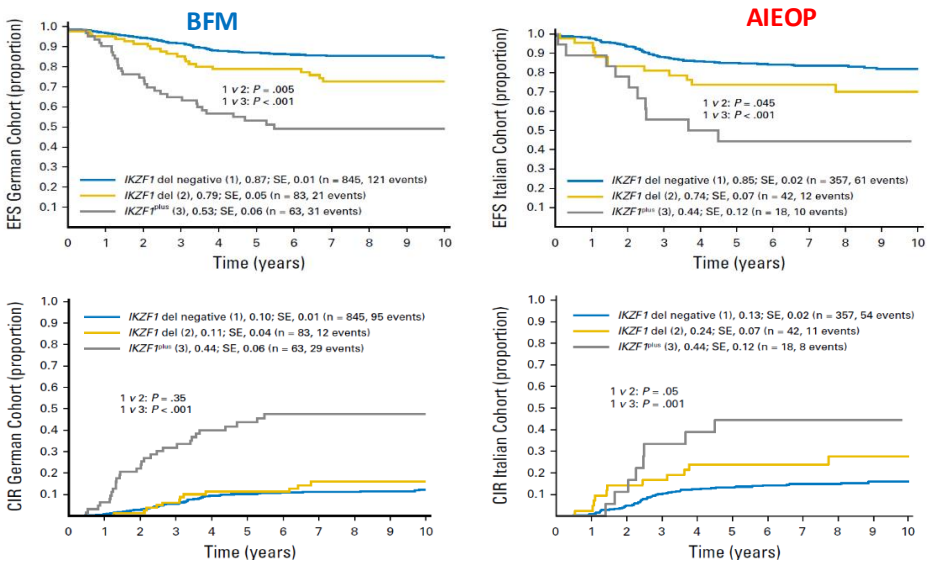
New prognostic profile

- Definition of IKZF1
  - Deletion of *IKZF1* and
  - *PAX5* and/or
  - *CDKN2A* and/or
  - *CDKN2B* and/or
  - *CRLF2 (PAR)* and
  - Negativity for *ERG* deletion

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

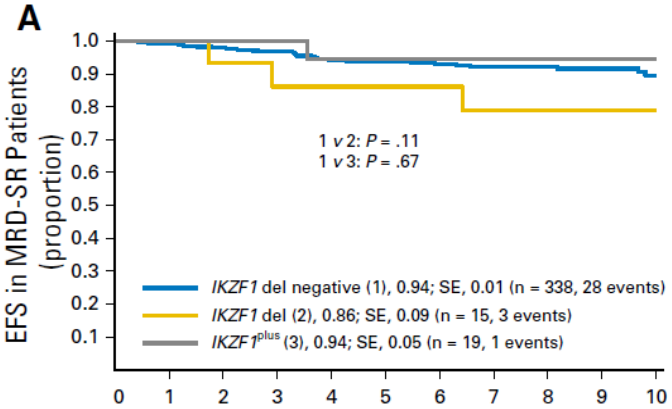
IKZF1^{plus} Defines a New Minimal Residual Disease–Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia

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

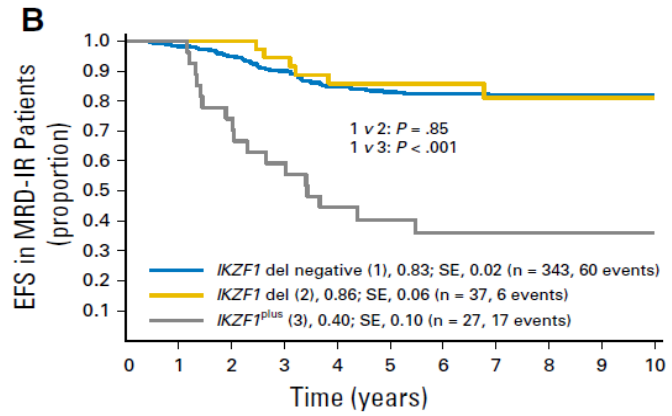


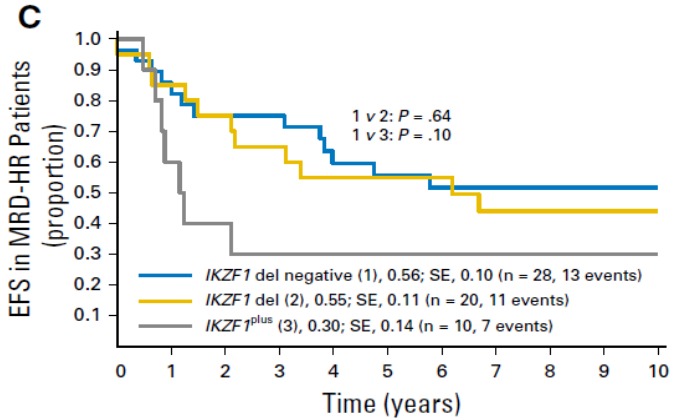
Stanulla M, et al. *J Clin Oncol.* 2018;36:1240-1249.

IKZF1^{plus} and MRD: Impact on EFS



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





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

Risk Stratification and Therapy

- The 2 main differences in stratification relate to the use of upfront criteria (eg, 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

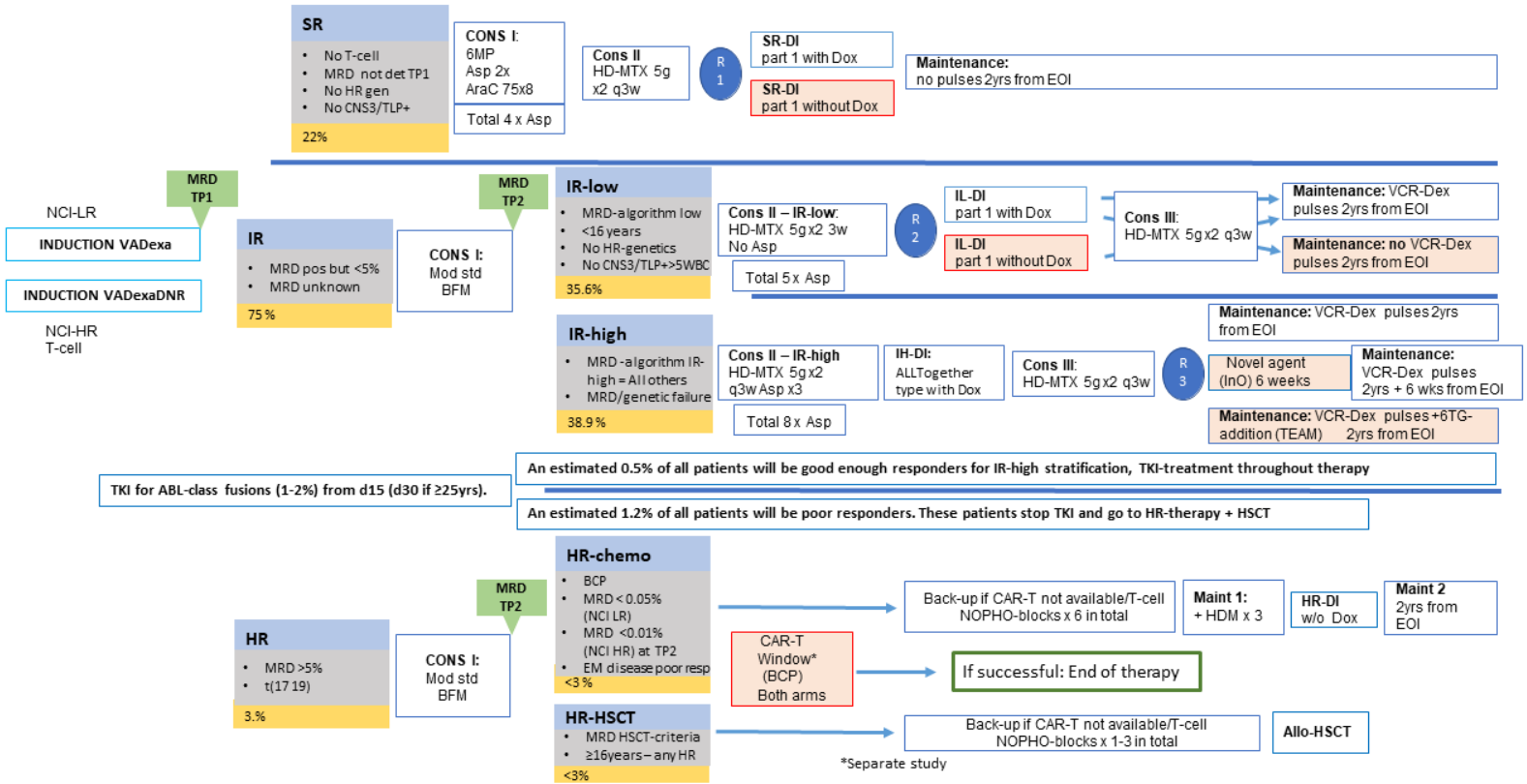
Buchmann S, et al. *Blood*. 2021 https://doi.org/10.1182/blood.2021012328

Contemporary Trials for Pediatric ALL in Europe

ALLTogether

EUDRACT number: 2018-001795-38

Therapy overview ALLTogether – including interventions



EUDRACT number: 2018-001795-38

AIEOP-BFM ALL 2017

Start of recruitment: July 2018

EUDRACT number: 2016-001935-12

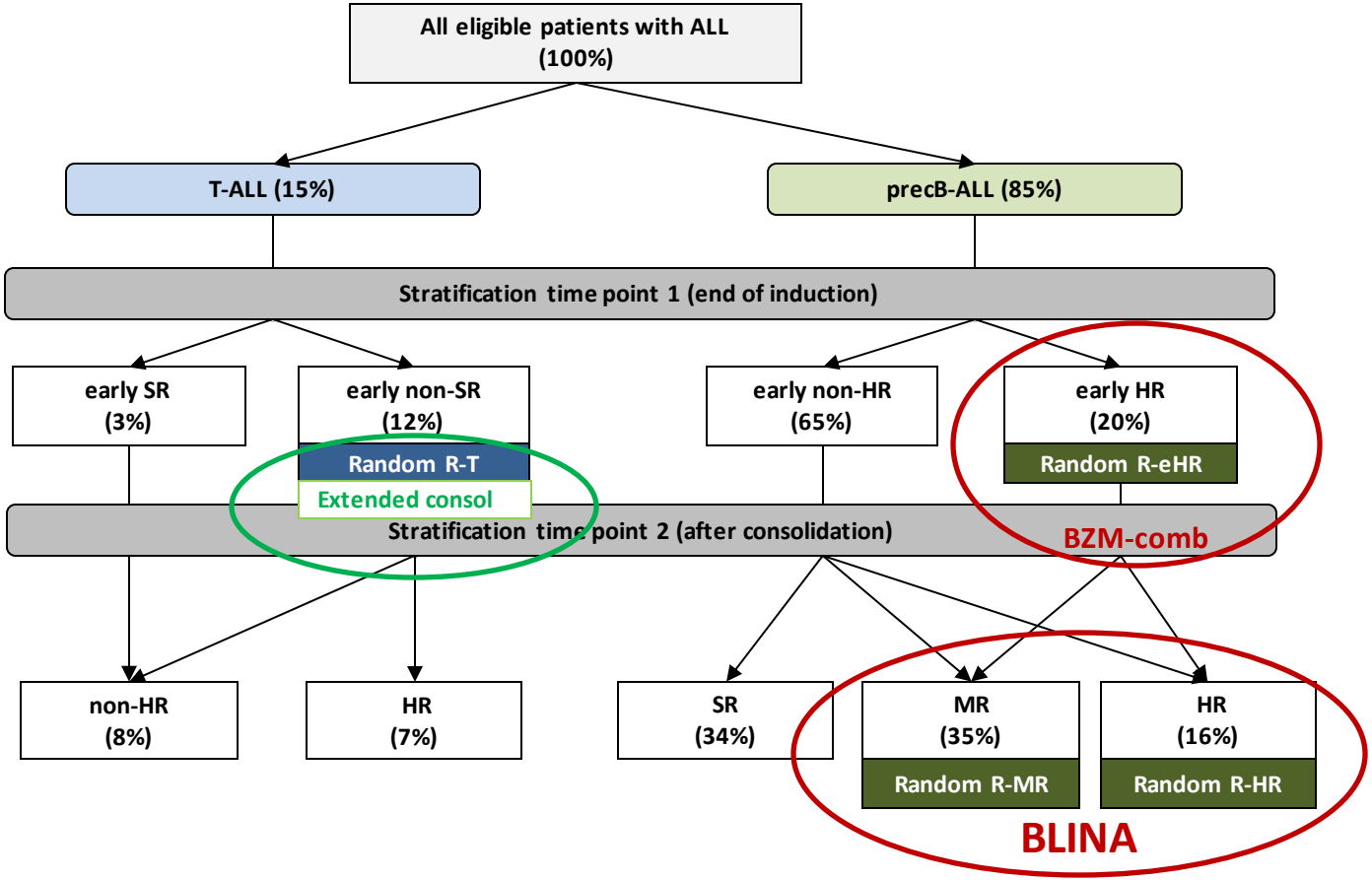
AIEOP-BFM ALL 2017: Risk Criteria for pB-ALL

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* <u>*not*</u> *ETV6-RUNX1* positive *or*
	•	*IKZF1*^{plus} *and* PCR-MRD at TP1 positive or inconclusive, *and* <u>*not*</u> positive for *ETV6-RUNX1*, *TCF3-PBX1,* or *KMT2Ar,* other than *KMT2A-AFF1 or*
	•	PCR-MRD at TP1 ≥$5x10^{-4}$ *and* positive <$5x10^{-4}$ at TP2 (PCR-MRD SER)
	•	PCR-MRD at TP2 ≥$5x10^{-4}$ (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

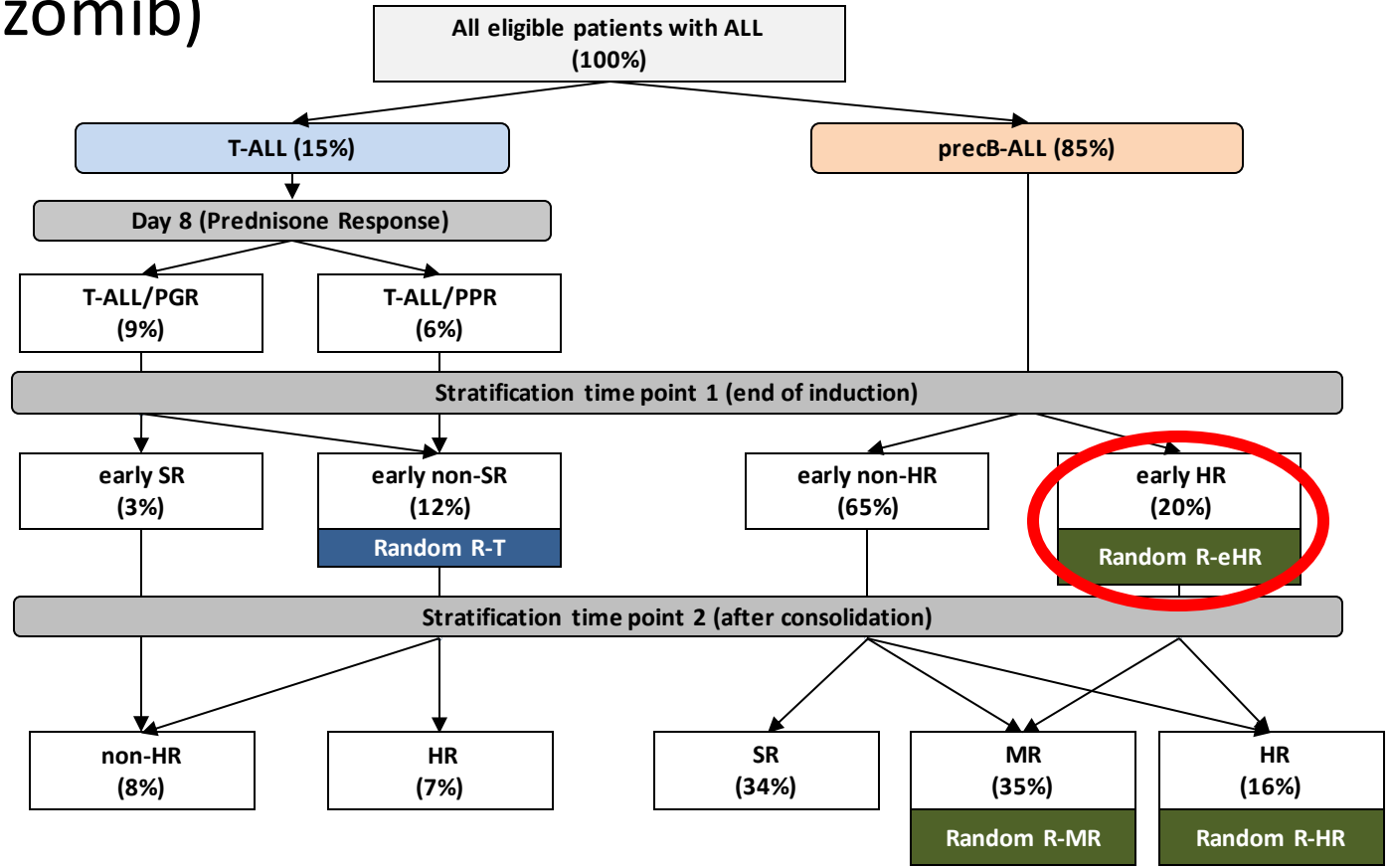
EUDRACT number: 2016-001935-12

AIEOP-BFM ALL 2017: Risk Stratification and Randomizations



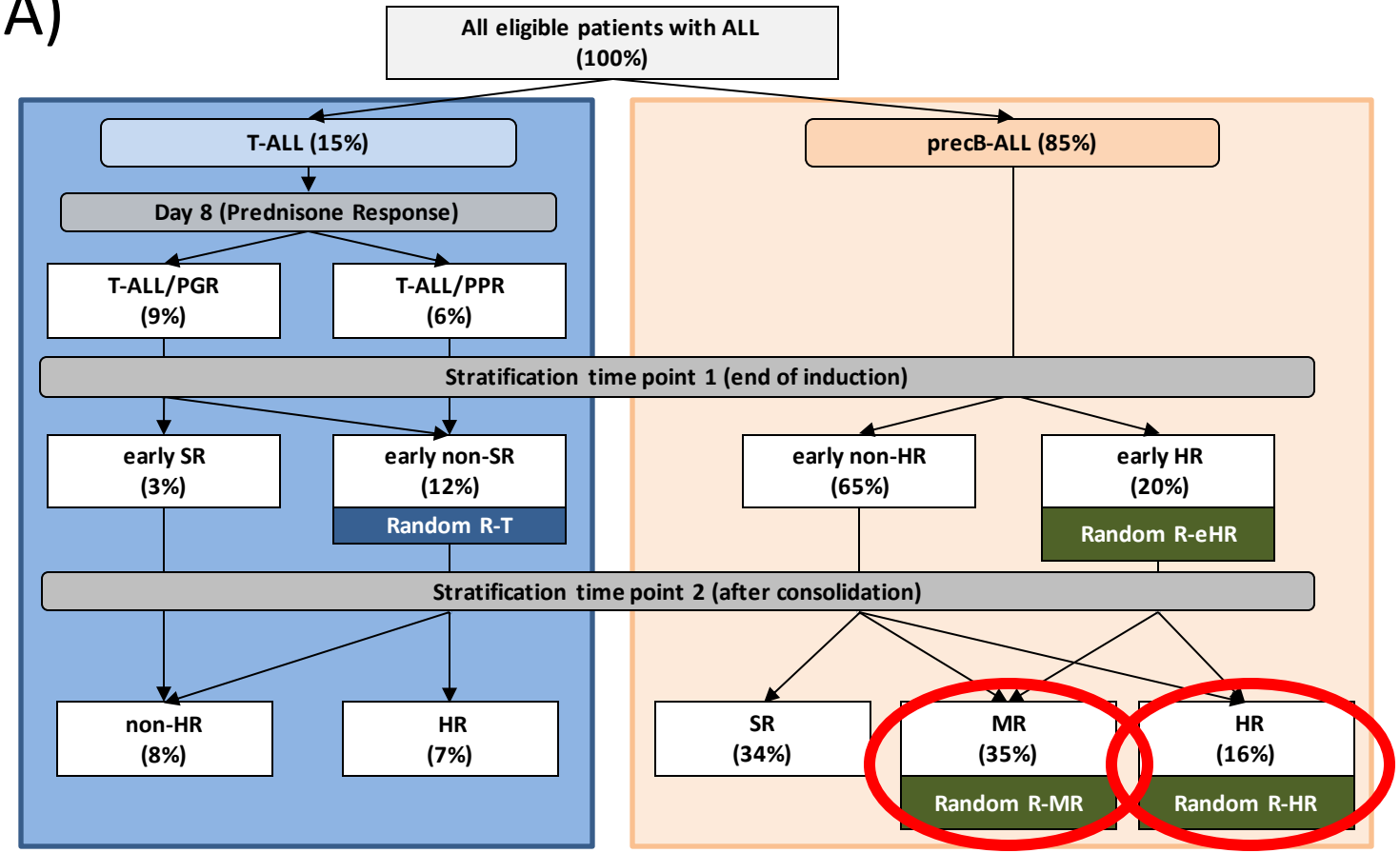
EUDRACT number: 2016-001935-12

AIEOP-BFM ALL 2017: Risk Stratification and Randomizations (Bortezomib)



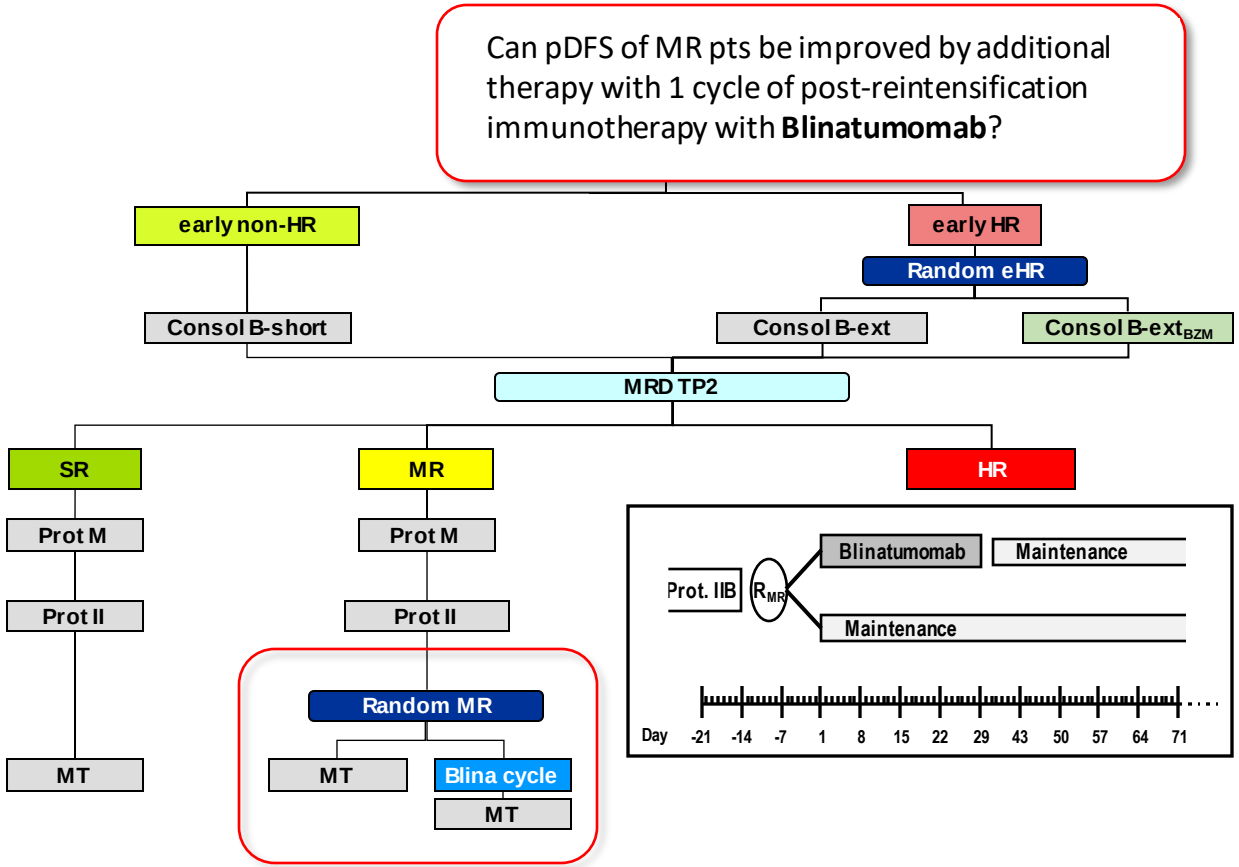
EUDRACT number: 2016-001935-12

AIEOP-BFM ALL 2017: Risk Stratification and Randomizations (BLINA)



EUDRACT number: 2016-001935-12

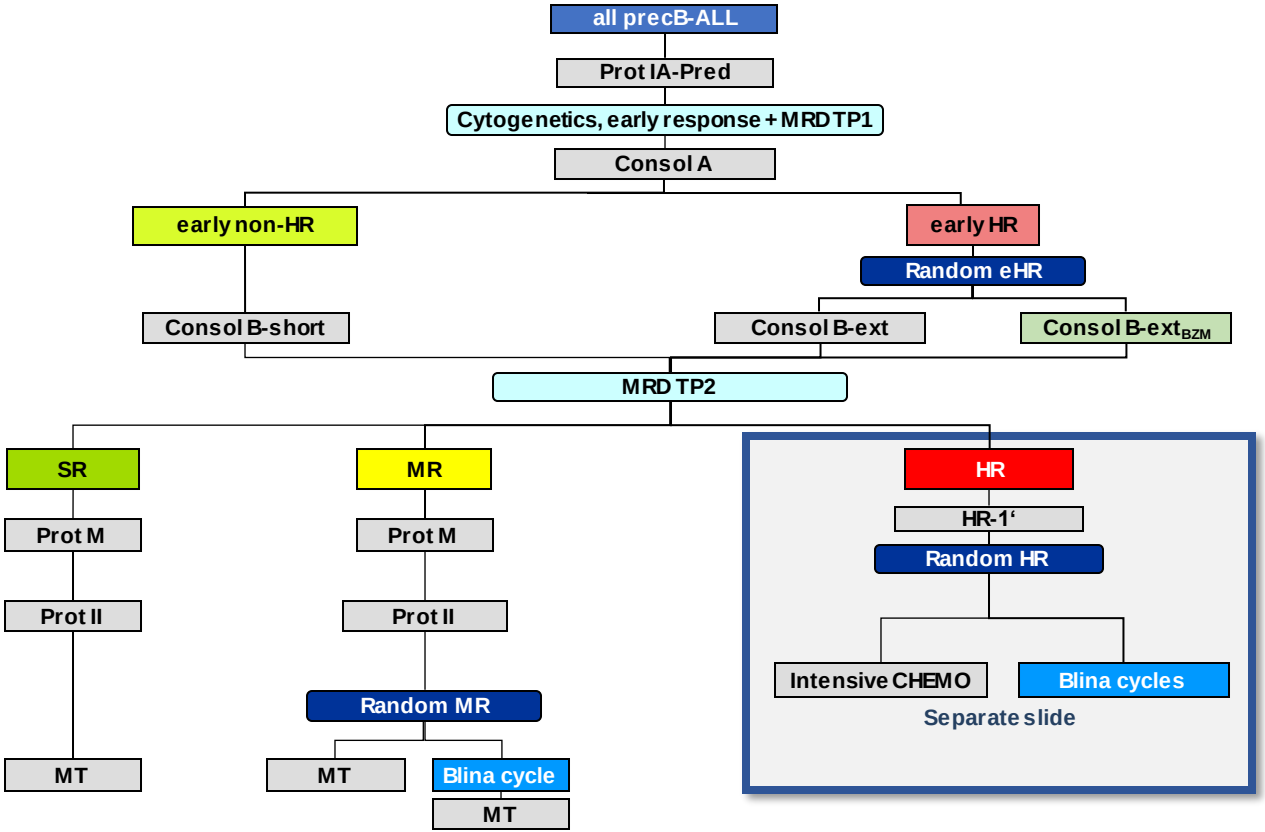
AIEOP-BFM ALL 2017: pB-ALL



EUDRACT number: 2016-001935-12

AIEOP-BFM ALL 2017: pB-ALL

Overview of treatment

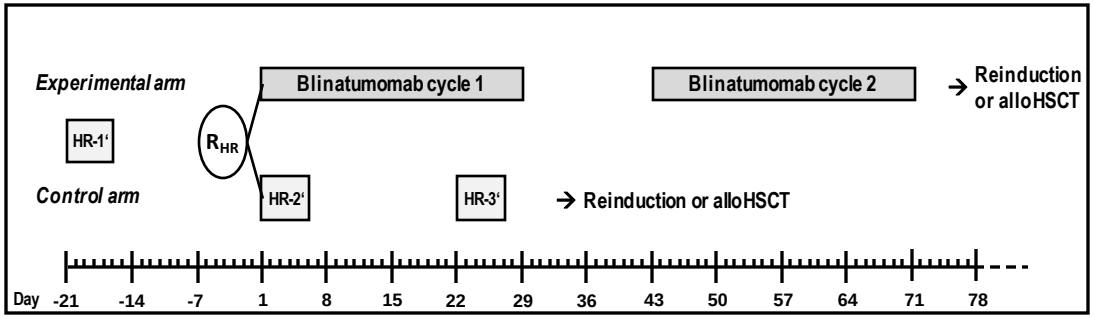


EUDRACT number: 2016-001935-12

AIEOP-BFM ALL 2017: pB-ALL

Approach for HR Patients: Randomization HR

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



Expected effects by novel post-consolidation therapy in HR patients

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

EUDRACT number: 2016-001935-12

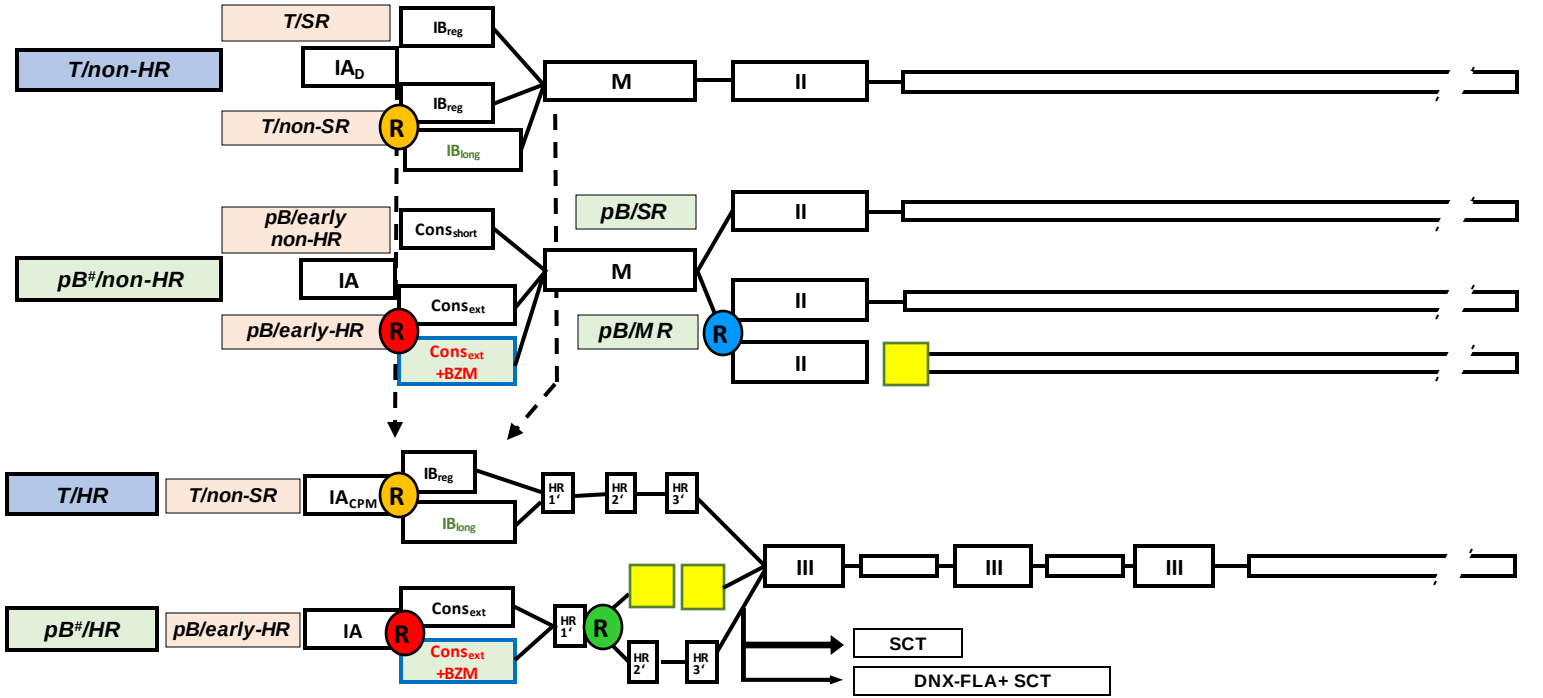
AIEOP-BFM ALL 2017: Genetic Screening and Consequences in Special Subgroups

- 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

EUDRACT number: 2016-001935-12

AIEOP-BFM ALL 2017: Treatment Overview

Randomizations

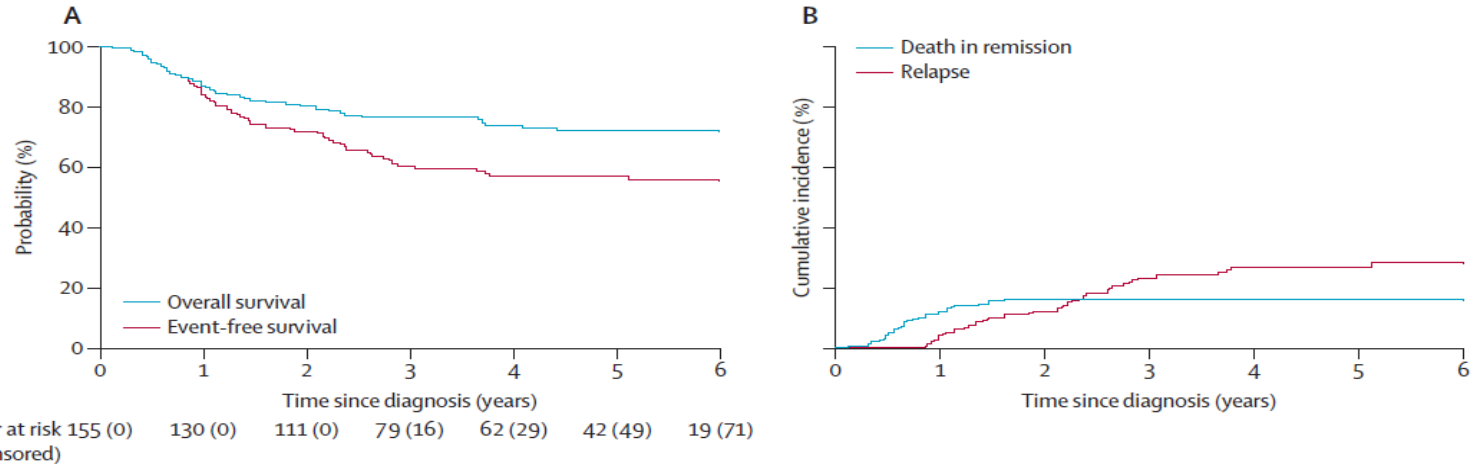


EUDRACT number: 2016-001935-12

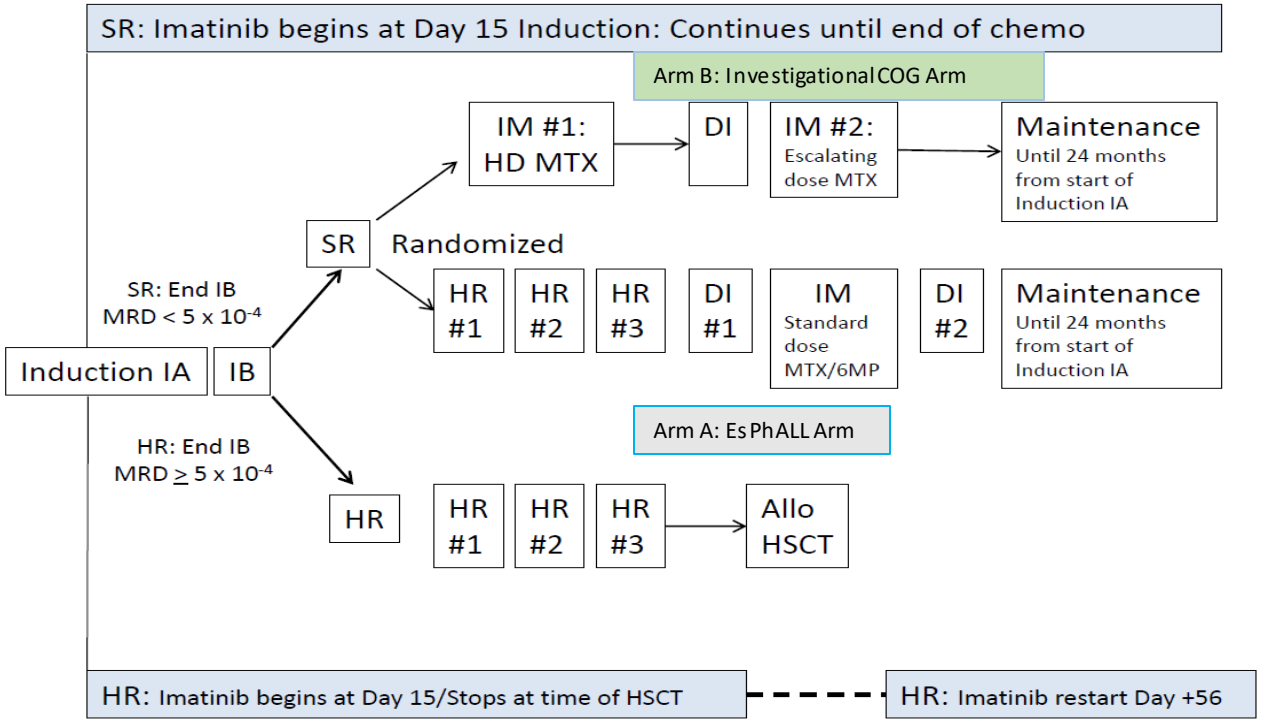
Imatinib treatment of paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (EsPhALL2010): a prospective, intergroup, open-label, single-arm clinical trial

THELANCETHAEMATOLOGY-D-18-00319
S2352-3026(18)30173-X

Andrea Biondi, Virginie Gandemer*, Paola De Lorenzo, Gunnar Cario, Myriam Campbell, Anders Castor, Rob Pieters, André Baruchel, Ajay Vora, Veronica Leoni, Jan Stary, Gabriele Escherich, Chi-Kong Li, Giovanni Cazzaniga, Hélène Cavé, Jutta Bradtke, Valentino Conter, Vaskar Saha, Martin Schrappe†, Maria Grazia Valsecchi†*



EsPhALL2017/COGAALL1631: Trial Summary



EUDRACT number: 2017-000705-20

ALLO-SCT for Children and Adolescents With ALL: ALL SCT Ped FORUM (For Omitting Radiation Under Majority Age)

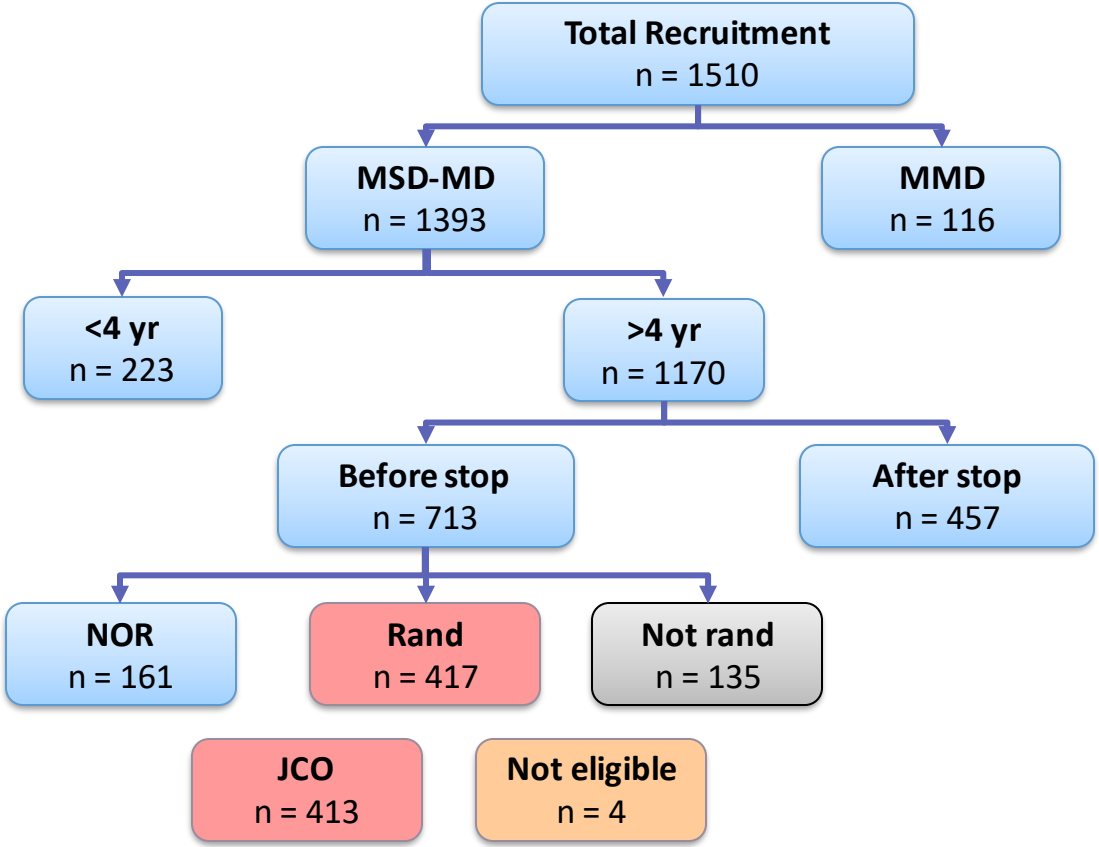
Christina Peters, Peter Bader, Franco Locatelli, Ulrike Pötschger, for the Study Group

Overall Recruitment (n = 1510)

2015	2016	2017	2018	2019	2020	2021
140 pts	194 pts	227 pts	270 pts	186 pts	220 pts	214 pts

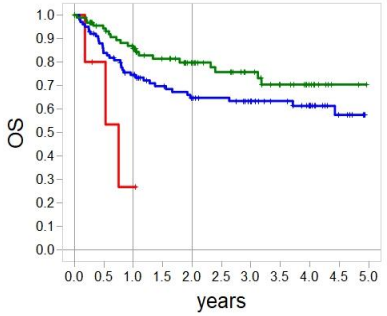
St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

ALL SCT pedFORUM

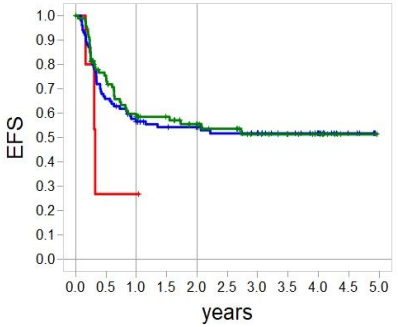

Total Recruitment
n = 1510
MSD-MD
n = 1393
MMD
n = 116
<4 yr
n = 223
>4 yr
n = 1170
Before stop
n = 713
After stop
n = 457
NOR
n = 161
Rand
n = 417
Not rand
n = 135
JCO
n = 413
Not eligible
n = 4

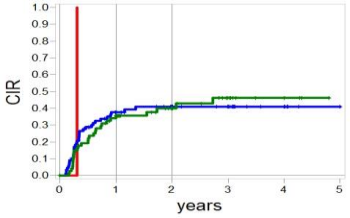
MSD/MD Younger Than 4 Years: Outcome According to Given Conditioning and Remission Status at TX

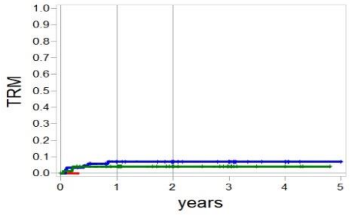
Overall survival

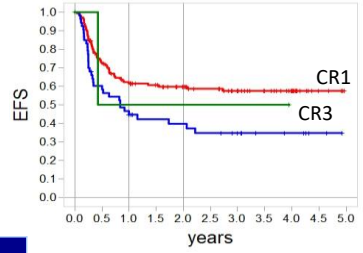


Event-free survival







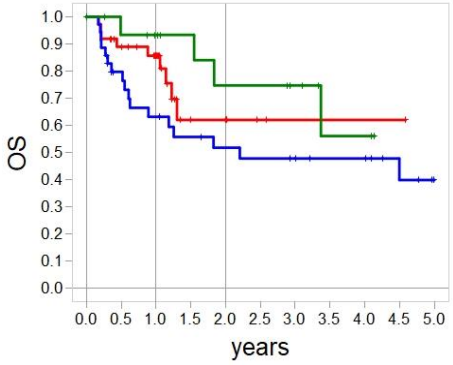


Conditioning	Patients	Events	2-yr OS	3-yr OS	*P* value*	Events	2-yr EFS	3-yr EFS	*P* value*
TBI/VP16	5	3	.27 ± .23	.27 ± .23		3	.27 ± .23	.27 ± .23	
FLU/THIO/BU	100	36	.65 ± .05	.63 ± .05	.075	47	.54 ± .05	.52 ± .05	.794
FLU/THIO/TREO	91	20	.80 ± .05	.76 ± .05		40	.55 ± .05	.51 ± .06	

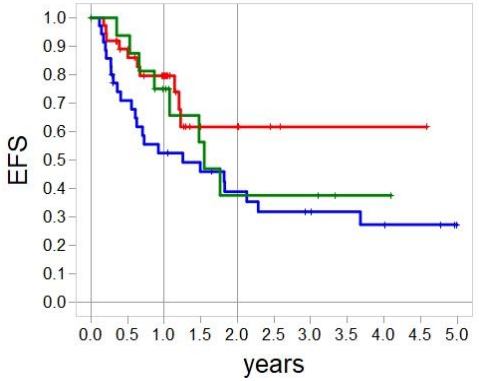
*Bu vs Treo

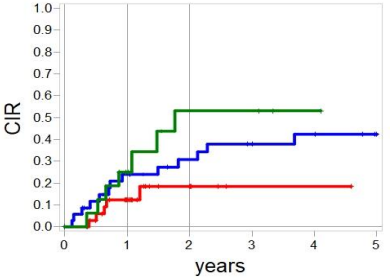
AlloHSCT From Mismatched Donors: n = 116
MMFD: n =72, CB: n = 24, MMUD: n = 6

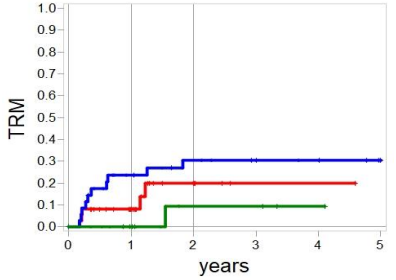
Overall survival



Event-free survival

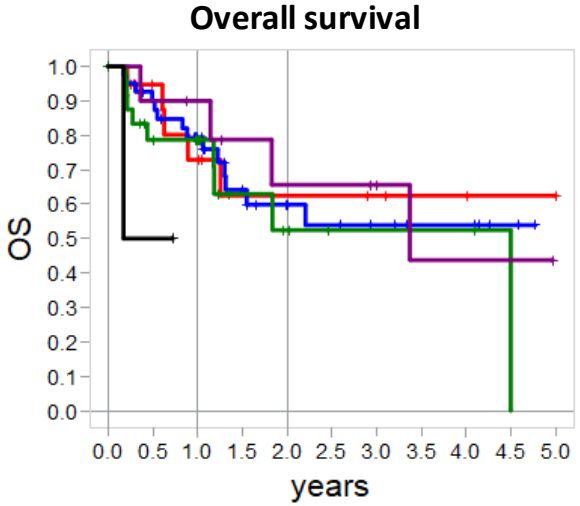


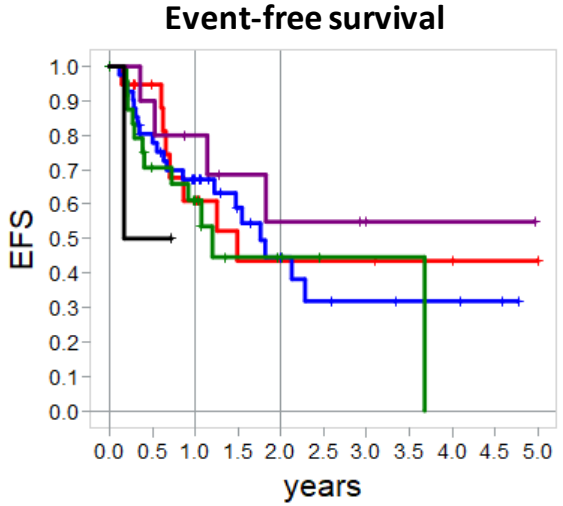




Conditioning	Patients	Events	2-yr OS	3-yr OS	*P* value	Events	2-yr EFS	3-yr EFS	*P* value
TBI/VP16	37	9	.62 ± .11	.62 ± .11	.203	10	.62 ± .11	.62 ± .11	.119
FLU/THIO/BU	35	17	.52 ± .09	.48 ± .09		23	.39 ± .09	.32 ± .08	
FLU/THIO/TREO	16	4	.75 ± .13	.75 ± .13		8	.38 ± .14	.38 ± .14	

MMD

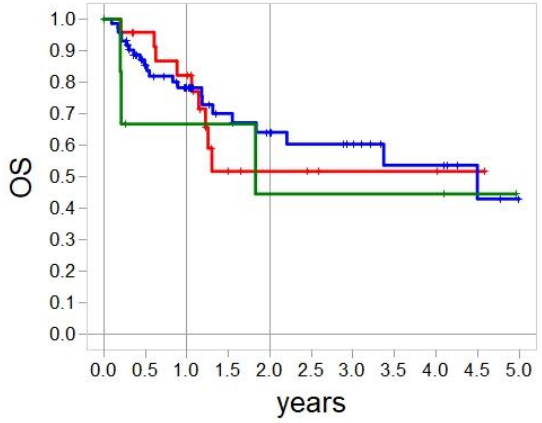


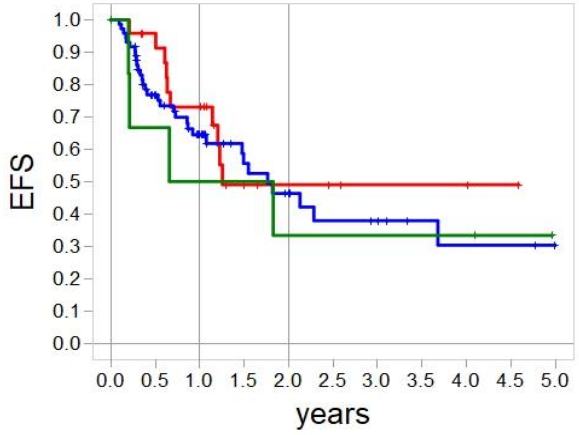


A group2	Patients	Events	2-yr OS	3-yr OS	*P* value
<4	19	5	.62 ± .14	.62 ± .14	.396
4–10	41	14	.60 ± .09	.54 ± .10	
10–14	24	9	.52 ± .14	.52 ± .14	
14–18	10	4	.66 ± .16	.66 ± .16	
>18	2	1	.50 ± .35	.50 ± .35	

Events	2-yr EFS	3-yr EFS	*P* value
8	.44 ± .14	.44 ± .14	.596
20	.45 ± .10	.32 ± .10	
12	.45 ± .13	.45 ± .13	
4	.55 ± .17	.55 ± .17	
1	.50 ± .35	.50 ± .35	

MMUD vs MMFD vs CB EFS + OS





	Patients	Events	1-yr OS	2-yr OS	*P* value
CB	24	9	.82 ± .08	.52 ± .12	.782
MMFD	72	22	.78 ± .05	.64 ± .07	
MMUD	6	3	.67 ± .19	.44 ± .22	

Events	1-yr EFS	2-yr EFS	*P* value
10	.73 ± .09	.49 ± .12	.714
32	.64 ± .06	.46 ± .08	
4	.50 ± .20	.33 ± .19	

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ALL SCT pedFORUM

Question 1

What genetic abnormality in pediatric ALL-patients is known to be a bad prognostic factor?

1. Hyperdiploid
2. *IKFZ1*^{plus}
3. *ETV6-RUNX1*

Question 2

Which pediatric patients are NOT candidates for allogeneic HSCT?

1. Children below 1 year of age and any *KMT2A* rearrangement
2. Patients not in complete morphological remission
3. Patients with hypodiploidy <45 chromosomes
4. Patients with T-ALL in second remission

Global Leukemia Academy

Current treatment options for relapsed ALL in children, including HSCT

Franco Locatelli

APTITUDE HEALTH

Question

Which children and adolescents 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

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.

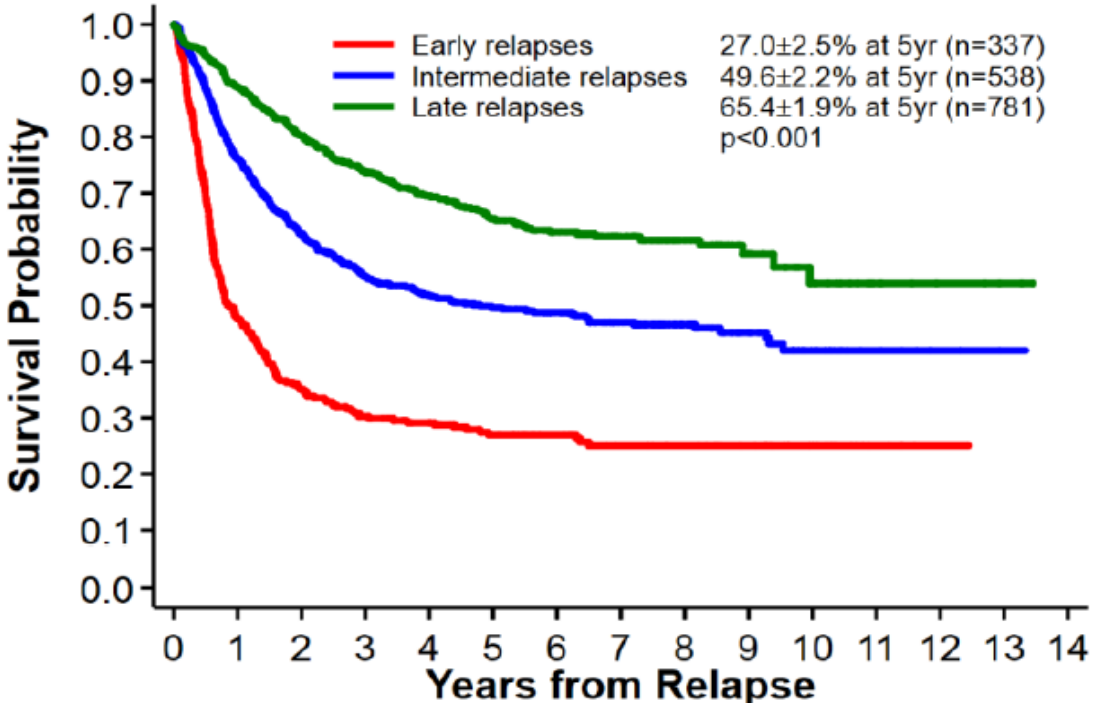
IntReALL: Definition of strategy groups SR and HR

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

VHR features

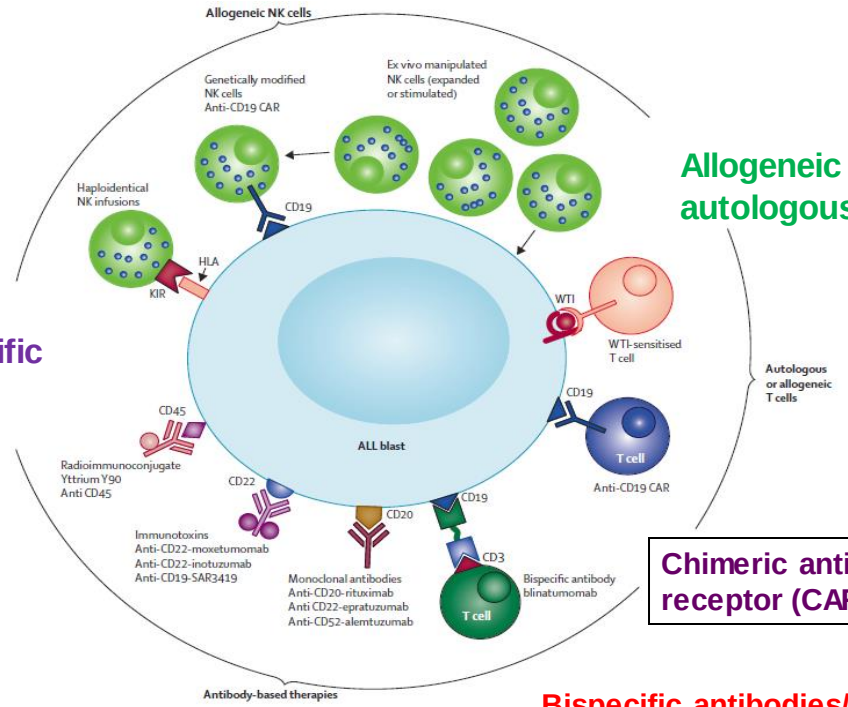
MLL rearrangements (MLL/AF4)
TCF3-PBX1 [t(1;19)]
TCF3-HLF [t(17;19)]
Hypodiploidy (ie, <44 chromosomes)
TP53 alterations
Very early (ie, <18 months from diagnosis) isolated or combined bone marrow relapse



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

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

New immunologic approaches under investigation in childhood ALL



Allogeneic and autologous NK cells

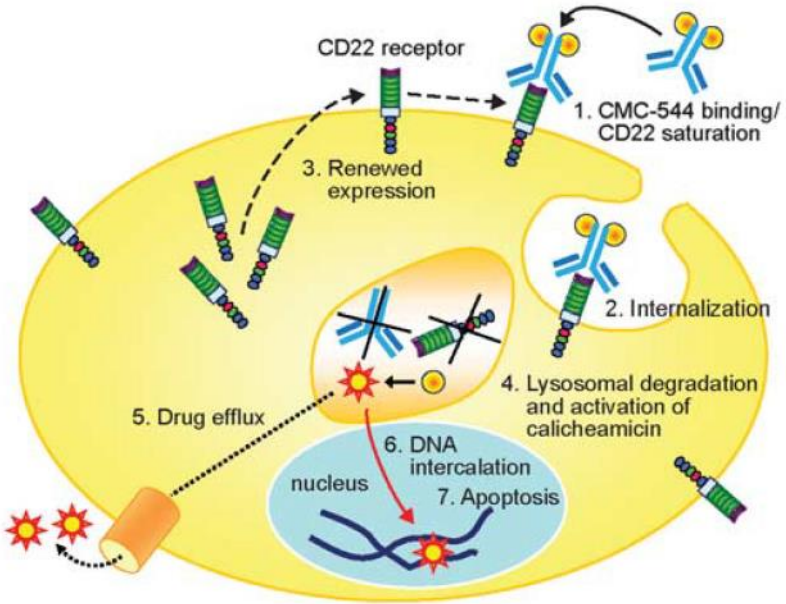
Immunotoxin-specific antibodies

Chimeric antigen receptor (CAR) T cells

Bispecific antibodies/antibody constructs

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

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.

Inotuzumab ozogamicin – pediatric experience

CLINICAL TRIALS AND OBSERVATIONS

A phase 1 study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study)

Erica Brivio,[1,2] Franco Locatelli,[3] Marta Lopez-Yurda,[1,4] Andrea Malone,[5] Cristina Díaz-de-Heredia,[6] Bella Bielorai,[7] Claudia Rossig,[8] Vincent H. J. van der Velden,[9] Anneke C. J. Ammerlaan,[1] Adriana Thano,[1,4] Inge M. van der Sluis,[1,2] Monique L. den Boer,[1,2,10] Ying Chen,[11] Barbara Sleight,[12] Benoit Brethon,[13] Karsten Nysom,[14] Lucie Sramkova,[15] Ingrid Øra,[16,17] Luciana Vinti,[3] Christiane Chen-Santel,[18,19] and Christian Michel Zwaan[1,2]

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

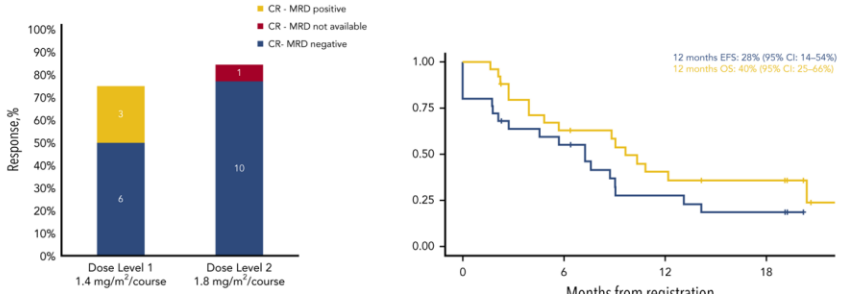
Safety
- Similar toxicity at DL1 and DL2 (1.4 and 1.8 mg/m^2/course)
- Gr 3/4 neutropenia and thrombocytopenia in almost all patients
- 2 SOS cases after additional chemotherapy (1 DL1, 1 DL2)

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

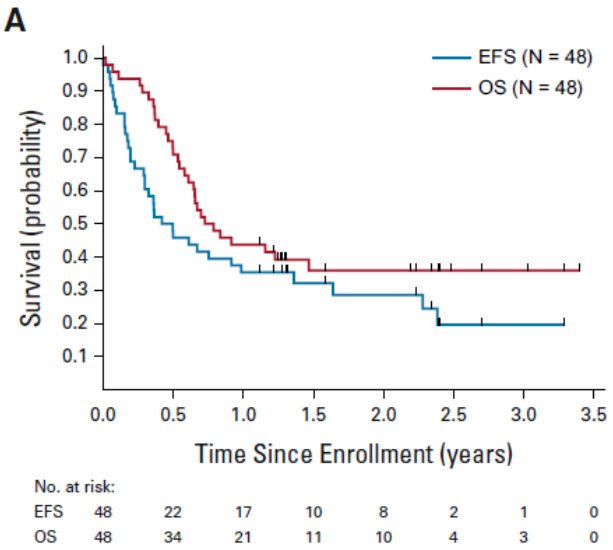
RP2D = DL2 (1.8 mg/m2/course)



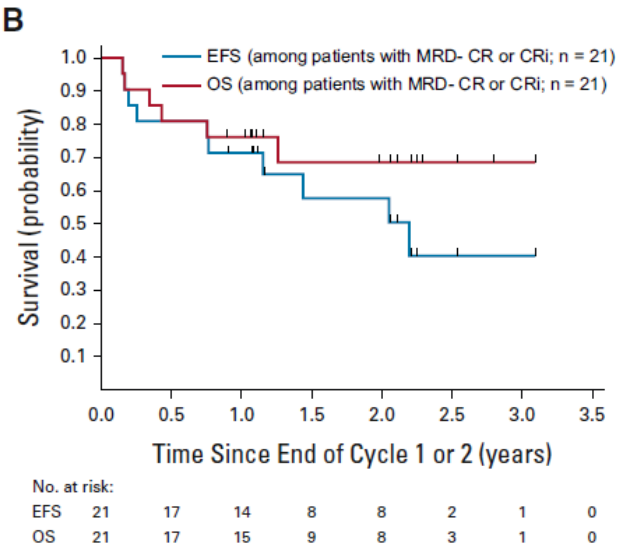
Brivio E, et al. *Blood*. 2021;137(12): 1582-1590.

Inotuzumab in R/R patients

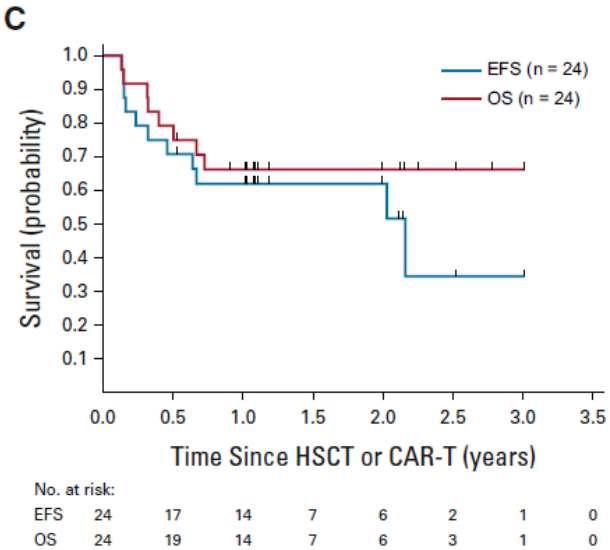
All patients



Patients who responded

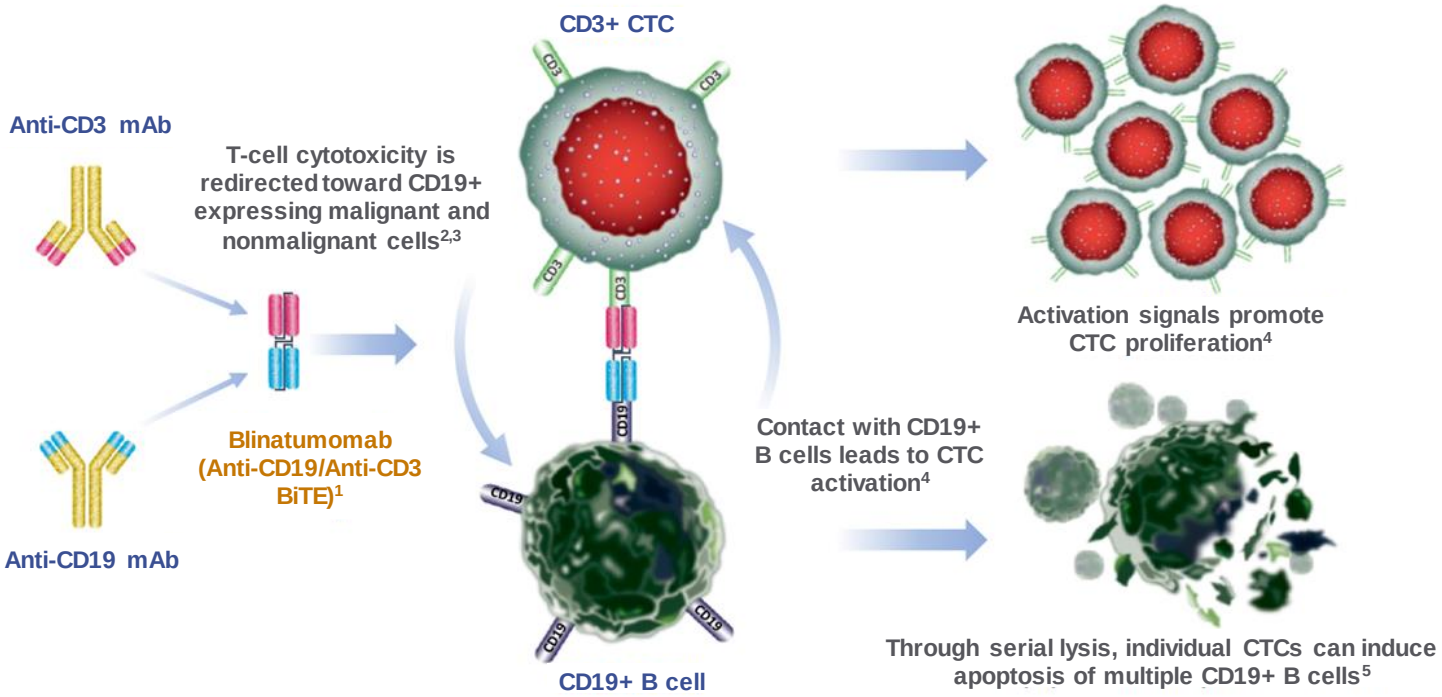


Patients receiving HSCT or CAR



O'Brien MM, et al. *J Clin Oncol*. 2022;40:956-967.

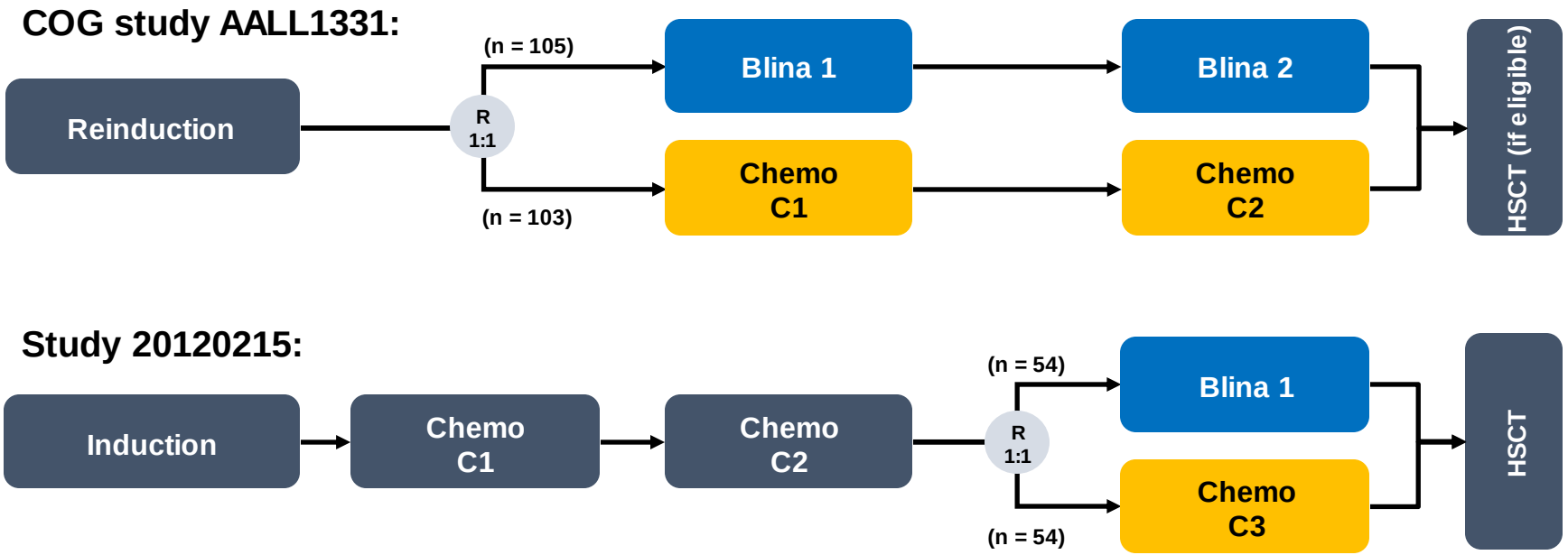
Blinatumomab (CD19 BiTE® molecule)



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

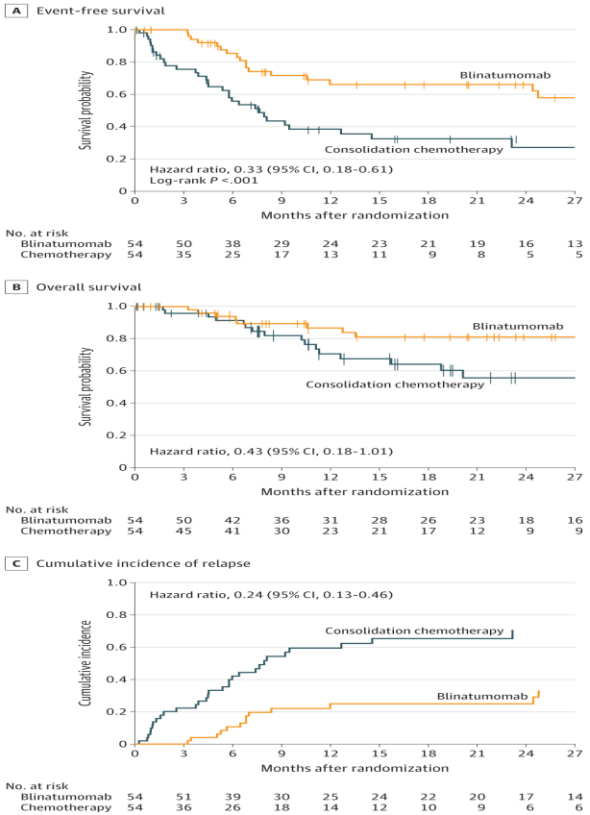


Brown PA, et al. *JAMA*. 2021;325:888-842; Locatelli F, et al. *JAMA*. 2021;325:843-854.

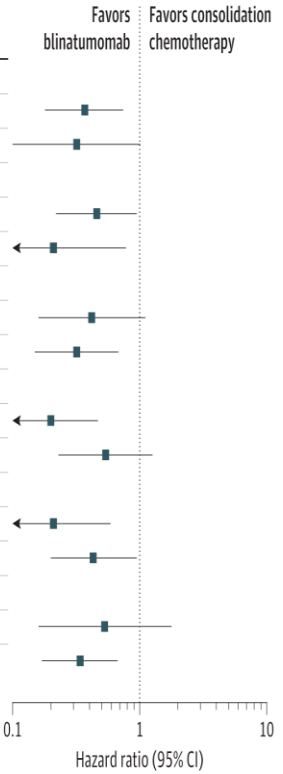
JAMA Network™

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

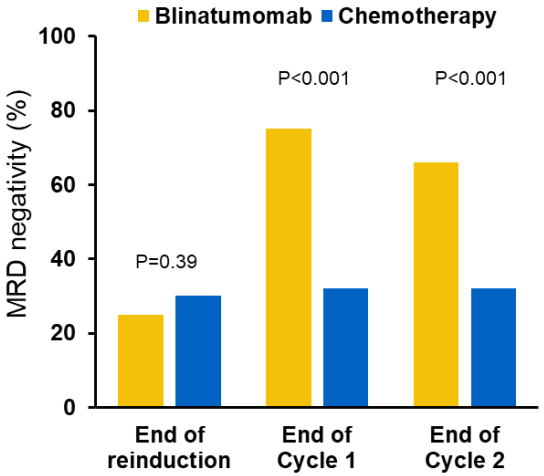


Subgroup	No. of events/No. treated (%) Blinatumomab	Consolidation chemotherapy	Hazard ratio (95% CI)
Age, y			
1-9	12/39 (30.8)	23/38 (60.5)	0.37 (0.18-0.74)
>9	5/15 (33.3)	8/16 (50.0)	0.32 (0.10-1.01)
Minimal residual disease at end of induction			
$<10^{-3}$ Blast cells	12/35 (34.3)	19/34 (55.9)	0.46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

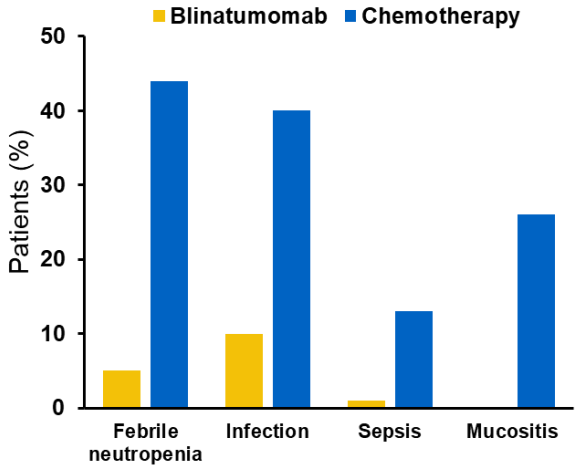


COG Study AALL1331: MRD, AEs, bridging to HSCT

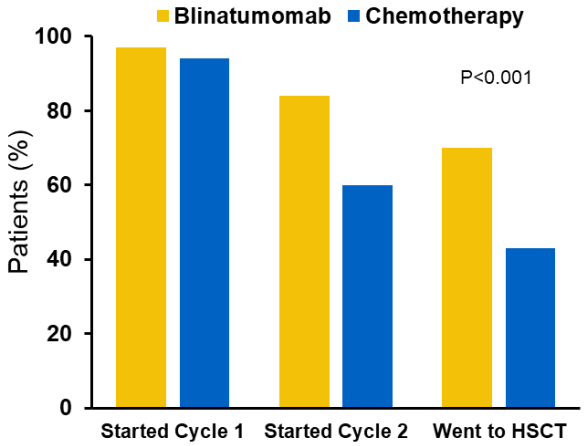
MRD clearance



Adverse events



Bridge to transplant

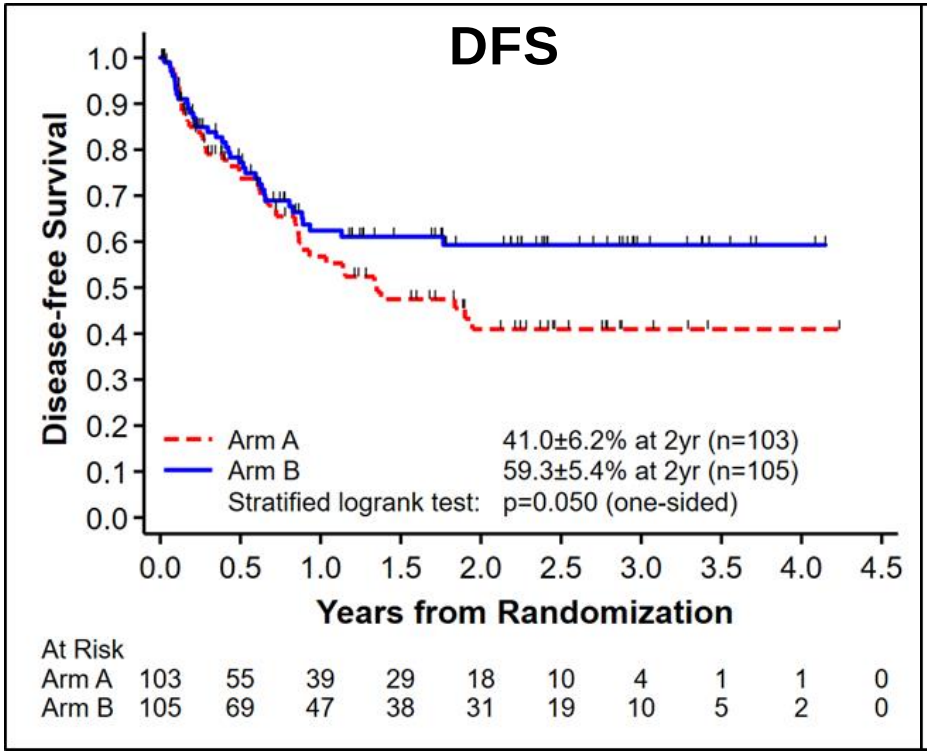


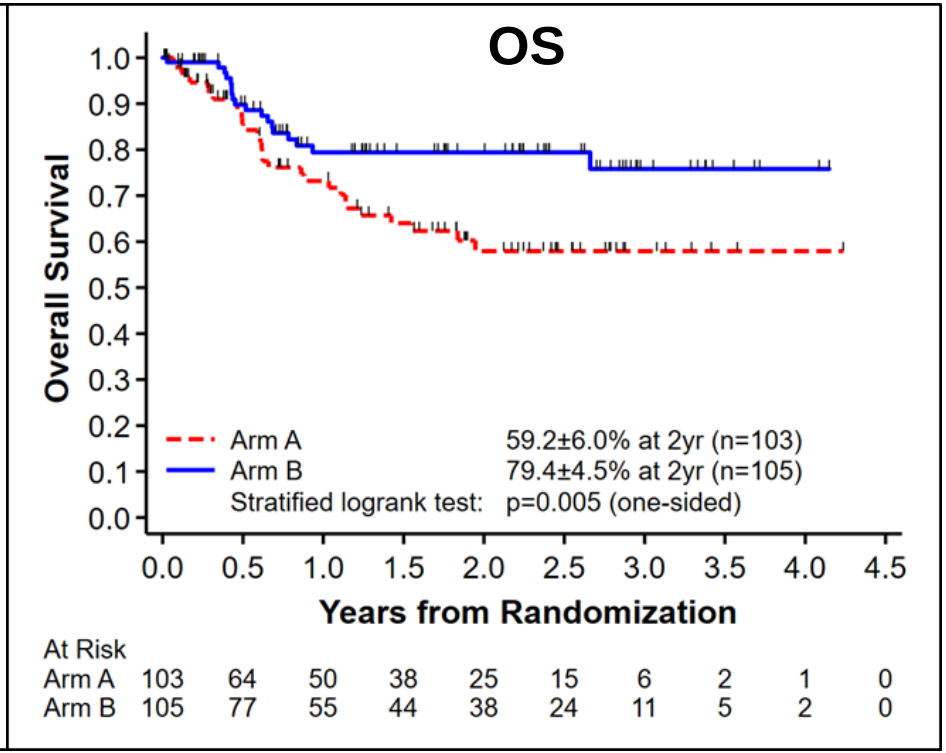
Important contributors to the improved outcomes for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may include better **MRD clearance, less toxicity and greater ability to successfully bridge to HSCT**

Brown PA, et al. JAMA 2021;325:888–42.

The dosing and administration of blinatumomab in this study may differ from that which is approved in your country. Please refer to your local Prescribing Information.

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

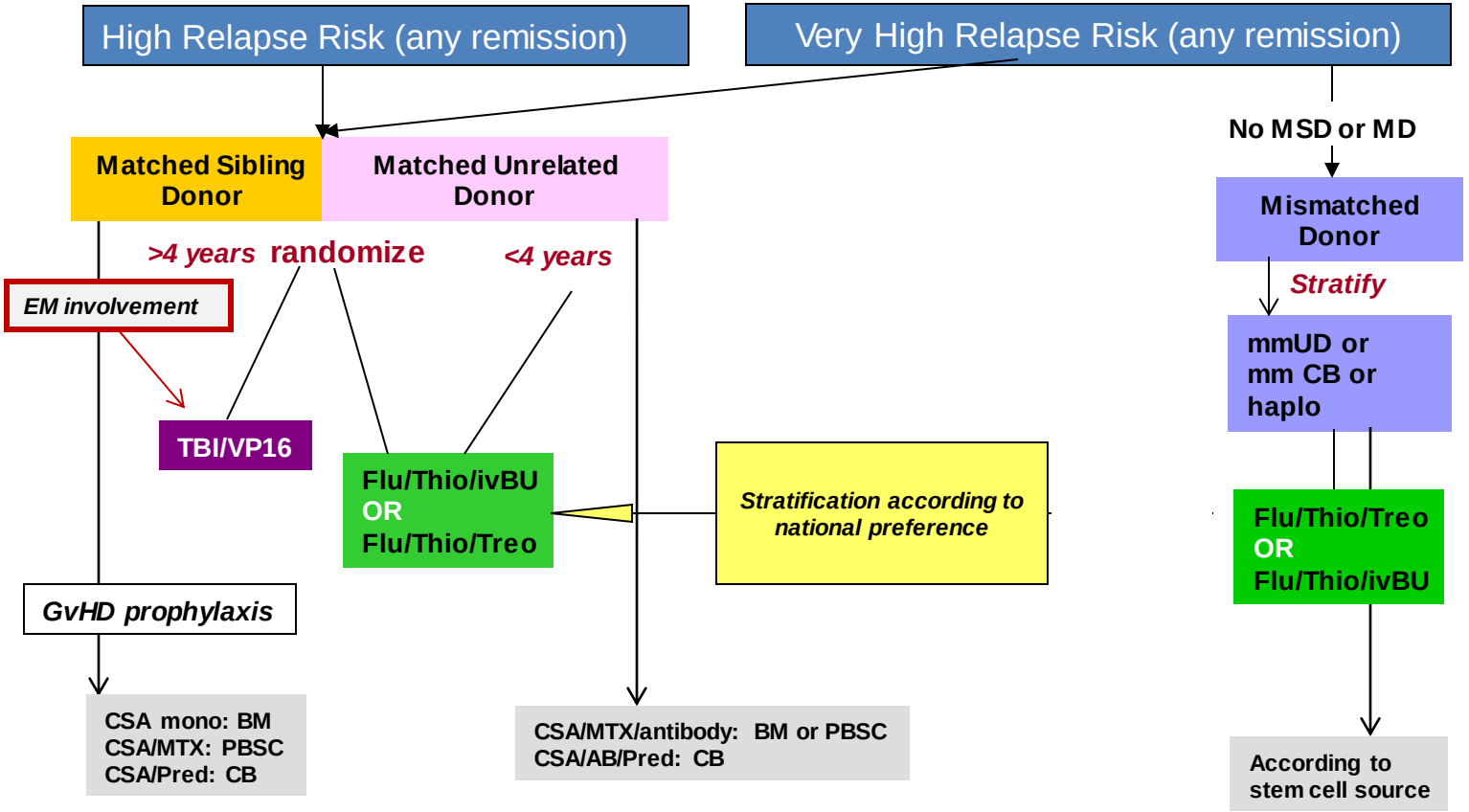




Median follow-up 1.4 years

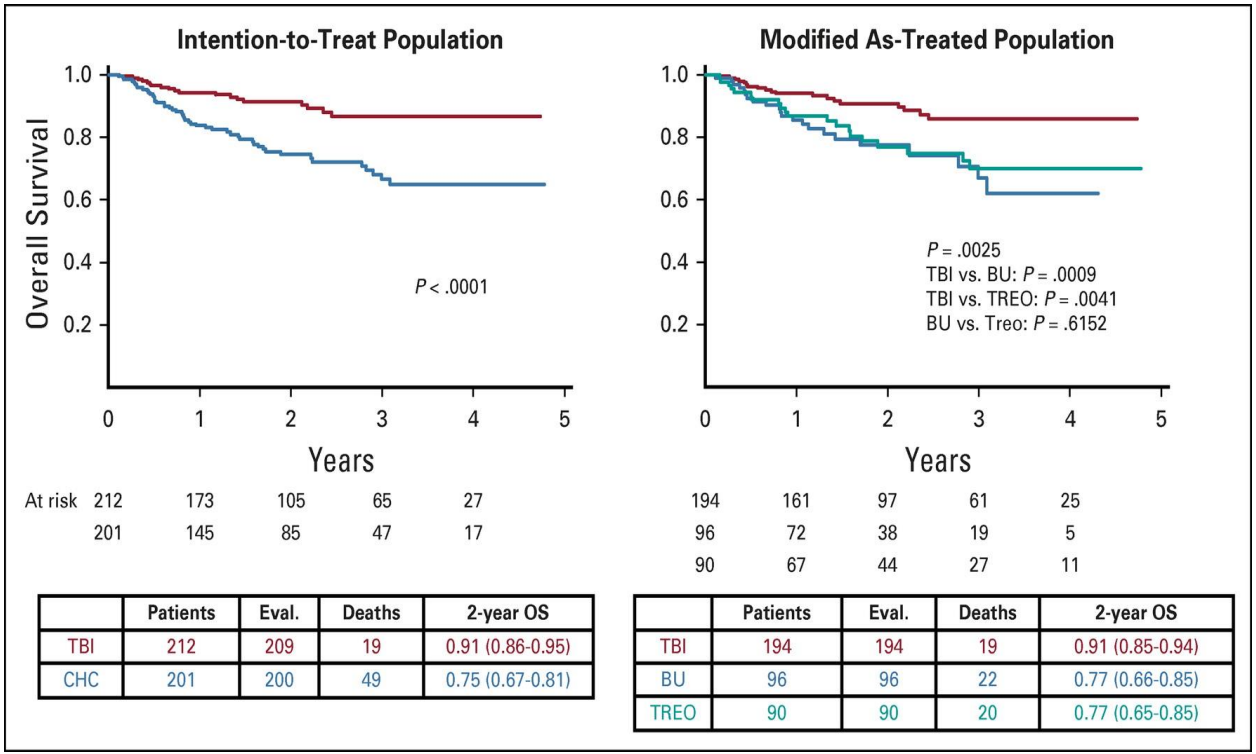
Brown PA, et al. *JAMA*. 2021;325:888-842.

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

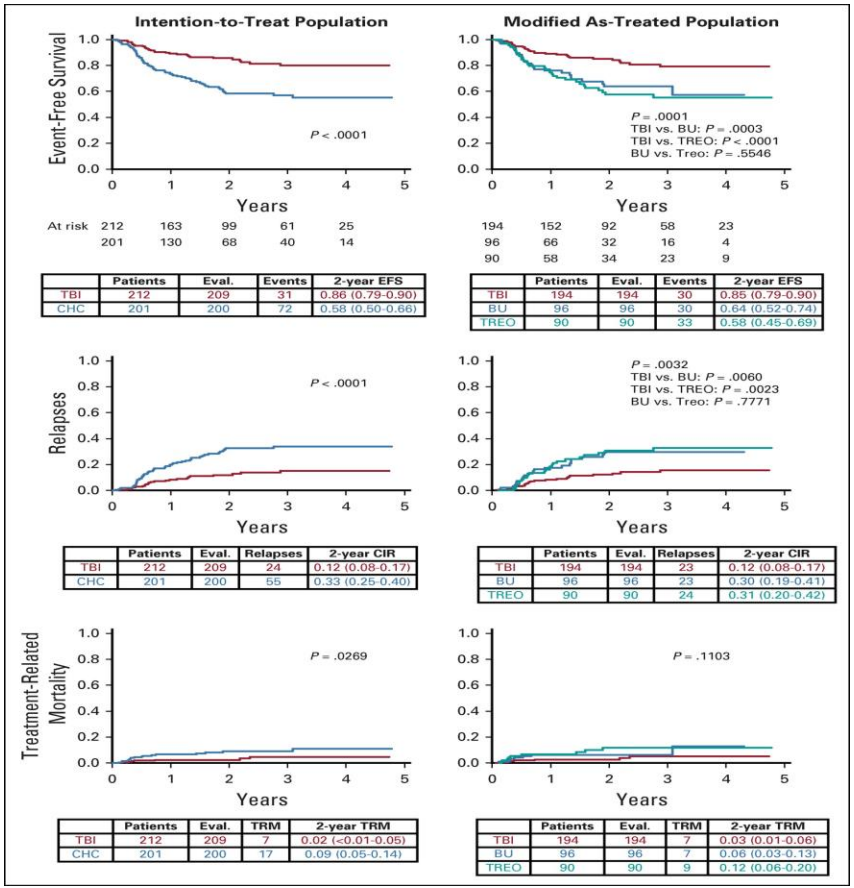


	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

	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



	Patients	Eval.	Events	2-year EFS
TBI	212	209	31	0.86 (0.79-0.90)
CHC	201	200	72	0.58 (0.50-0.66)

	Patients	Eval.	Events	2-year EFS
TBI	194	194	30	0.85 (0.79-0.90)
BU	96	96	30	0.64 (0.52-0.74)
TREO	90	90	33	0.58 (0.45-0.69)

	Patients	Eval.	Relapses	2-year CIR
TBI	212	209	24	0.12 (0.08-0.17)
CHC	201	200	55	0.33 (0.25-0.40)

	Patients	Eval.	Relapses	2-year CIR
TBI	194	194	23	0.12 (0.08-0.17)
BU	96	96	23	0.30 (0.19-0.41)
TREO	90	90	24	0.31 (0.20-0.42)

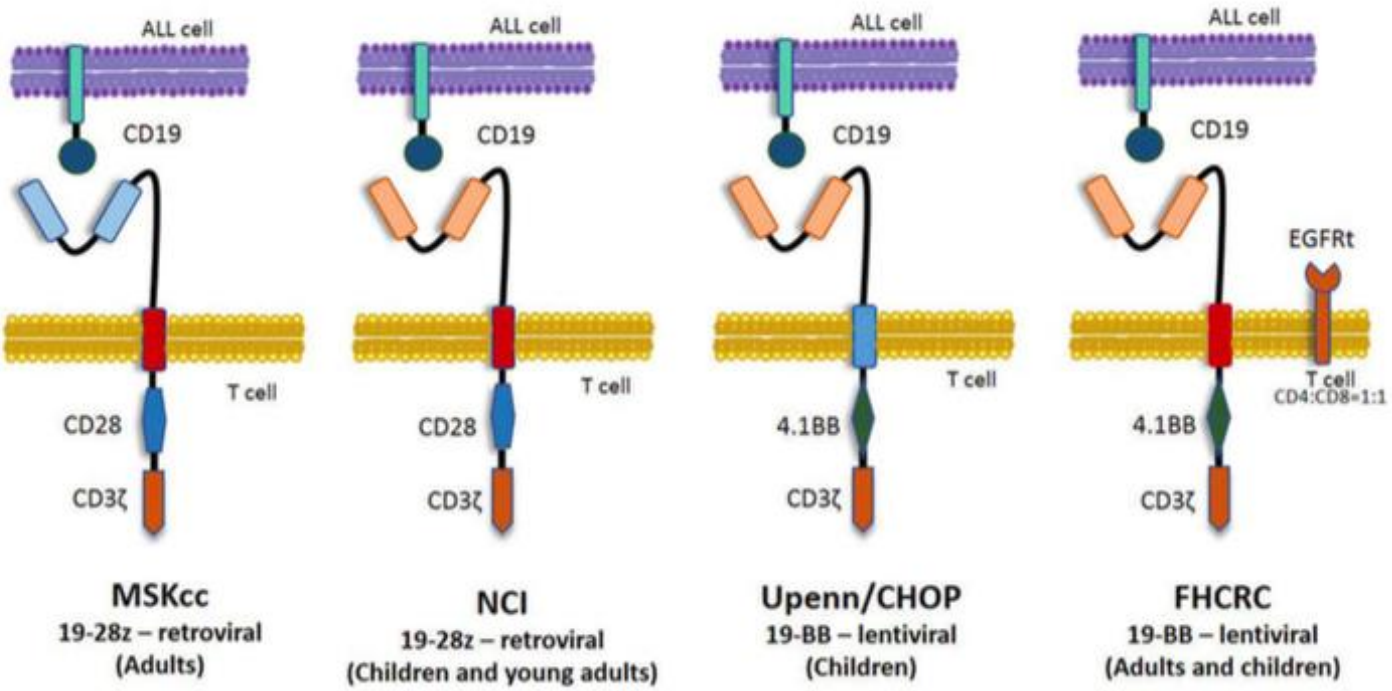
	Patients	Eval.	TRM	2-year TRM
TBI	212	209	7	0.02 (<0.01-0.05)
CHC	201	200	17	0.09 (0.05-0.14)

	Patients	Eval.	TRM	2-year TRM
TBI	194	194	7	0.03 (0.01-0.06)
BU	96	96	7	0.06 (0.03-0.13)
TREO	90	90	9	0.12 (0.06-0.20)

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

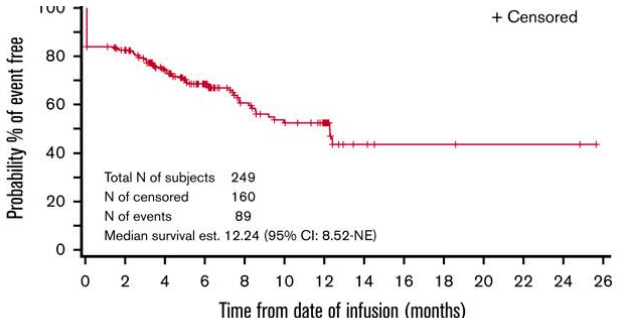
CAR design important for persistence and sustained efficacy

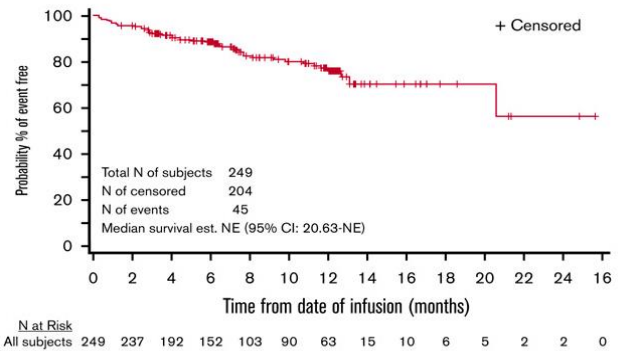


Del Bufalo F, Locatelli F, et al. *Expert Rev Clin Immunol*. 2019;15:497-509.

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

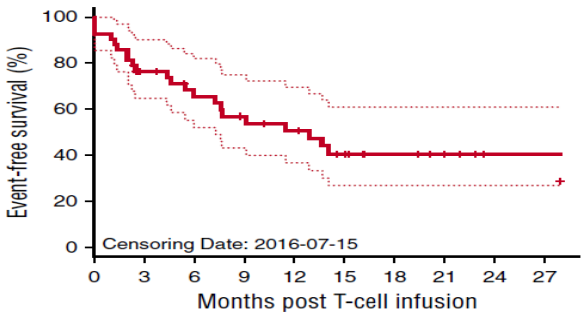
Tisagenlecleucel – real-world evidence (Novartis)

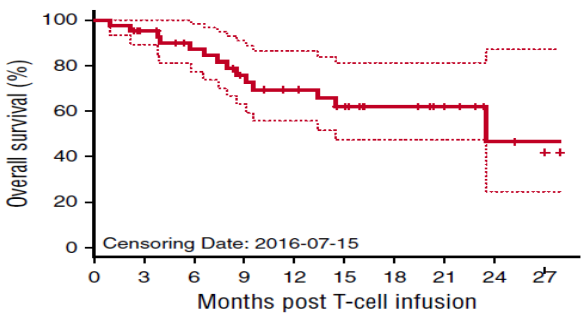




Pasquini MC, et al. *Blood Adv.* 2020;4:5414-5424.

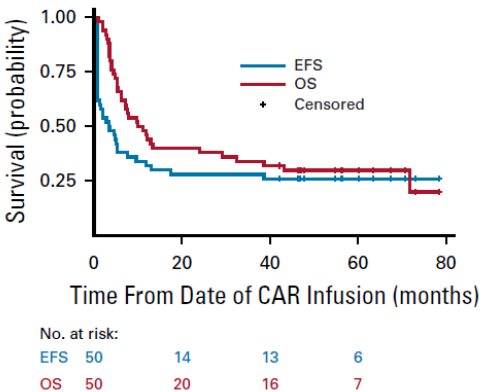
1:1 CD4:CD8 CD19CAR-T2A-EGFRt (Seattle)





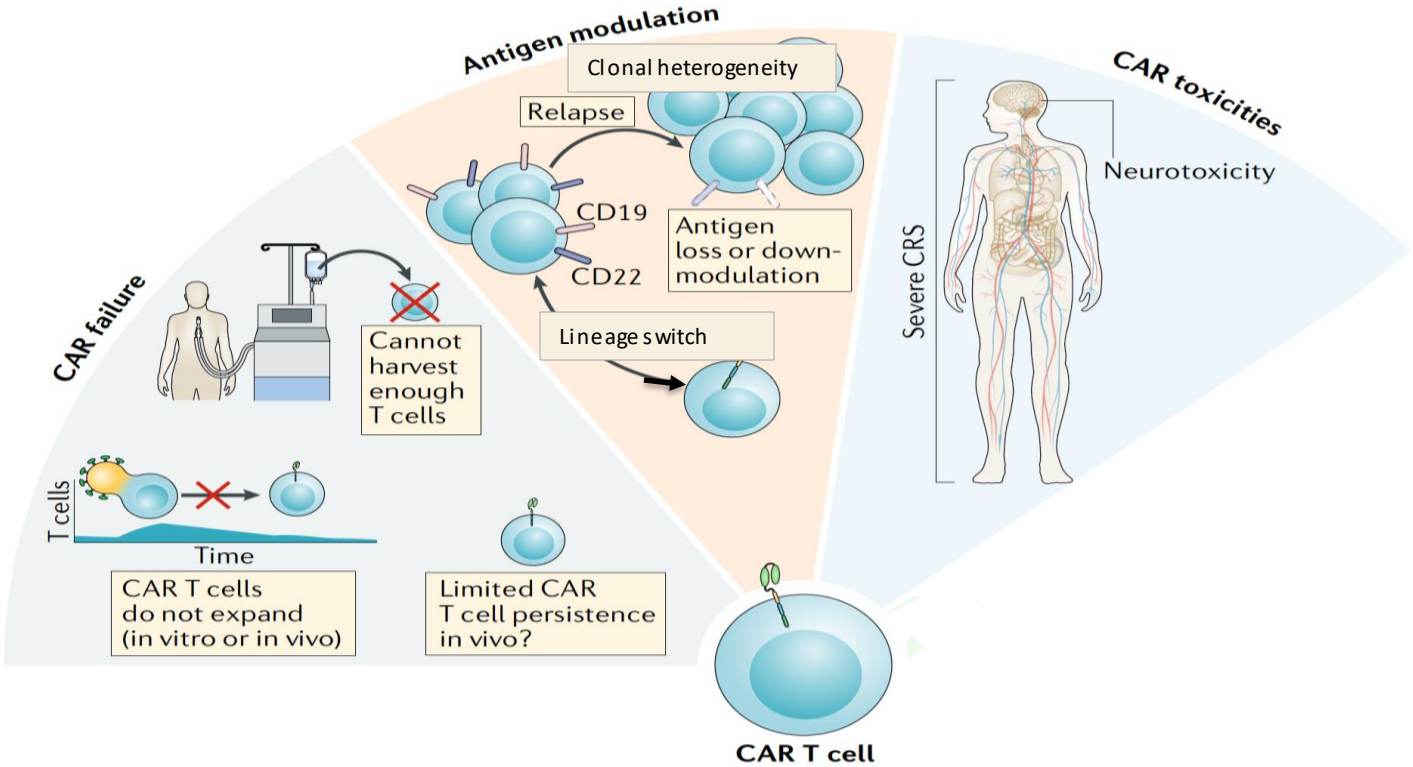
Gardner RA, et al. *Blood*. 2017;129:3322-3331.

CD19.28ζ-CAR T (NCI)



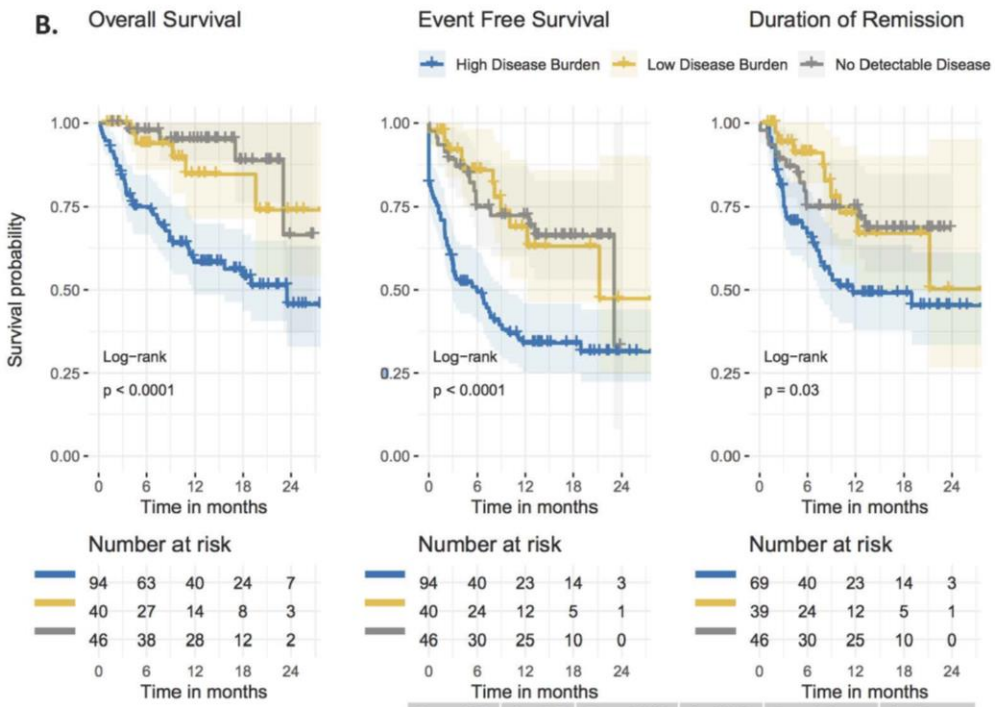
Shah NN, et al. *J Clin Oncol*. 2021;39:1650-1659.

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

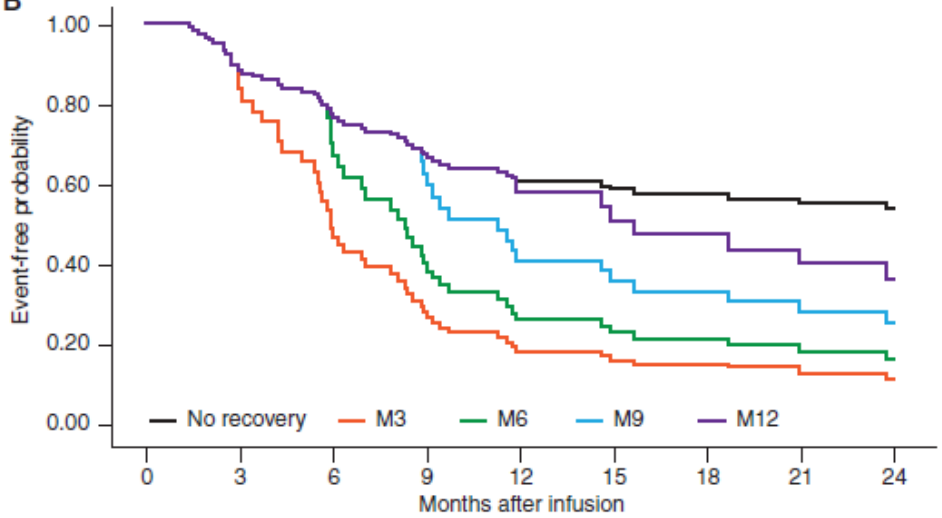
Schultz LM, et al. ASH 2020. Abstract 468.

B-cell aplasia and relapse after tisagenlecleucel

A

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

B

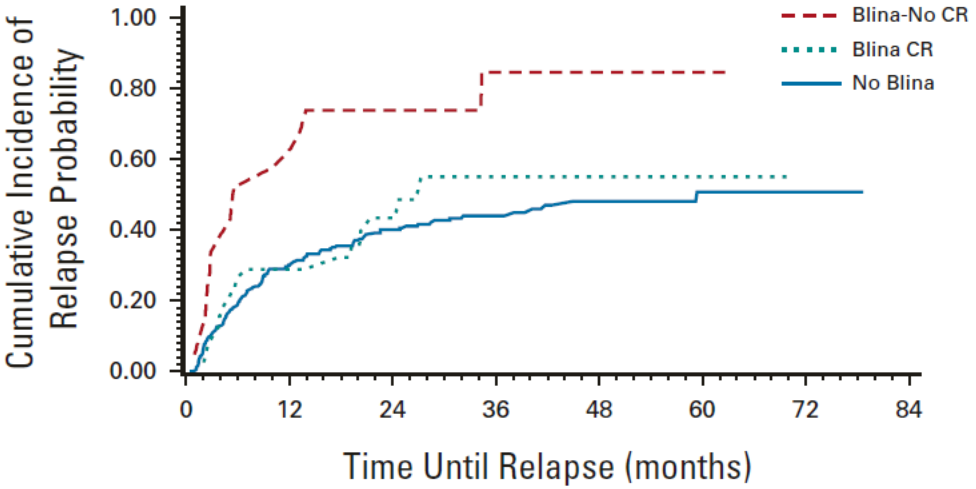


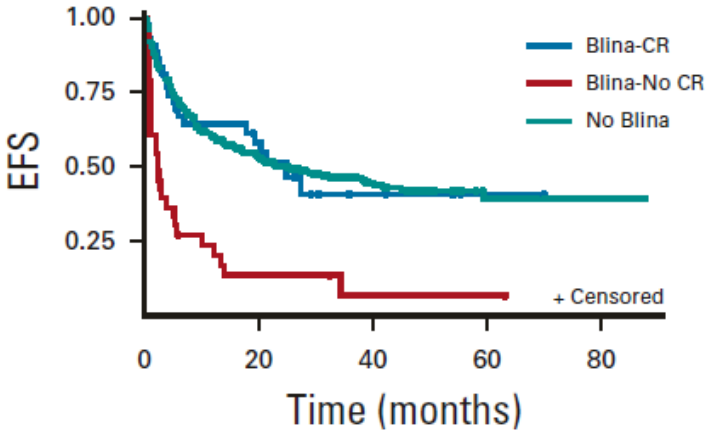
Cumulative risk for BCA loss within 12 months

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

Pulsipher MA, et al. *Blood Cancer Discov*. 2022;3:66-81.

Patients who respond to blinatumomab have identical survival with "*blina-naive*" individuals





No. at risk:					
Blina-CR	43	18	4	1	0
Blina-No CR	34	4	1	1	0
No Blina	343	143	48	16	1

Myers RM, et al. *J Clin Oncol*. 2021;40:932-944.

CD19-CAR_Lenti: Peculiarities

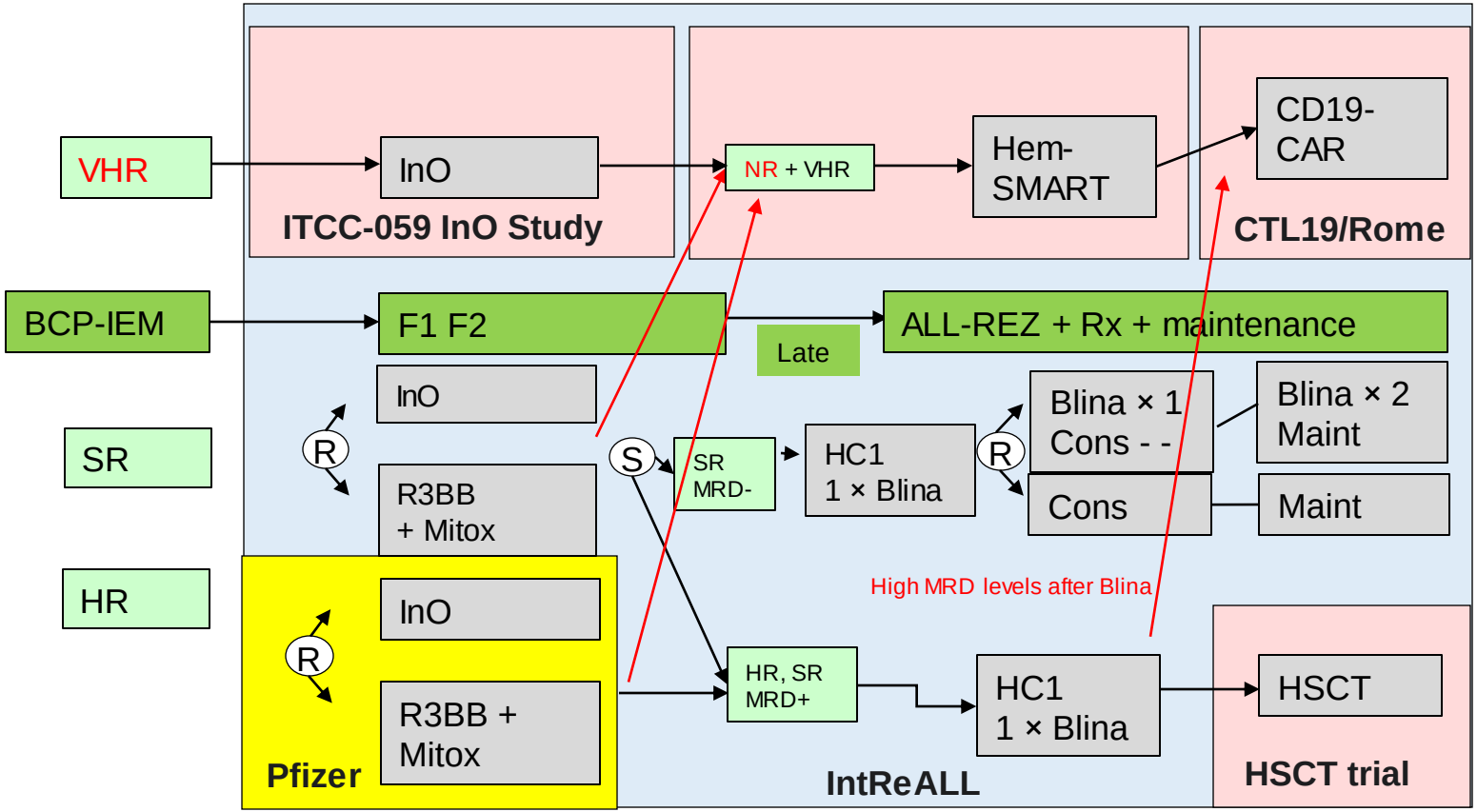
Viral platform	Lentivirus
Viral supernatant	Provided by Miltenyi Biotec
Reagents	Granted by Miltenyi Biotec at reduced costs
Production	Automated (CliniMACS Prodigy®)
Starting material	Fresh apheresis (0.75-1.5 × 10^9 total WBC)
	CD4/CD8 enriched cells (20-200 × 10^6 cells)
Release	Fresh drug product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

Bambino Gesù
OSPEDALE PEDIATRICO

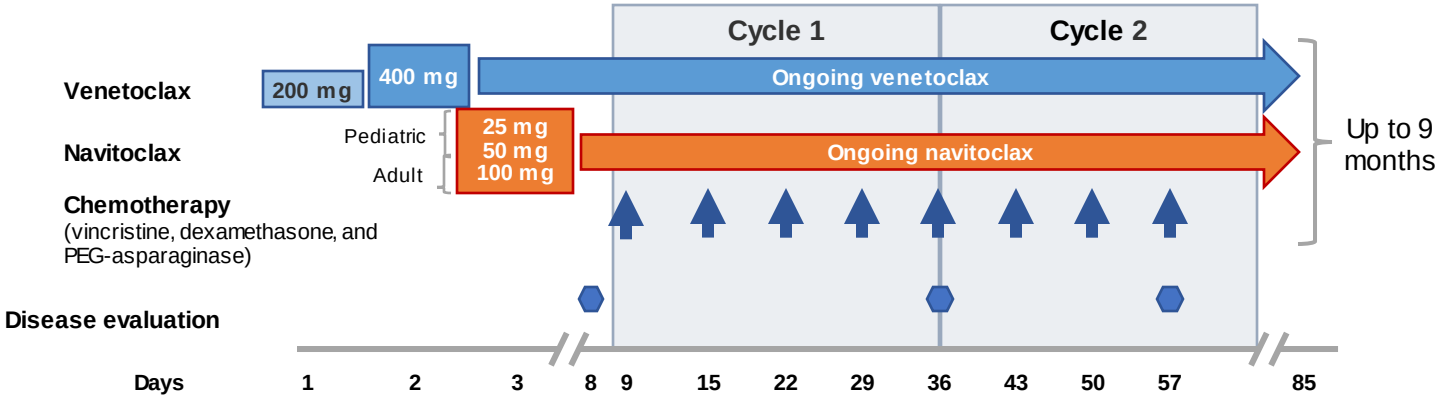
Patient outcomes

	Pt ID	Gender	Age (y)	Cytogenetic anomalies	Disease phase at infusion	Previous allogeneic HSCT	BM blasts at lymphodepletion	Response at d+28	Status at last FUP
	001	M	7	None	ALL 2nd relapse	No	8.9%	CR	Relapse (9 mo)
DL1	002	F	5	None	ALL 3rd relapse	Yes	15.7%	CR	Relapse (9 mo)
	003	F	7	47, XX (+21)	ALL 1st very early relapse	No	2.8%	CR	CR (8 mo)
	004	M	4	None	ALL 2nd relapse (combined BM + CNS)	Yes	0.6%	CR	CR (7 mo)
DL2	005	M	12	t(1;19)	ALL 1st refractory relapse (combined BM + bone)	No	2.3%	BM: CR Bone: PR	Deceased
	006	F	13	None	ALL 1st very early relapse (combined BM + bone + lymph nodes)	Yes	10%	CR	CR (4 mo)
	007	F	6	47, XX (+21)	ALL 1st refractory relapse	No	3%	CR	CR (3 mo)
DL3	008	F	5	None	ALL 1st refractory relapse	No	0.1%	CR	CR (2 mo)
	009	M	3	t(11;19)	ALL 1st refractory relapse	No	0.2%	CR	CR (1 mo)

Design IntReALL-BCP 2020



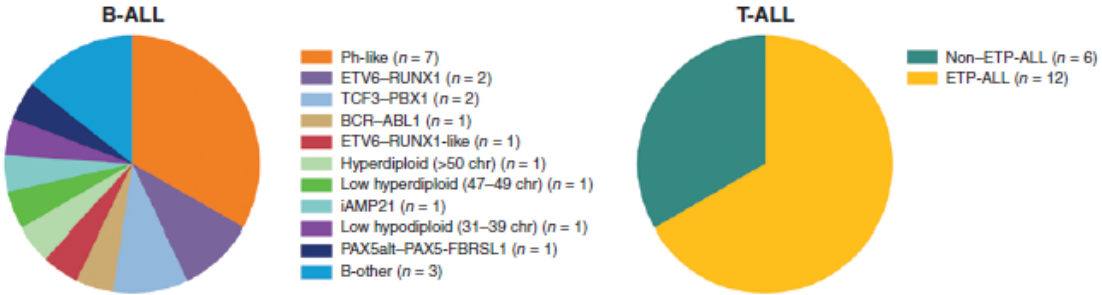
Study design and ALL subtypes profiling



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.

Summary of efficacy

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**

Question

Which children and adolescents 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

Global Leukemia Academy

Bispecifics for pediatric and AYA B-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, St. Anna Children's Hospital, Children Cancer Research Institute, Vienna, Austria

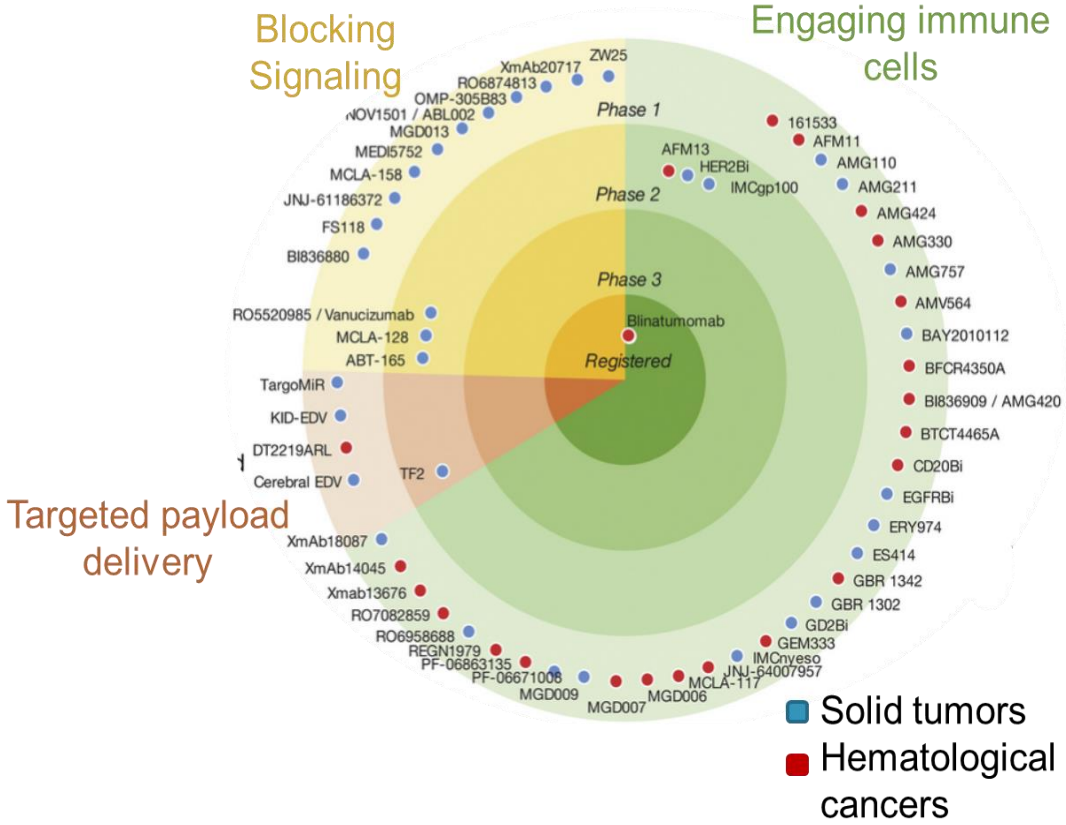
Global Leukemia Academy 2022

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

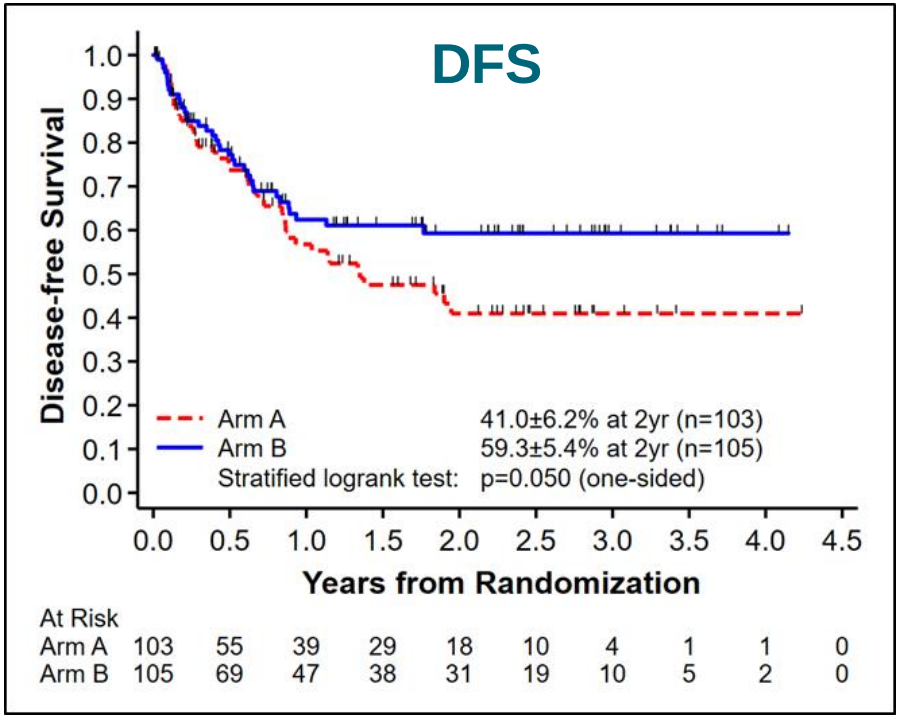
- Blinatumomab cIV infusion leads to rapid depletion of B-cells during Cycle 1, which is associated with decrease in serum immunoglobulin levels[1–3]
- Blinatumomab leads to a transient decrease in T-cell counts, followed by an accelerated recovery[1,3–5]
  - May induce peripheral expansion of T-cell 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

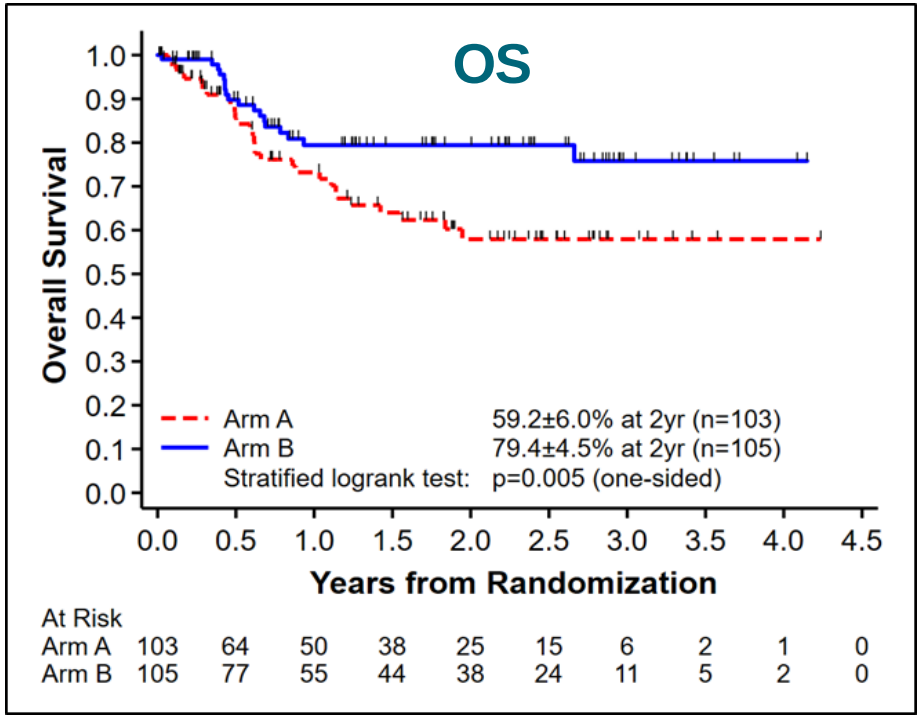
1. Zhu M, et al. *Clin Pharmacokinet.* 2016; 2. Zugmaier G, et al. *Blood Cancer J.* 2014;4:244; 3. Schub A, et al. ASCO 2013. Abstract 7020 and poster presentation; 4. Klinger M, et al. *Blood.* 2012;119:6226-6233; 5. Topp MS, et al. *J Clin Oncol.* 2011;29:2493-2498; 6. Topp MS, et al. *Lancet Oncol.* 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 First Relapse: Survival: Arm A (Chemotherapy) vs Arm B (Blinatumomab)





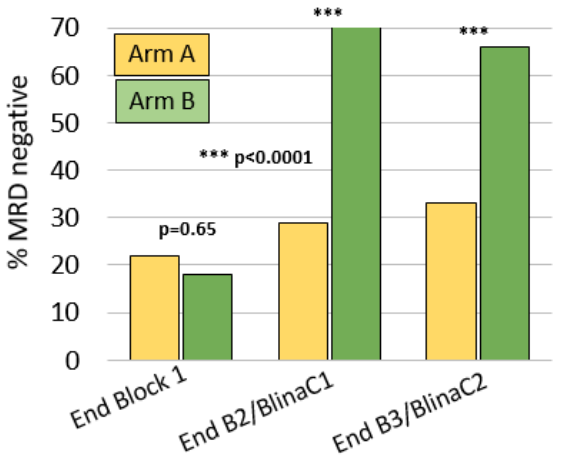
CHILDREN'S ONCOLOGY GROUP

Median follow-up 2.9 years

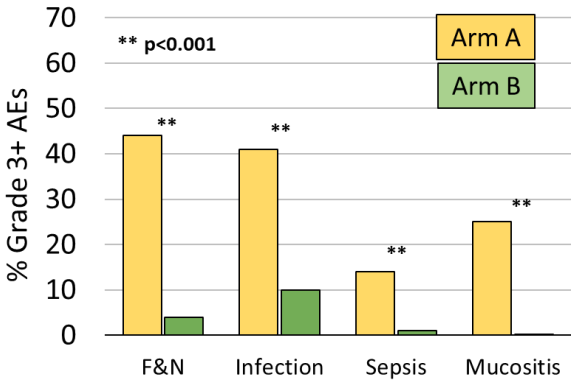
Brown P, et al. *JAMA*. 2021;325(9):833-842.

Other Endpoints: MRD, AEs, HSCT Bridging

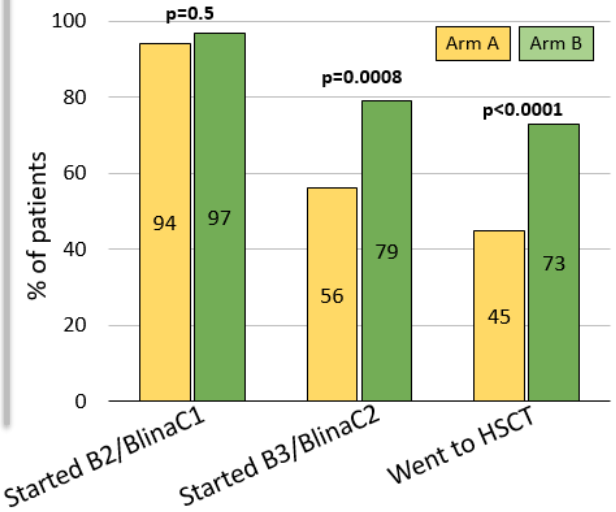
MRD Clearance



Adverse Events



Bridge to Transplant



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

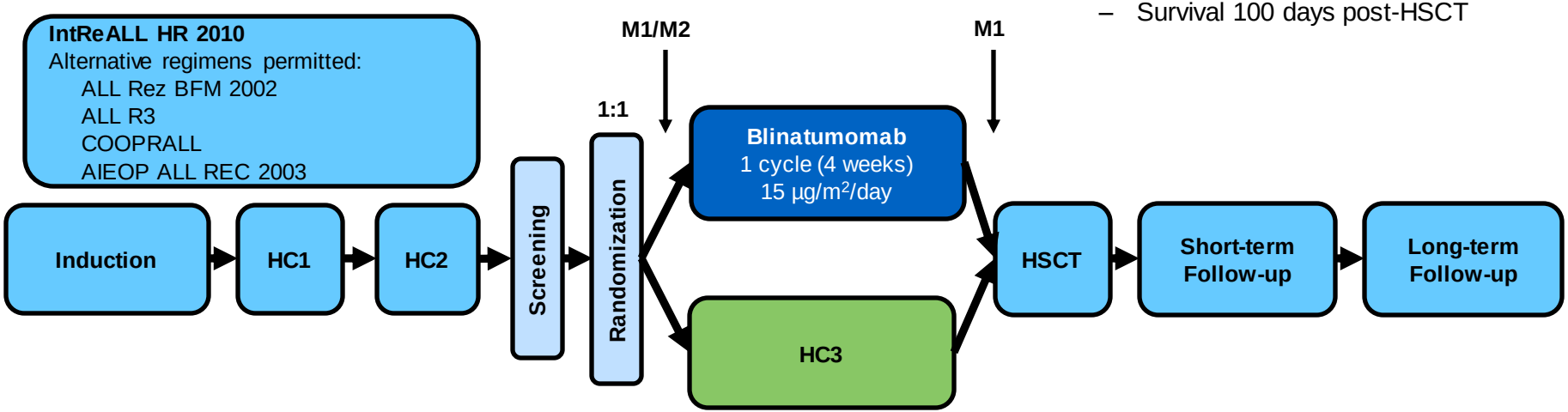
Brown P, et al. *JAMA*. 2021;325(9):833-842.

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

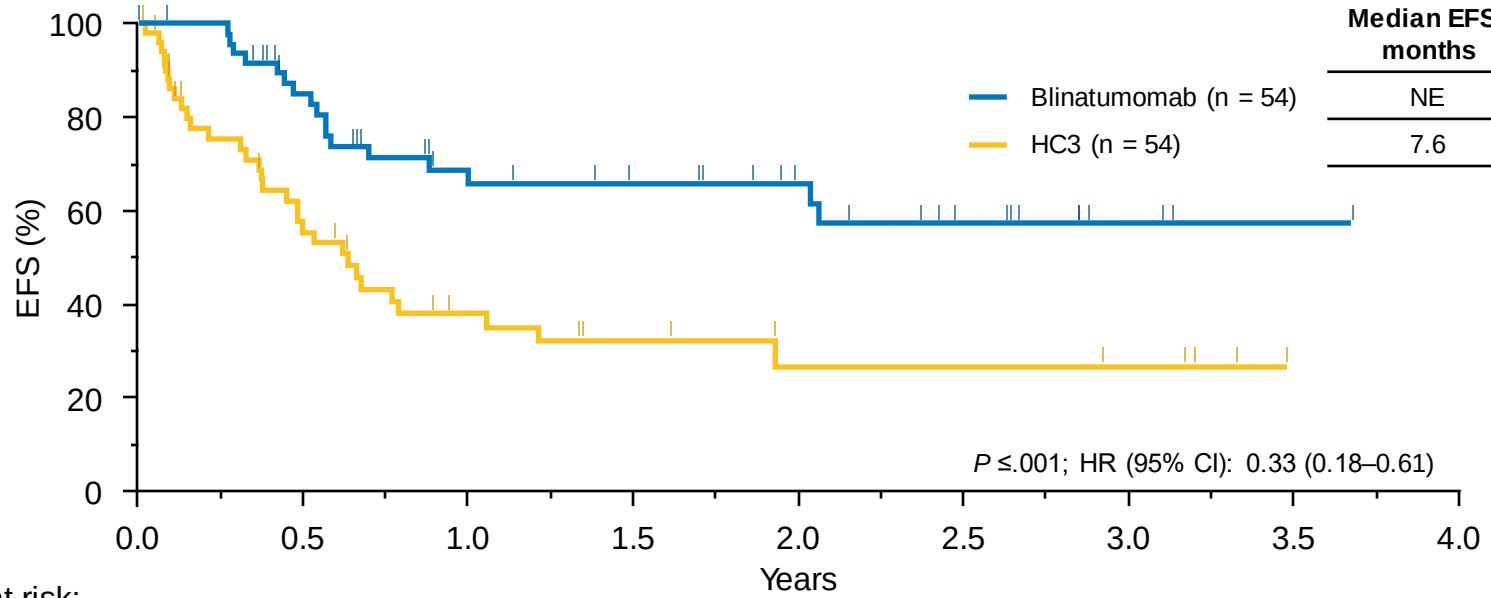
Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post-HSCT



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

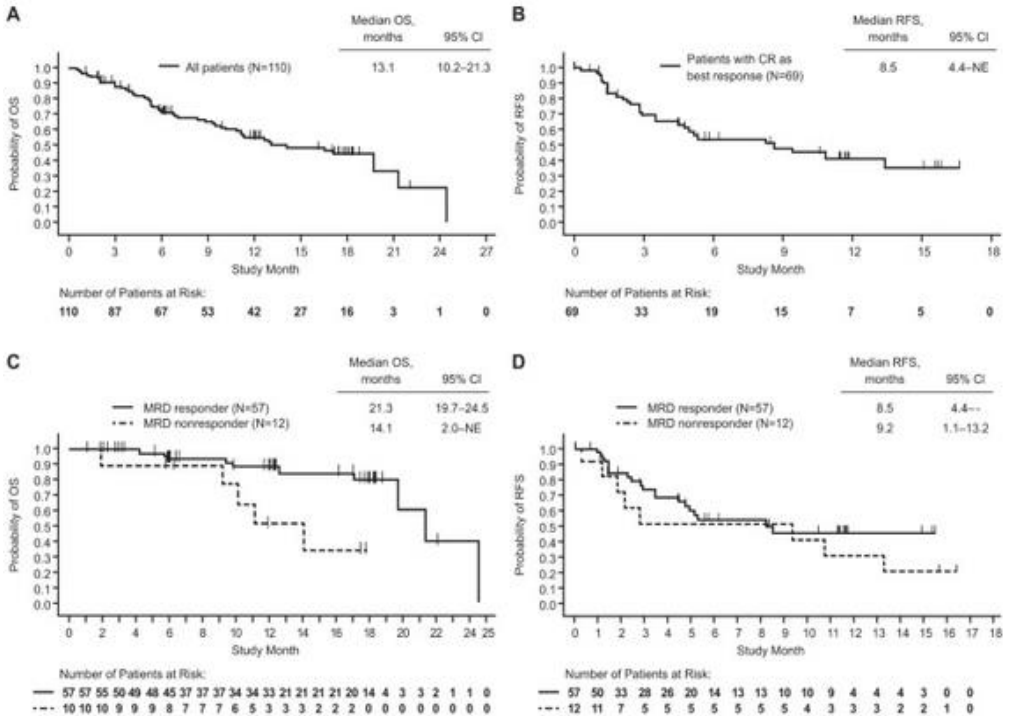
Patients at risk:

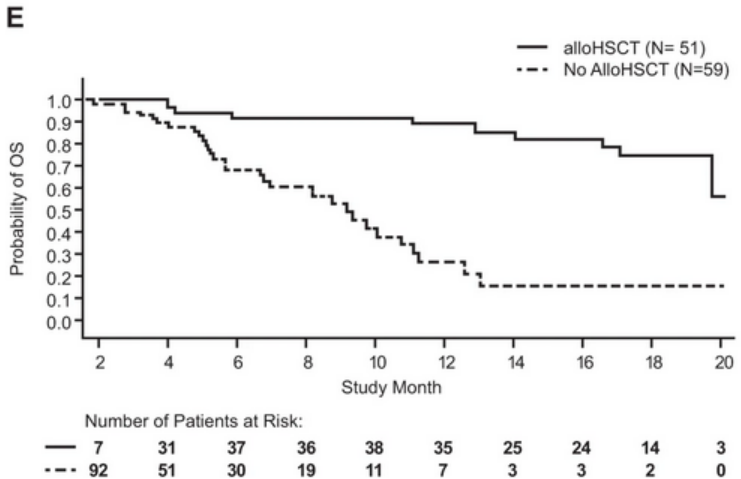
Blinatumomab	54	50	38	29	24	23	21	19	16	13	10	7	4	1	1	0
HC3	54	35	25	17	13	11	9	8	5	5	5	5	4	2	0	

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..

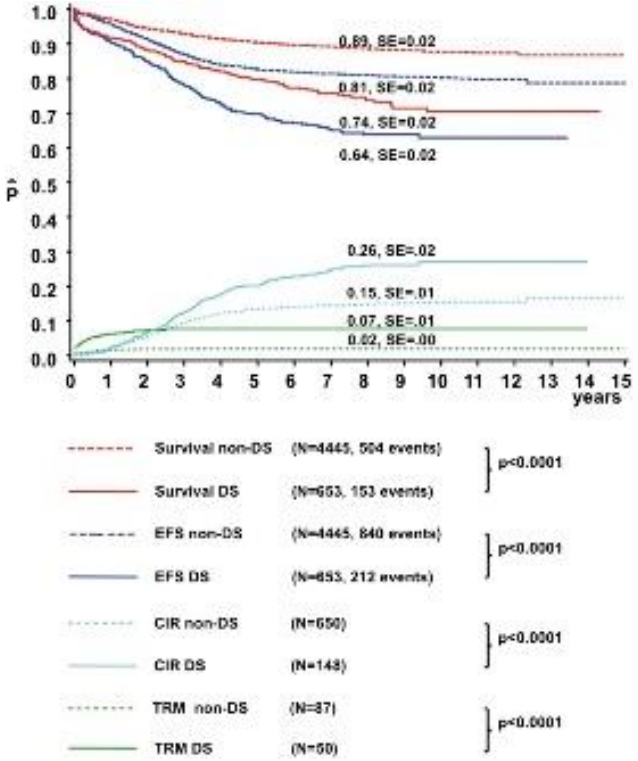


Image: Buitenkamp TD, et al. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood.* 2014;123(1):70-77.

New Trials for Patient With DS and ALL

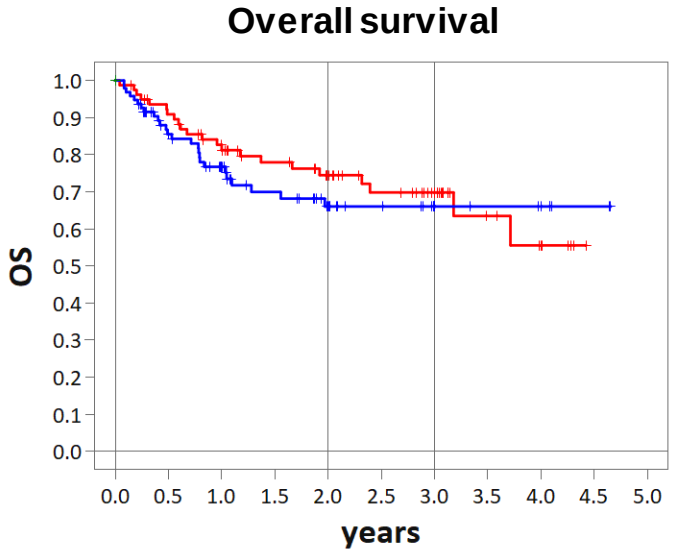
- A Phase III Trial Investigating Blinatumomab in Combination With Chemotherapy in Patients With Newly Diagnosed Standard Risk or Down Syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients With Localized B-Lymphoblastic Lymphoma (B-LLy): *NCT03914625 (NCI)*
  - Primary Outcome Measure: 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

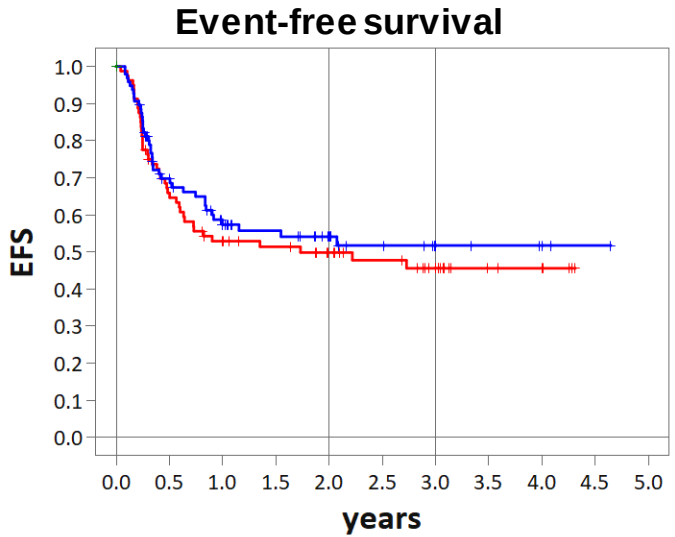
- Some frontline trials are now enabling DS-patients with high-risk features access to upfront-access with Blinatumomab: NCT03643276 (AIEOP 2017) , NCT04307576 (AllTogether1) and NCT03117751 (TOTAL St. Jude)

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 Years



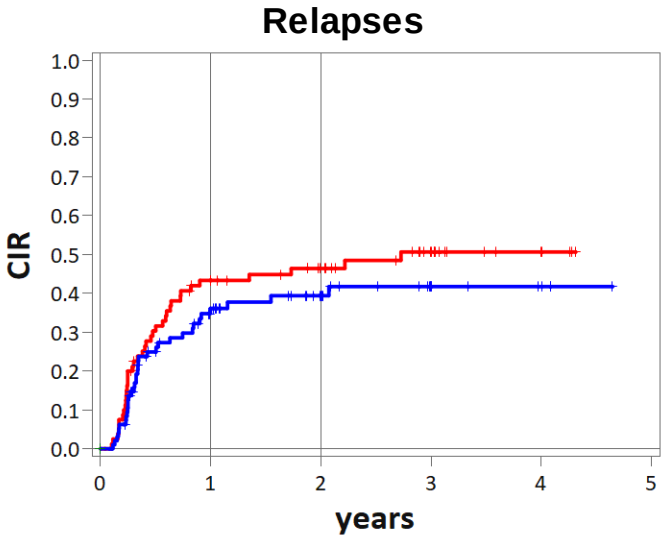


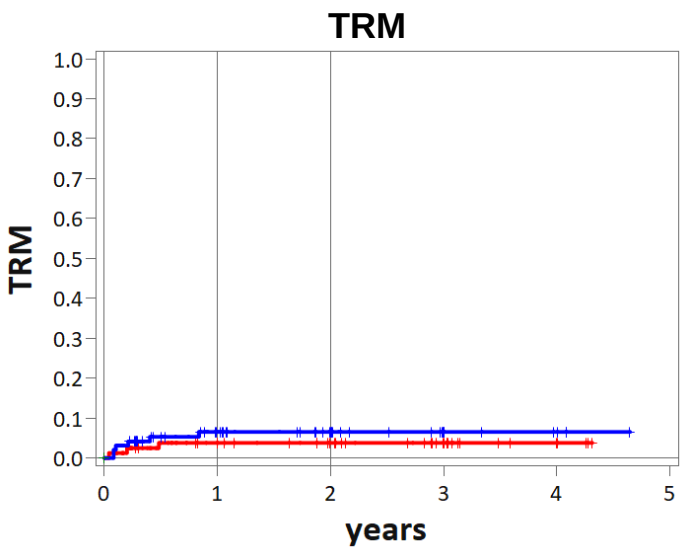
Age	Patients	Events	2-yr OS	3-yr OS	P Value
0–2	86	22	0.74 ± 0.05	0.70 ± 0.06	.612
2–4	101	26	0.66 ± 0.06	0.66 ± 0.06	

Events	2-yr EFS	3-yr EFS	*P* Value
41	0.50 ± 0.06	0.46 ± 0.06	.472
41	0.54 ± 0.05	0.52 ± 0.06	.

ALL SCTped FORUM

MSD/MD <4 Years: Flu/Thio/Bu; Flu/Thio/Treo





Age	Patients	n(CIR)	2-yr CIR	n(TRM)	2-yr TRM	n(Sec. mal)	2-yr 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			.255		.442		.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.

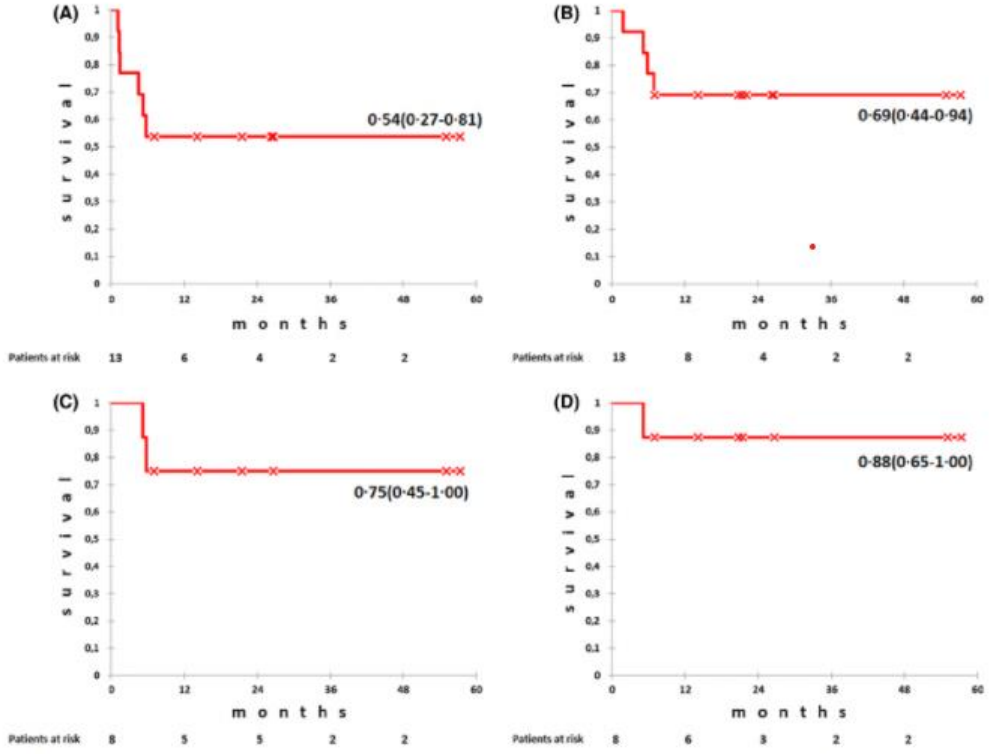


Fig 1. Disease-free survival (panels A and C) and overall survival (panels B and D) of all studied patients (n = 13, panels A and B), as well as of eight infants, who were treated with blinatumomab with subsequent haematopoietic stem cell transplantation in first complete remission because of slow clearance 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]

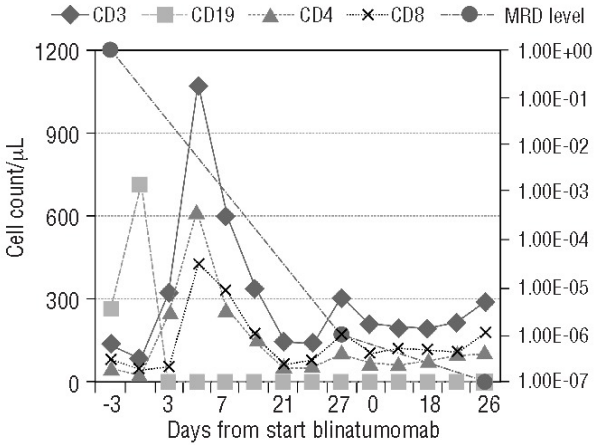
Other Rare Pediatric Conditions

- 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.
- 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.
- 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.

Blinatumomab After HSCT

- Handgretinger R, Zugmaier G, Henze G, Kreyenberg H, Lang P, von Stackelberg A. Complete remission after blinatumomab-induced donor T-cell activation in three pediatric patients with post-transplant relapsed acute lymphoblastic leukemia. *Leukemia.* 2011;25(1):181-184.
- 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)**



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

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

Global Leukemia Academy

Case 1: Pediatric ALL

Irene Medina

APTITUDE HEALTH

ALL Patient Case

Irene Medina Castillo, MD (third-year fellow)
Oscar González Ramella, MD, PhD

Hospital Civil de Guadalajara
Mexico

Case Presentation (1/3)

6-year-old female

Previously healthy

Family history of high blood pressure

- 10 days of evolution with fever, malaise, and abdominal pain
- Previously evaluated by a primary care physician and treated as pharyngotonsillitis
- Review of systems: decreased activity level
- Physical examination: hematoma on the right arm
- Laboratory work-up

Leukocytes 0.470 per microliter, Hgb 8.1 g/dl, Platelets 34.000 per microliter

Cr 0.25, urea 22, K 4, P 3.9, Ca 8.2

- Diagnostic images
- Chest X-ray without mediastinal mass

Case Presentation (2/3)

High-risk lymphoblastic leukemia

1. Immunophenotype

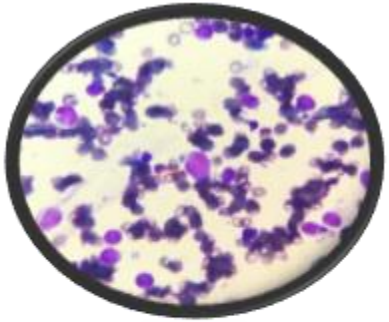
- Immunophenotype: positive for CD81, CD34, CD38, CD7, CD99, CD5, HLA-DR, CD33, CD56, TdT, and CD3 (cytoplasmic)
- Cytogenetics: Karyotype of the female sex that presents a clone 46,XX,t(12;13)(p13;q14) in 65% and a subclone with hyper diploidy in 5% of the metaphases analyzed
- DNA index 1. FISH negative for all leukemia translocations
- LCR: CNS stage 1
- MAS ALL 2018
- MRD of day 21: 0.01%

Case Presentation (3/3)

Morphology

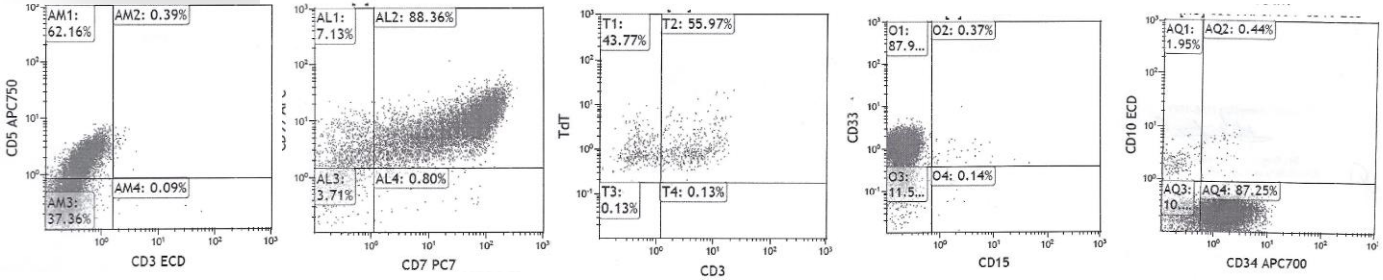
Predominance of immature forms by lymphoid blasts

Immunophenotype



INMUNOFENOTIPO

Marcadores Linaje T	%	Marcadores Linaje Mieloide	%	Marcadores Citoplasmáticos y Nucleares	%	Marcadores No Específicos de Linaje	%
CD4	1.3	HLA-DR	26.2	TdT	99.6	CD81	96.5
CD3	0.4	CD15	0.3	MPO	7.6	CD58	0.1
CD8	0.4	CD13	0.1	CD3	56.0	CD34	87.6
CD7	89.1	CD117	0.0	CD79a	9.9	CD38	81.3
CD5	62.4	CD33	88.2	IgM	2.6	CD99	95.4
		CD16	0.2				
		CD65	0.8				
		CD14	0.2				
		CD56	99.0				
		CD11c	6.2				
		CD36	2.2				
		CD64	0.5				



Question 1

According to the immunophenotype, what is a possible diagnosis?

1. Mixed lineage leukemia (biphenotypic and bilinear)
2. Early T-cell precursor leukemia
3. Pro B-cell leukemia
4. None of the above

Early-T Leukemia

THE AEIOP-BFM subclassification of ALL

Subtype	Discriminators	Remarks
B-I (pro-B)	$CD10^{neg}$	BCP-ALL lineage criteria fulfilled
B-II (common)	$CD10^{pos}$	/
B-III (pre-B)	$iIgM^{pos}$	$CD10^{neg\ or\ weak\ pos}$ may occur[b]
B-IV (mature B)	κ- or λ-$chain^{pos}$	may occur with FAB L1/L2 morphology[c]
T-I (pro-T)[d]	only $iCD3^{pos}$ and $CD7^{pos}$	T-ALL lineage criteria fulfilled
T-II (pre-T)	≥1 of $CD2^{pos}$, $CD5^{pos}$, $CD8^{pos}$	surface (s) $CD3^{weak\ pos}$ allowed[e]
T-III (cortical T)	$CD1a^{pos}$	$sCD3^{weak}$ may occur[e]
T-IV (mature T)	$CD1a^{neg}$ and $sCD3^{pos}$	$sCD3^{strong}$, or $sCD3^{weak\ pos}$ with TCR^{pos}
ETP (only additive to T-I or T-II)	$CD1a^{neg}$, $CD8^{neg}$ usually $CD5^{neg\ or\ weak\ pos}$ and ≥1^{pos} of HLADR, CD11b,13,33,34,65,117	if $CD5^{strong\ pos}$: ≥2^{pos} of HLADR, CD11b,13,33,34,65,117; $sCD3^{weak\ pos}$ may occur[e]

Treatment Regimen: Five Phases

1. PROPHASE

Prednisone	40 mg/m^2/day

2. INDUCTION

Prednisone	40 mg/m^2/day
Vincristine	1.5 mg/m^2/day (max. 2 mg)
Daunorubicin	25 mg/m^2/day
Dexrazoxane	250 mg/m^2/day
L- asparaginase	10,000 UI/m^2/dose
Triple intrathecal	Ver 4.2.6
Folinic acid	5 mg/m^2/dose
Imatinib	340 mg/m^2/day (max. 600 mg)

3. CONSOLIDATION

Methotrexate	5 g/m^2/dose
L-asparaginase	15,000 UI/m^2
Mercaptopurine	50 mg/m^2/day
Triple intrathecal	
Imatinib	340 mg/m^2/day

4. EARLY MAINTENANCE

1. ***Interim maintenance:*** Mercaptopurine, L-asparaginase, doxorubicin, vincristine, and dexamethasone
2. ***Reinduction 1 and 2:*** cyclophosphamide-HD

5. LATE MAINTENANCE

Mercaptopurine, doxorubicin, methotrexate, vincristine, and dexamethasone

Clinical Evolution (1/2)

Cytopenias during maintenance therapy

- Dose adjustments are made due to high sensitivity to chemotherapy
- TPMT determination was requested: TPMT 1/TPMT3A, indicating heterozygous mutation with partial function
- The patient was hospitalized and treated for profound neutropenia and severe pneumonia

Question 2

What would you consider to be the most appropriate following management?

1. Continue with the original protocol
2. Modify Purinethol dose with total neutrophil count
3. Present the patient to the TPH team
4. Use immunotherapy with blinatumomab
5. Definitively suspend the Purinethol

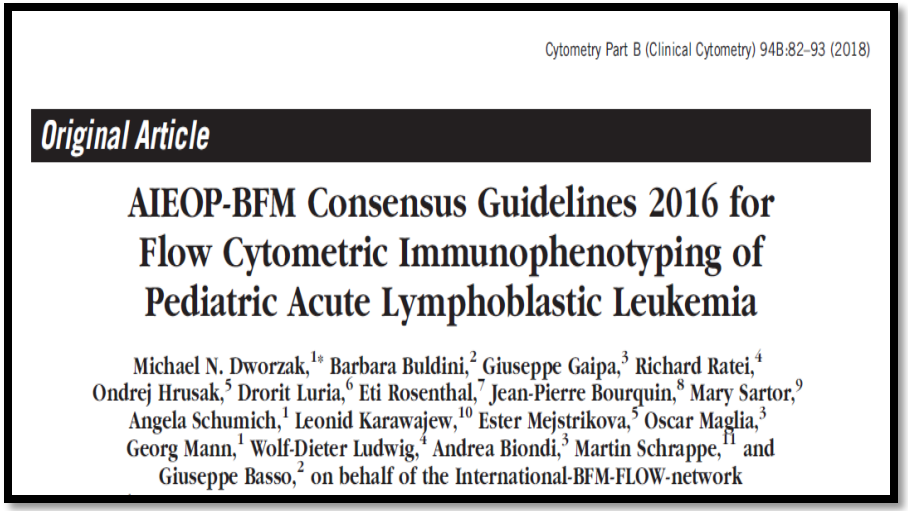
Clinical Evolution (2/2)

Dose adjustment

- Absolute neutrophil count follow-up
- Decrease in mercaptopurine dose (28.7 mg/m^2/day)
- She has had no subsequent hospitalizations
- MRD day 84: 0.01%

Conclusions

- Conventional intensive chemotherapy remains the mainstay of treatment for ETP-ALL
- The prognostic impact of ETP-ALL phenotype alone is controversial from findings in recent studies
- The evidence from recent studies indicates that risk-adapted therapy with treatment intensification carries survival benefits to both pediatric and adult ETP-ALL patients

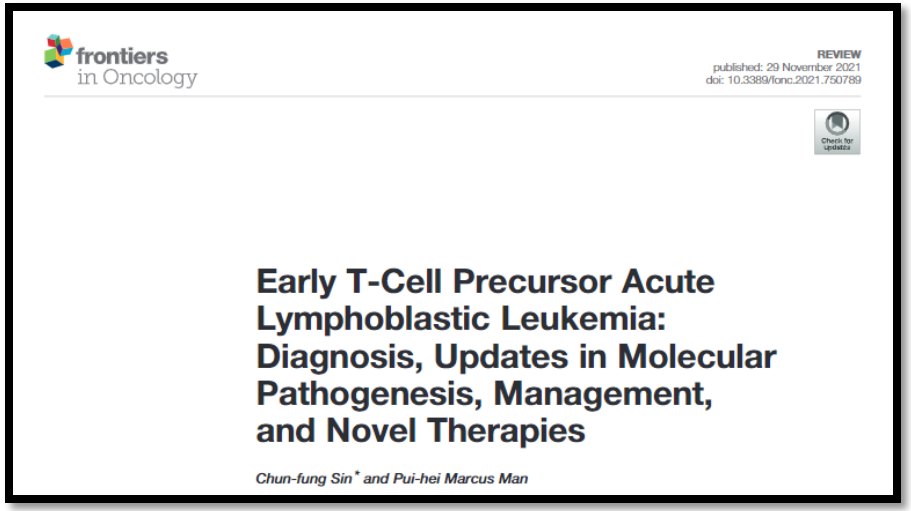


Cytometry Part B (Clinical Cytometry) 94B:82–93 (2018)

Original Article

AIEOP-BFM Consensus Guidelines 2016 for Flow Cytometric Immunophenotyping of Pediatric Acute Lymphoblastic Leukemia

Michael N. Dworzak,[1*] Barbara Buldini,[2] Giuseppe Gaipa,[3] Richard Ratei,[4] Ondrej Hrusak,[5] Drorit Luria,[6] Eti Rosenthal,[7] Jean-Pierre Bourquin,[8] Mary Sartor,[9] Angela Schumich,[1] Leonid Karawajew,[10] Ester Mejstrikova,[5] Oscar Maglia,[3] Georg Mann,[1] Wolf-Dieter Ludwig,[4] Andrea Biondi,[3] Martin Schrappe,[11] and Giuseppe Basso,[2] on behalf of the International-BFM-FLOW-network



frontiers in Oncology

REVIEW
published: 29 November 2021
doi: 10.3389/fonc.2021.750789

Early T-Cell Precursor Acute Lymphoblastic Leukemia: Diagnosis, Updates in Molecular Pathogenesis, Management, and Novel Therapies

Chun-fung Sin and Pui-hei Marcus Man*

APTITUDE HEALTH®

Thank you!
Gracias!
Obrigada!

Global Leukemia Academy

Case 2: Pediatric ALL

Jorge Buitrago

APTITUDE HEALTH

Case
Acute Lymphoblastic Leukemia

JORGE LUIS BUITRAGO ESCOBAR
Pediatric Hematologist and Oncologist
Clínica Imbanaco

CARLOS ANDRÉS PORTILLA FIGUEROA
Pediatric Hematologist and Oncologist
Bone Marrow Transplantation
Clínica Imbanaco

Medical History

- 8y 9m, male, born in Ecuador
- ALL-B diagnostic 03/2014 (no cytogenetic information), CNS neg
- Early hematologic relapse 09/2016 (no cytogenetic information)
- First rescue in his country
- Arrived at Cali on 22/11/2018 for consolidation with HSCT in CR2

Fever, abdominal pain, and asthenia

BM: 94% lymphoblasts by flow cytometry, with CD19+ expression. CNS neg. No cytogenetic alteration

Question 1

In your practice, what would be the best alternative for treatment?

1. UK ALLR3
2. ALL-REZ BFM
3. Clofarabine
4. Blinatumomab
5. CAR T cells

Outcomes with most popular salvage regimens

Table 2. Recent completed phase 3 trials for first ALL relapse

Trial	Years of accrual	Patient age (y)	No. of patients	Outcomes
UKALL R3[15] NCT00967057	2003-2009	1-18	239 (216 randomized)	3-y PFS 65%; 3-y OS 69% (mitoxantrone arm)
ALL-REZ-BFM 2002[16] NCT00114348	2003-2012	1-18	538 (420 randomized)	5-y EFS 60%; 5-y OS 69% (Prot II-IDA arm)
COG AALL0433[10] NCT00381680	2007-2013	1-30	275* (271 eligible)	3-y EFS 64%; 3-y OS 72%
COG AALL1331[17] NCT02101853	2014-2019	1-30	220† (208 randomized)	2-y disease-free survival 59%; 2-y OS 79% (blinatumomab arm)

Hunger SP, Raetz EA. *Blood*. 2020;136(16):1803-1812.

Clinical case

The patient had received high doses of chemotherapy in his country and at that moment blinatumomab was not available in Colombia.

Cycle 1: CLOVE *(clofarabine + etoposide + cyclophosphamide)*

- 13/12/2018: CR3 with MRD 0.78% by FC

Cycle 2: *Clofarabine + mitoxantrone + etoposide*

- 16/01/2019: CR3 with MRD 0.18% by FC

Complications

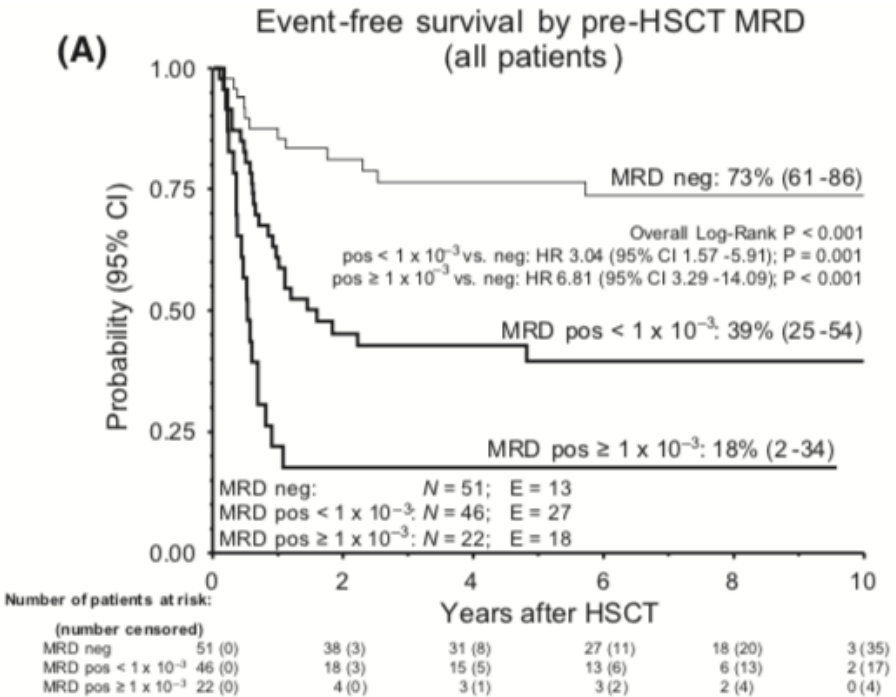
- **Neutropenic fever**
- **Hemorrhagic cystitis due to BK polyomavirus**
- **Sepsis with blood culture positive for Rothia spp.**

Question 2

What is the optimal level of MRD before HSCT?

1. <1%
2. <0.1%
3. <0.01%
4. Negative
5. It does not matter

Association of MRD pre-transplant with clinical outcome



Lovisa BF, et al. *Br J Haematol.* 2018;180:680-693.

Bone marrow transplant

- 31/01/2019: Related donor allogeneic **(haploidentical)**
- Donor: Sister, 7y; source: BM
- 4.06 million CD34+/kg weight
- Conditioning regimen: Myeloablative (*fludarabine + etoposide + TBI)*
- GVHD prophylaxis CY + CSA + MTX

Complications

- Acute GVHD G IV (skin: G I, GI: G IV, liver: G III); refractory to steroids
  - Treatment: CSA + abatacept + ruxolitinib
- Chronic GVHD (skin)
  - Treatment: CSA + abatacept + ruxolitinib + low doses of prednisone

Post-transplant follow-up

- 09/01/2020: Asymptomatic; blood count: WBC 4.46, N 0.71, L 2.13, Hb 11.4, Plt 59,000

10/01/2020: BM 70% lymphoblast by flow cytometry with CD19+ expression. CNS Neg. No cytogenetic alteration

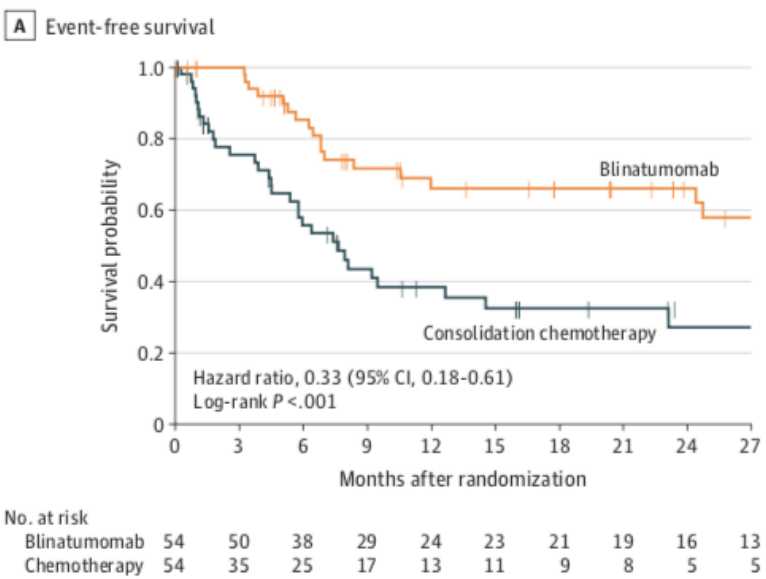
Third hematologic relapse at day +356. CNS neg. No cytogenetic alteration.

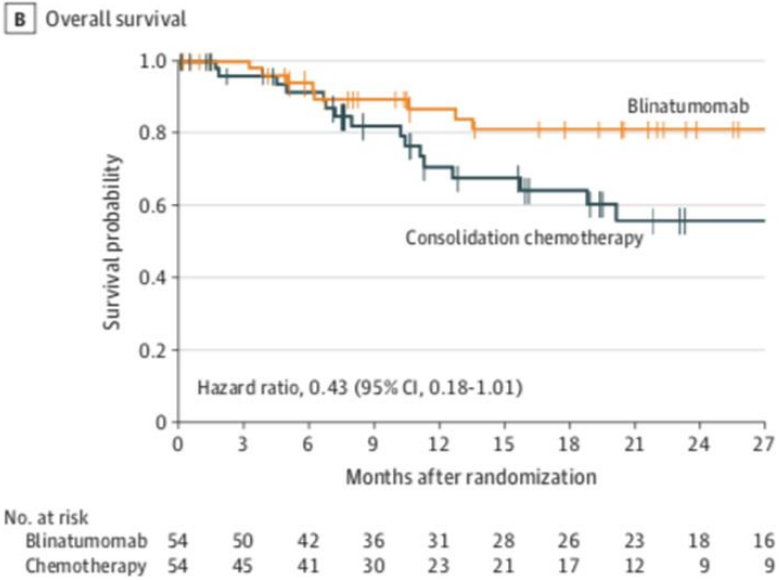
Rescue # 2: Blinatumomab

Cycle 1: 22/01/2020 (no significant complications)
- 26/02/2020: CR4 with MRD 0.1% by FC

Cycle 2: 02/03/2020 (no significant complications)
- 01/04/2020: CR4 with MRD <0.01% by FC

Blinatumomab vs chemotherapy





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

Second bone marrow transplant

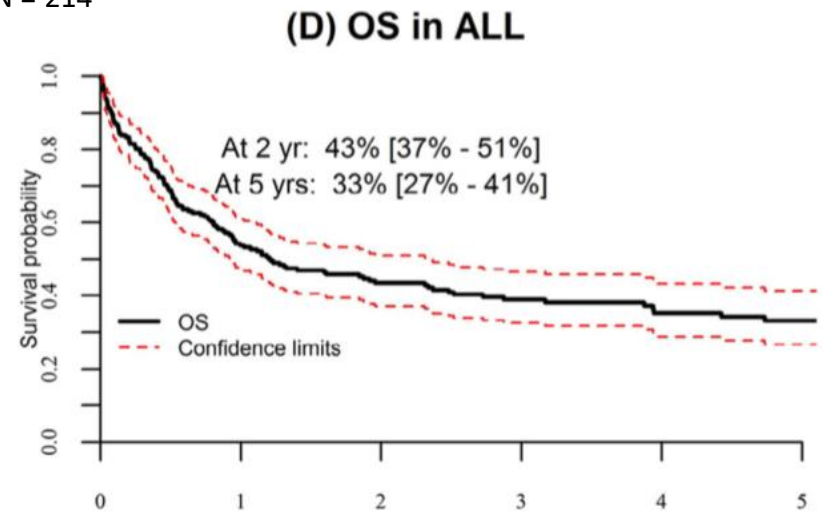
- 17/04/2020: Related donor allogeneic **(haploidentical)** bone marrow transplant
- Mother, 26y; peripheral blood
- 21.5 million CD34+/kg weight
- Conditioning regimen: Myeloablative, RIC

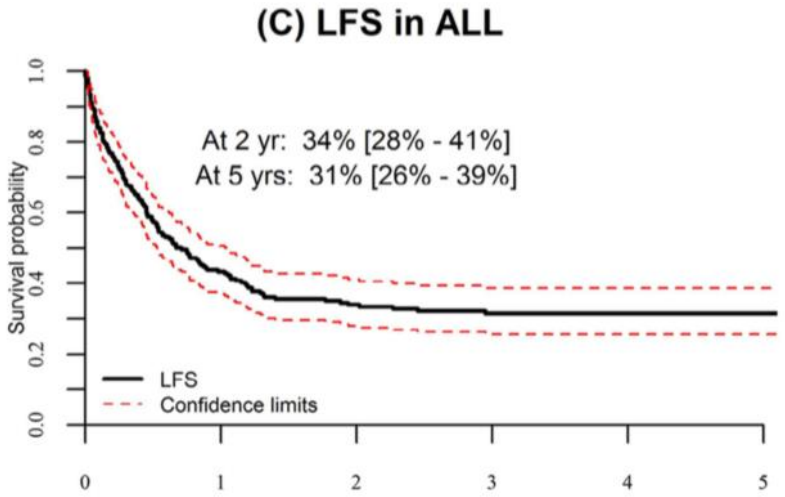
  FAB (*fludarabine + cytarabine + busulfan)*
- GVHD prophylaxis ATG + CY post + CSA + abatacept

Complications
- Neutropenic fever
- Acute GVHD G I (Skin: G I) and thrombocytopenia. Good response to steroid
- Chronic GVHD (Skin mild and anemia mild)
  - Treatment: Low doses of prednisone

Second HSCT for post-transplantation relapse

N = 214





Post-second transplant follow-up

- 31/03/2021 (1 year after HSCT) BM morphologically normal, MRD <0.01% by FC. CSF cytology: negative

- 03/02/2022: Day +652. Asymptomatic. Lansky 100%. No clinical signs of GVHD. Blood count: WBC: 4656, N: 2410, L: 1227, Mn: 690, E: 260, Hb: 15, Plt: 159,000

Unidad de Hematología y Oncología
Clínica Imbanaco
Doctores:
Oscar Ramírez
Margarita Quintero
Jesús Ardila
Diana Rendón
Carlos Narváez
Diana Castrillon
Natalia Sanclemente
Lina Loaiza

Psicología
Mayra Alejandra Puentes

Trabajo Social
Lina M. Garcia

Unidad de Trasplante de Médula Ósea Pediátrica

Universidad del Valle –
Departamento de Pediatría

Sistema de Vigilancia
de cáncer pediátrico de Cali
VIGICANCER

Registro poblacional de
Cáncer de Cali

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de Hematología y Oncología Pediátrica
ACHOP

Clínica Imbanaco
Grupo quirónsalud

Universidad del Valle

Gracias!

Global Leukemia Academy

ALL case-based panel discussion

Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla




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BREAK

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Current treatment options for pediatric AML

Franco Locatelli

APTITUDE HEALTH

Current Treatment Options for Pediatric AML

Franco Locatelli, MD

Università Sapienza, Roma

Dipartimento di Oncoematologia, Terapia Cellulare e Genica

IRCCS Ospedale Bambino Gesù, Roma

Question 1

The outcome of patients with KMT2A-rearranged AML is influenced by the partner gene. Which of the following statements is wrong?

a) Patients with translocation t(6;11) have a dismal outcome
b) Patients with translocation t(1;11) have an excellent/good outcome
c) Patients with translocation t(10;11) have a dismal outcome
d) Patients with translocation t(1;11) have a poor outcome

Question 2

Which of the following statements is correct?

a) Gemtuzumab ozogamicin (GO) improves the outcome of patients with KMT2A translocations

b) Gemtuzumab ozogamicin (GO) doesn't influence the outcome of patients with KMT2A translocations

c) Gemtuzumab ozogamicin (GO) worsens the outcome of patients with KMT2A translocations

d) There are no data on the effect of Gemtuzumab ozogamicin (GO) on the outcome of patients with KMT2A translocations

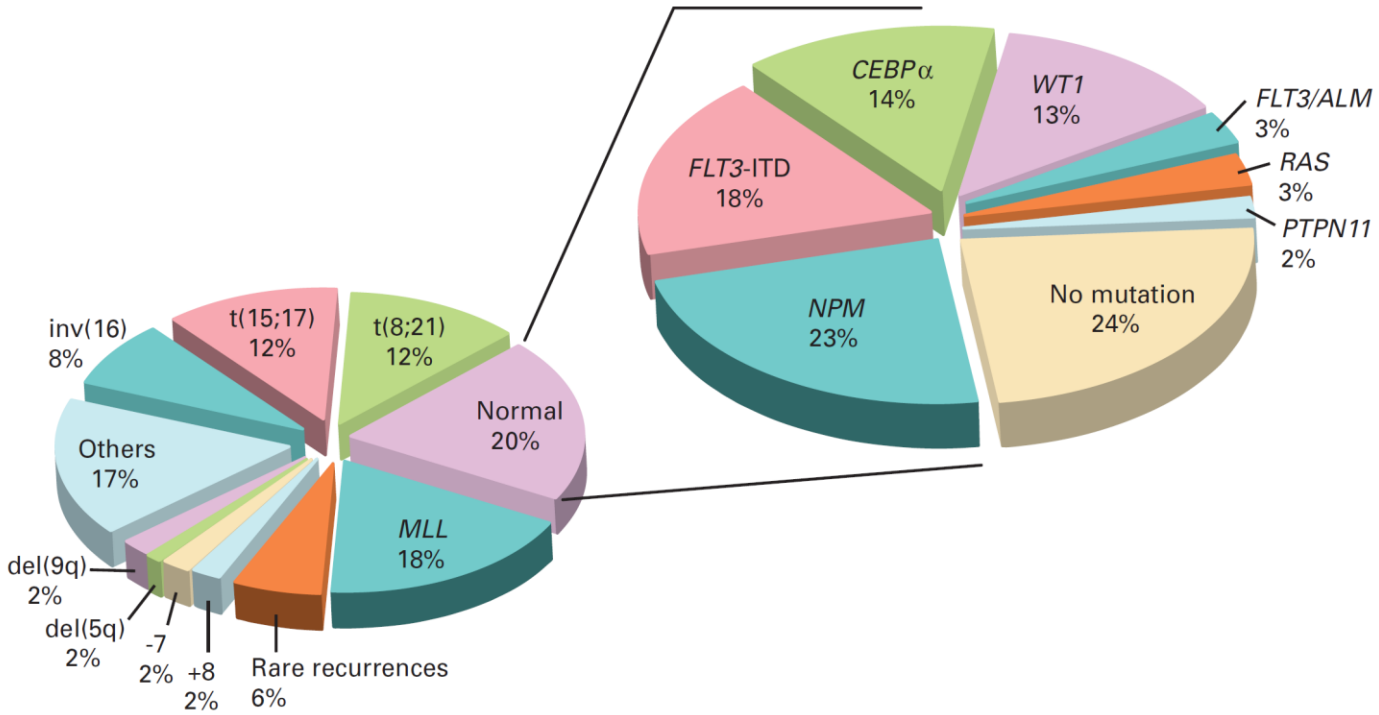
Outline of the Presentation: Basic Concepts and Development of Therapeutic Options in *de novo* Childhood AML

- Accounts for 20% of childhood leukemia. Heterogeneous disease to be treated with risk-adapted therapy
- New genetic subgroups
- Role of MRD for patient stratification
- Conventional treatment: induction therapy containing anthracyclines, followed by HD-AraC–based consolidation courses
- Rescue therapy for relapsed children
- Treatment of patients with Down syndrome
- New agents

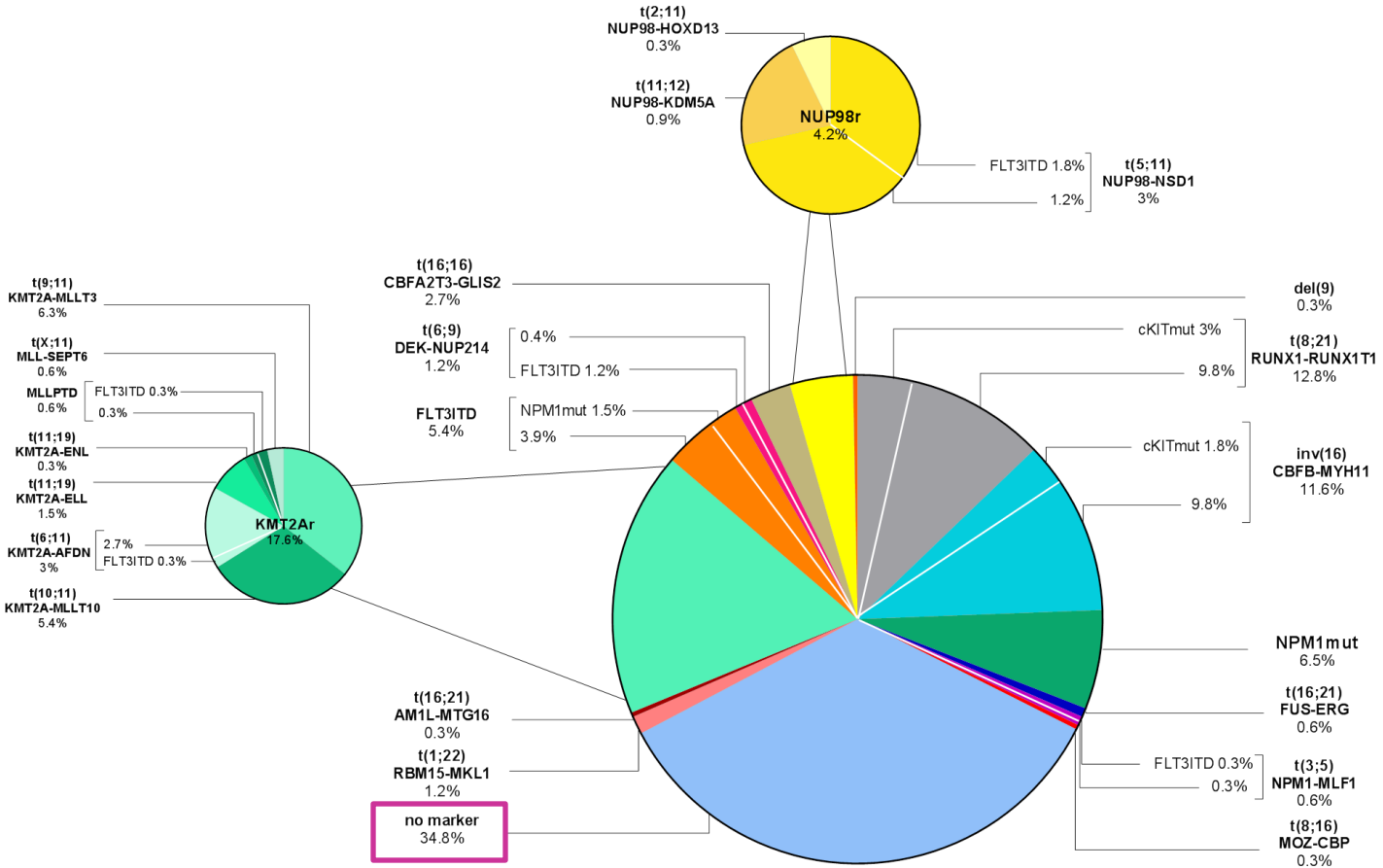
Biology, Risk Stratification, and Therapy of Pediatric Acute Leukemias: An Update

Ching-Hon Pui, William L. Carroll, Soheil Meshinchi, and Robert J. Arceci

VOLUME 29 · NUMBER 5 · FEBRUARY 10 2011
JOURNAL OF CLINICAL ONCOLOGY

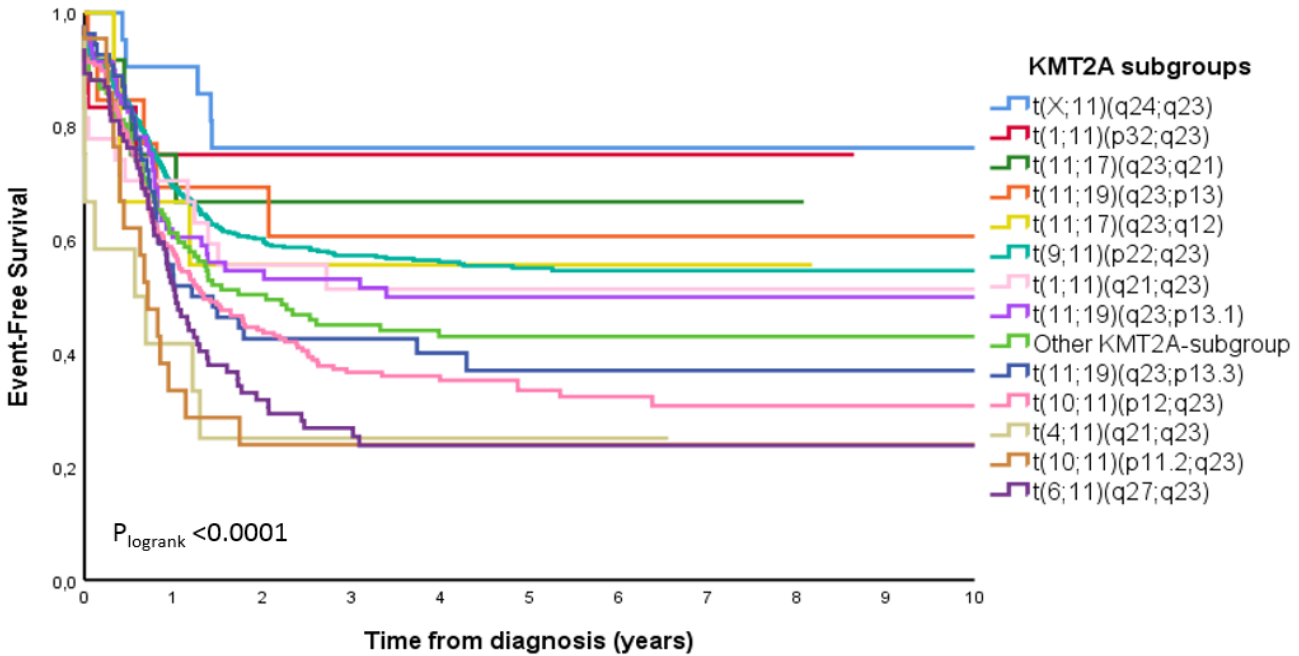


Pediatric AML Molecular Landscape: November 2021



Outcome of (Novel) Subgroups in 1257 Pediatric Patients with KMT2A-Rearranged Acute Myeloid Leukemia and the Significance of Minimal Residual Disease Status: A Retrospective Study by the I-BFM-SG

Figure 1. Kaplan Meier Curve: Probability of Event-Free Survival for KMT2A subgroups

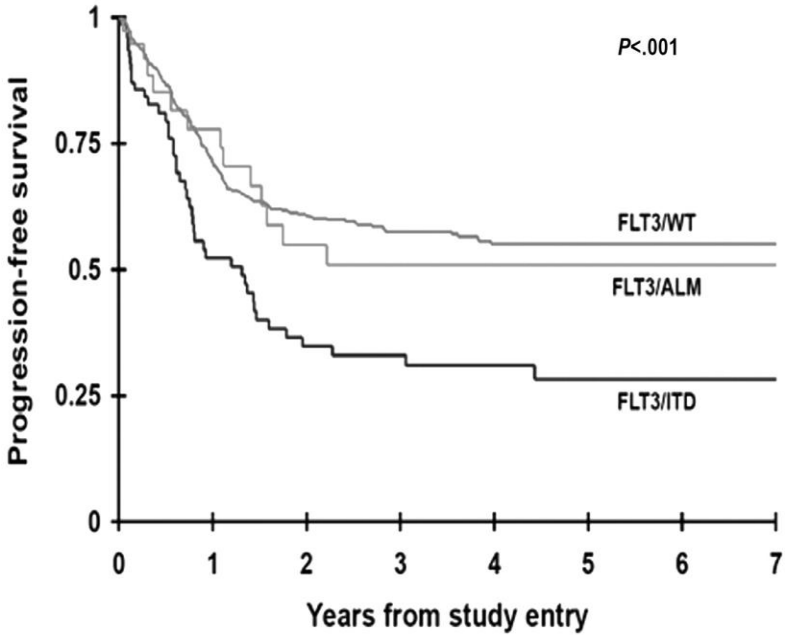


The 5-year probability of event-free survival (pEFS) and numbers of patients per KMT2A subgroup: t(X;11)(q24;q23) pEFS 76%, *n*=21; t(1;11)(p32;q23) pEFS 75%, *n*=12; t(11;17)(q23;q21) pEFS 67%, *n*=12, t(11;19)(q23;p13) pEFS 61%, *n*=13; t(11;17)(q23;q12) pEFS 56%, *n*=10; t(9;11)(p22;q23) pEFS 55%, *n*=508; t(1;11)(q21;q23) pEFS 51%, *n*=27; t(11;19)(q23;p13.1) pEFS 50%, *n*=70; other KMT2A-subgroup pEFS 43%, *n*=127; t(11;19)(q23;p13.3) pEFS 37%, *n*=54; t(10;11)(p12;q23) pEFS 33%, *n*=206; t(4;11)(q21;q23) pEFS 25%, *n*=12; t(10;11)(p11.2;q23) pEFS 24%, *n*=22; t(6;11)(q27;q23) pEFS 24%, *n*=84.

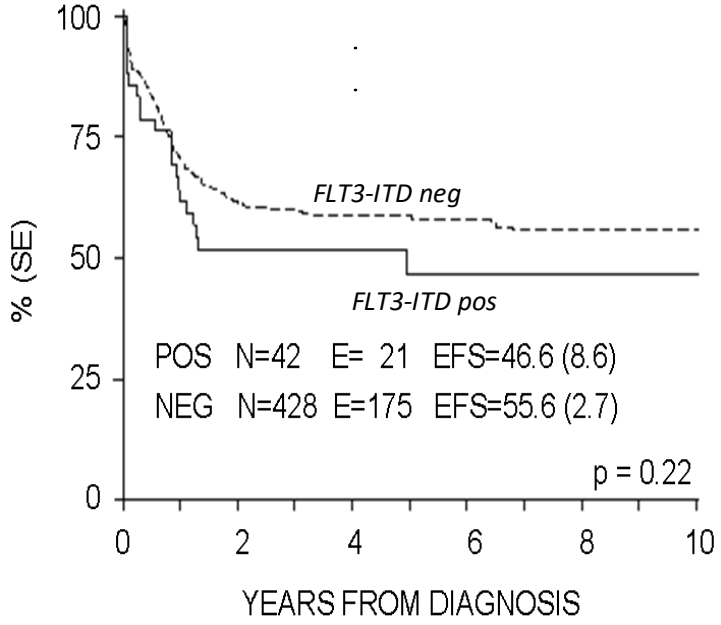
van Weelderen, et al. ASH 2020.

PROTOCOL AIEOP LAM 2002/01

Focus on *FLT3*-ITD



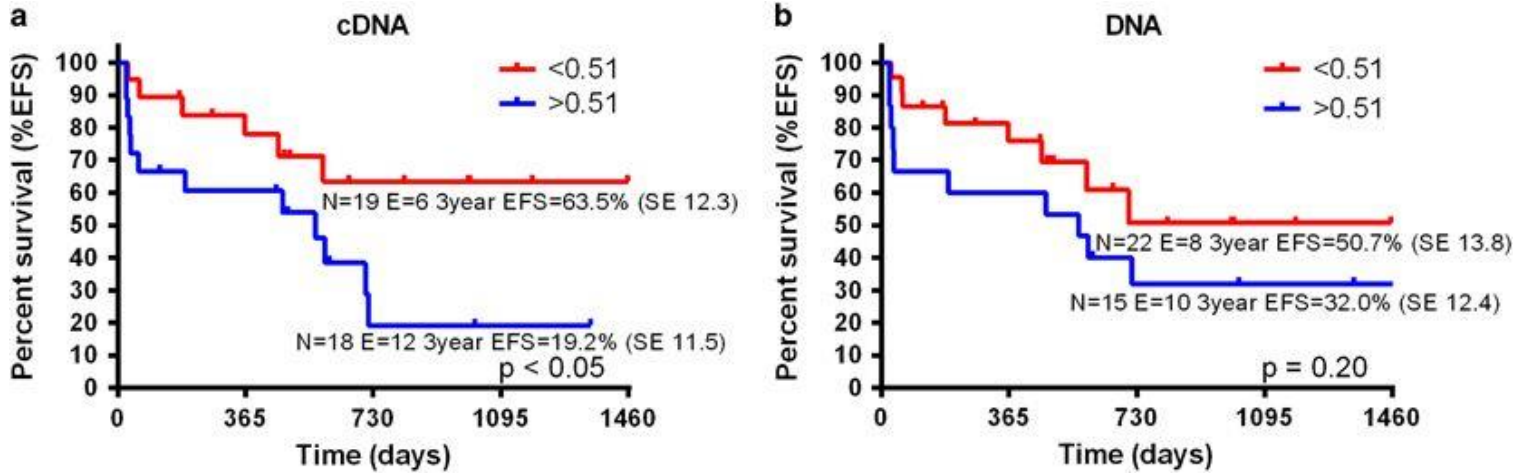
Meshinchi S, et al. *Blood.* 2006.



Pession A, Masetti R. Locatelli F. *Blood.* 2013.

FLT3-ITD AR in Acute Myeloid Leukemia

- ✓ ITD-AR measured on cDNA (*N* = 53) revealed that children with high ITD-AR (>.51) had an increased WBC at diagnosis in comparison to patients with low ITD-AR (<.51) (mean WBC: 123 vs 77 × $10^9/l^{-1}$, *P* <.05), and carried more frequently a second genetic event, such as a recurrent translocation (55 vs 17%, *P* <.01)
- ✓ Survival analyses at 3 years on this cohort revealed that high ITD-AR patients had a worse EFS compared to those with low ITD-AR when calculated on cDNA (19.2 vs 63.5%, *P* <.05), whereas AR performed on DNA was never prognostically significant
- ✓ The incidence of relapse was not influenced by ITD-AR either on cDNA or DNA (CIR not significant), mainly because the most frequent event occurring in patients with a higher AR was failure to achieve CR (No CR = 12/29 (41%) vs 2/24 (8%), *P* <.05

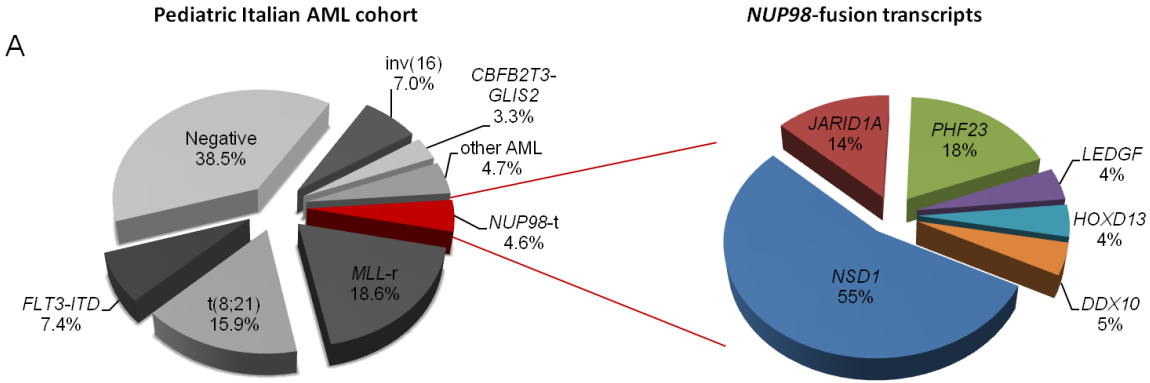


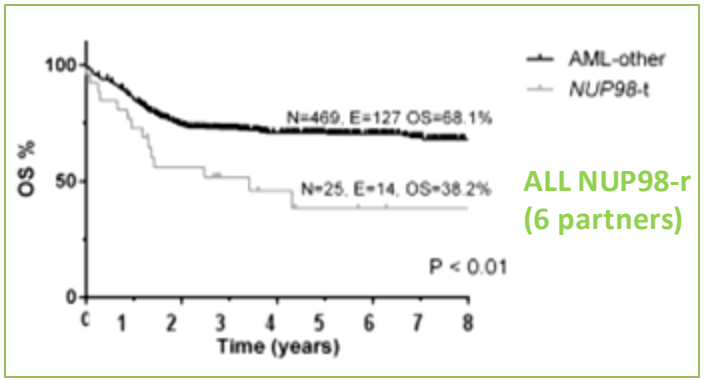
Manara E, et al. *Leukemia.* 2017.

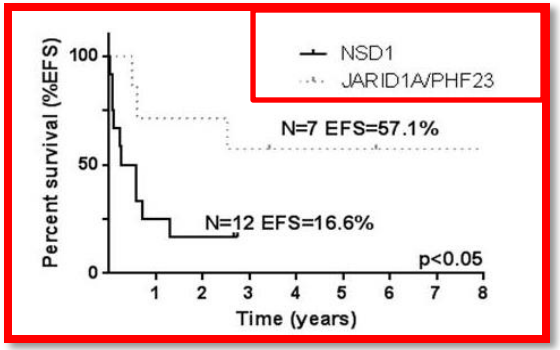
NUP98 Fusions-AIEOP

13 partner genes: NSD1, PHF23, HOXC11, HOXA9, JARID1A, HOXD13, LEDGF, DDX10, HHEX, ADD3, NSD3, LOC348801

N = 482 AIEOP 2002/01 = 172 patients negative for molecular biology







Togni M, et al. *JHO.* 2015; Bisio V, et al. *Leukemia.* 2017.

Shared Phenotypic and Molecular Determinants of Risk Equalities and Differences in Risk Stratification

Risk groups and stratification according to

1. Genetics
2. Early response to treatment (MRD)
3. Morphology

Risk groups and stratification according to

1. Early response to treatment (MRD)
2. Molecular genetics (*FLT3*-ITD)

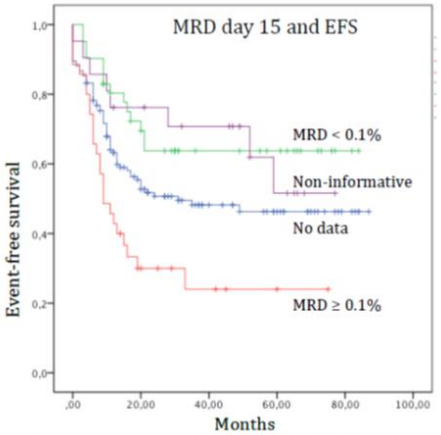
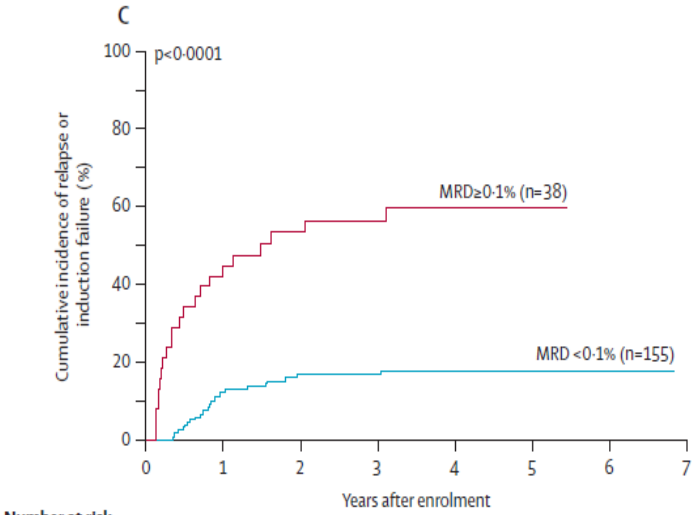
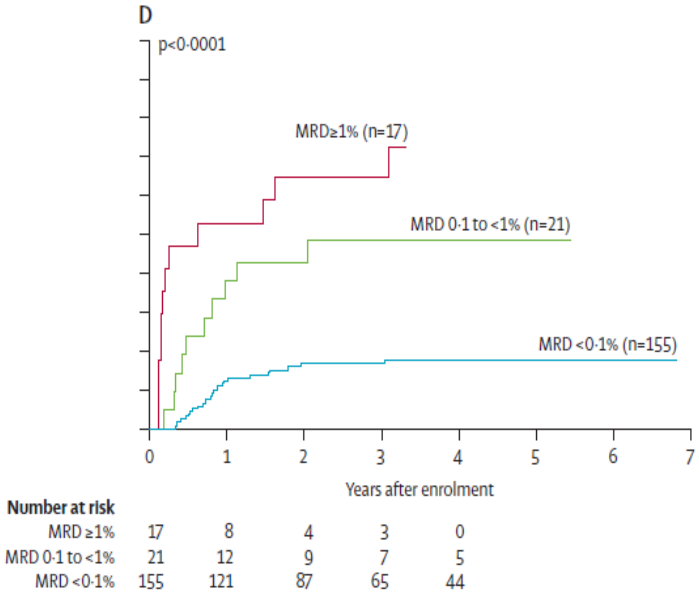


Figure 7. EFS in 41 patients with MRD <0.1% and 35 with ≥0.1% leukemic cells at day 15 after AIET. NI = non-informative data.

Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: results of the AML02 multicentre trial

Jeffrey E Rubnitz, Hiroto Inaba, Gary Dahl, Raul C Ribeiro, W Paul Bowman, Jeffrey Taub, Stanley Pounds, Bassem I Razzouk, Norman J Lacayo, Xueyuan Cao, Soheil Meshinchi, Barbara Degar, Gladstone Airewele, Susana C Raimondi, Mihaela Onciu, Elaine Coustan-Smith, James R Downing, Wing Leung, Ching-Hon Pui, Dario Campana





Rubnitz JE, et al. *Lancet Oncol.* 2010.

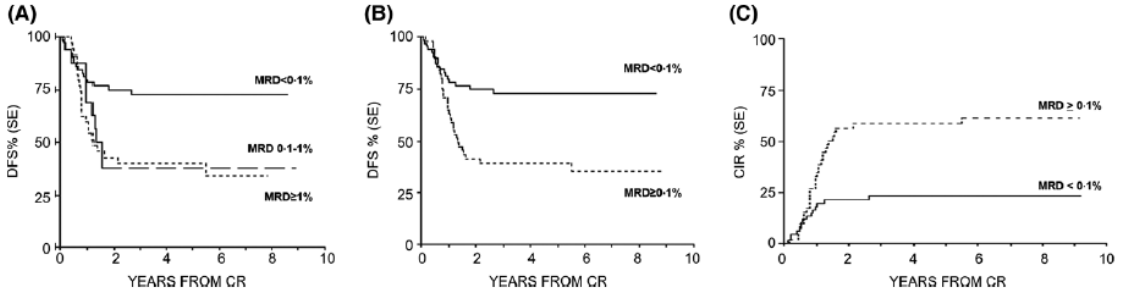


Fig 2. DFS by MFC-MRD status at the end of induction course 1. According to MRD levels, patients were stratified into (A) three MRD groups (MRD <0·1%; MRD 0·1–1%; MRD ≥1%) and (B) into two MRD groups (MRD <0·1%; MRD ≥0·1%). Cumulative incidence of relapse at 8 years in patients with MRD <0·1% or ≥0·1% at the end of the first induction course (C). CIR, cumulative incidence of relapse; CR, complete remission; DFS, disease-free survival; MFC, multi-colour flow cytometry; MRD, minimal residual disease; SE, standard error.

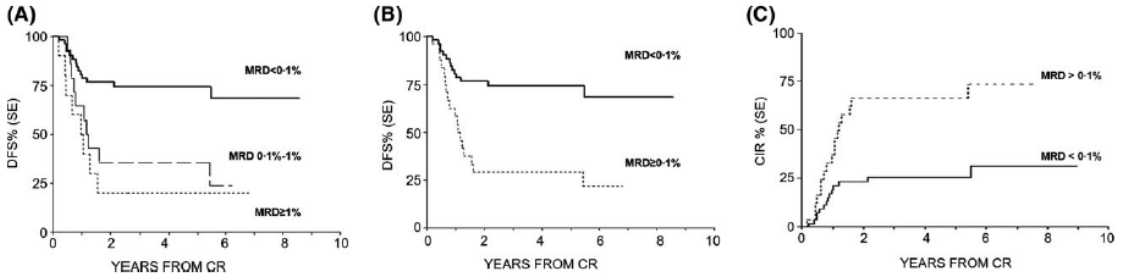
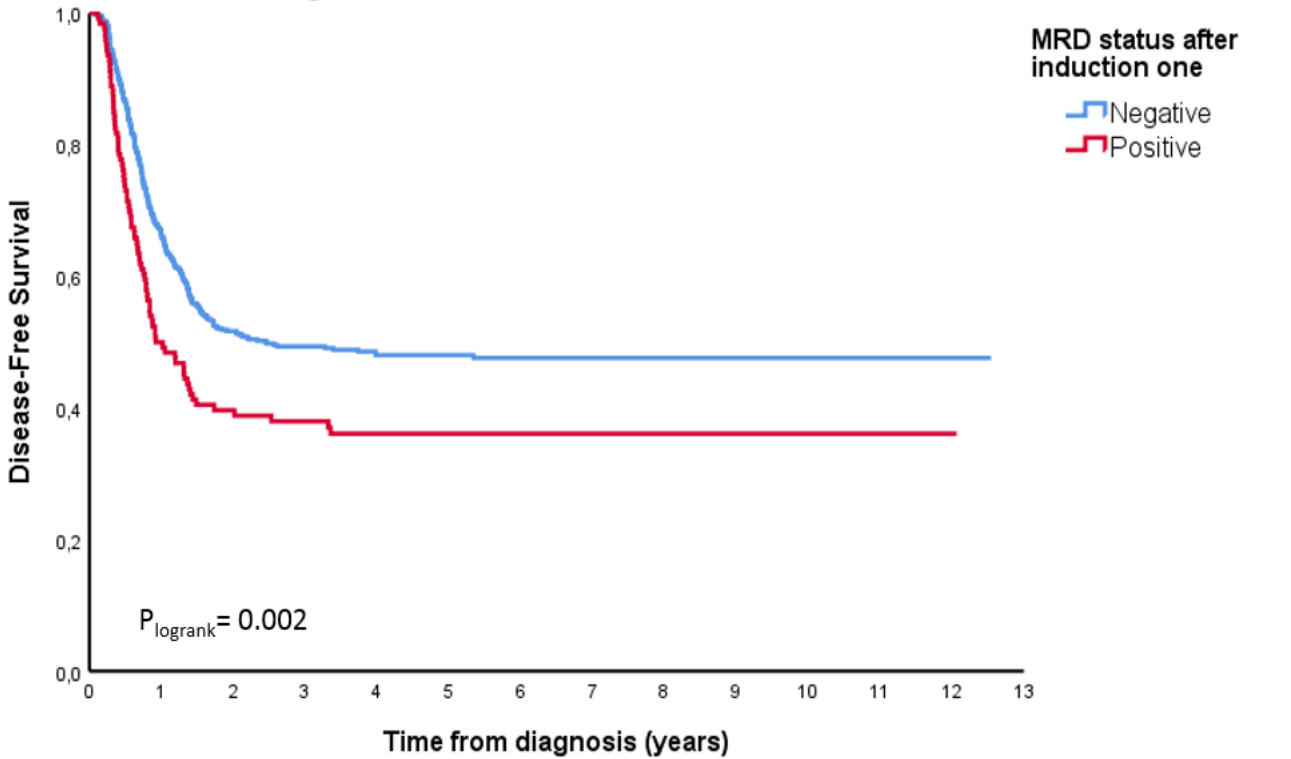


Table II. Multivariable analysis of prognostic factors.

Variable	Hazard ratio	95% CI	*P* value
ICE1-MRD (≥0·1% vs. <0·1%)	4·619	1·436–14·856	**0·010**
ICE2-MRD (≥0·1% vs. <0·1%)	1·386	0·570–3·370	0·471
MK (positive *versus* negative)	6·928	1·352–35·484	**0·020**

Outcome of (Novel) Subgroups in 1257 Pediatric Patients with KMT2A-Rearranged Acute Myeloid Leukemia and the Significance of Minimal Residual Disease Status: A Retrospective Study by the I-BFM-SG

Figure 2A. Kaplan Meier Curve: Probability of Disease-Free Survival for KMT2A-rearranged pAML Patients according to MRD Status after Induction One



van Weelderen, et al. ASH 2020.

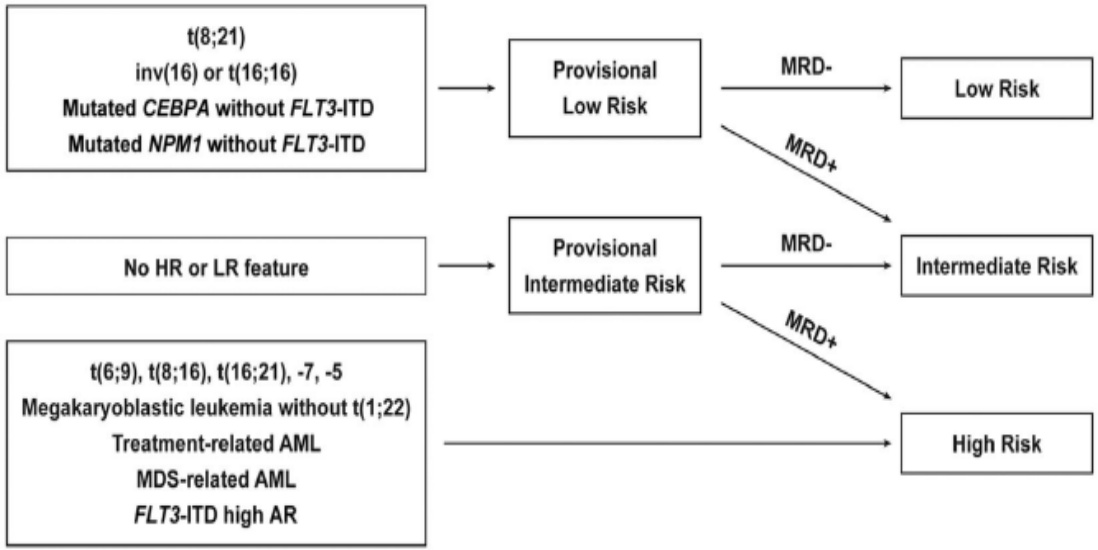
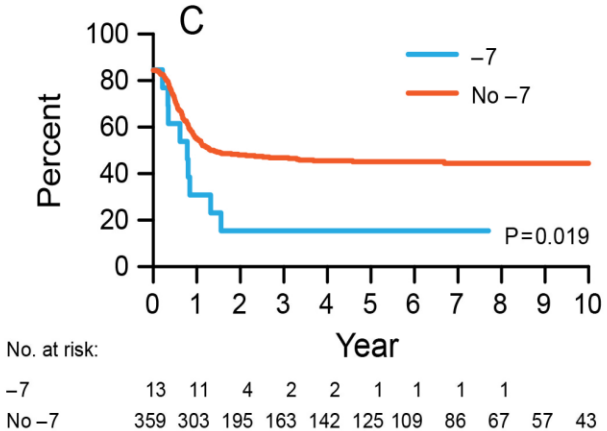


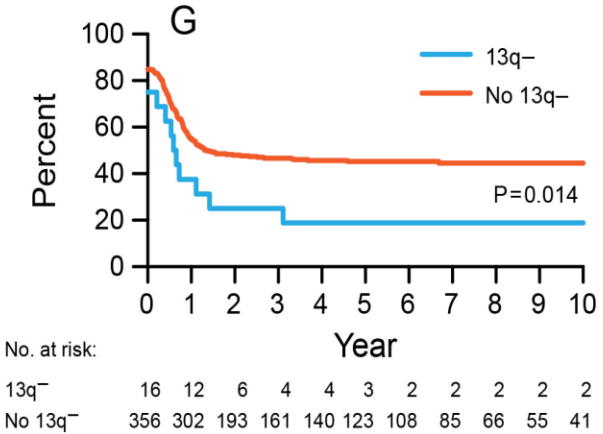
Figure 2. Risk classification of patients with AML. Risk classification scheme based on features at diagnosis and the presence of MRD. LR indicates low-risk; HR, high-risk; and AR, allelic ratio. Patients with t(8;21), inv(16), or t(16;16) are considered to be provisional LR regardless of other genetic alterations. Patients with *NPM1* mutations or biallelic *CEBPA* mutations are provisional LR, except in the presence of *FLT3*-ITD. Provisional LR patients are moved to the intermediate-risk group if they are MRD-positive after one course of induction therapy. HR patients include those with any of the features indicated in the box on the lower left, regardless of response to therapy. Patients who lack LR and HR features are provisionally classified as intermediate risk but are moved to the HR group if they have a poor response to therapy as assessed by MRD.

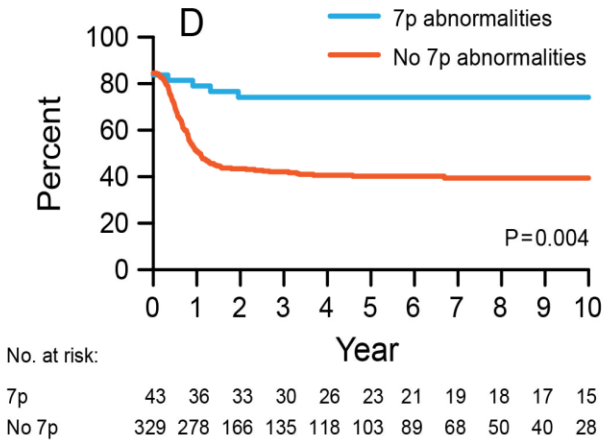
In Rare Diseases, Like Childhood AML, How Can We Improve Patient's Outcome?

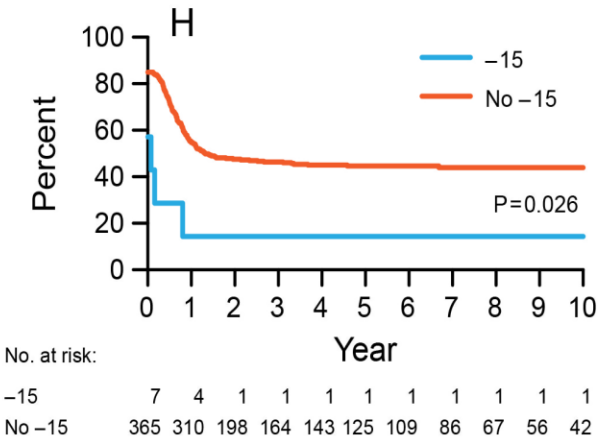
The examples of international collaboration and the translational research model

Outcome of Patients With M7-AML



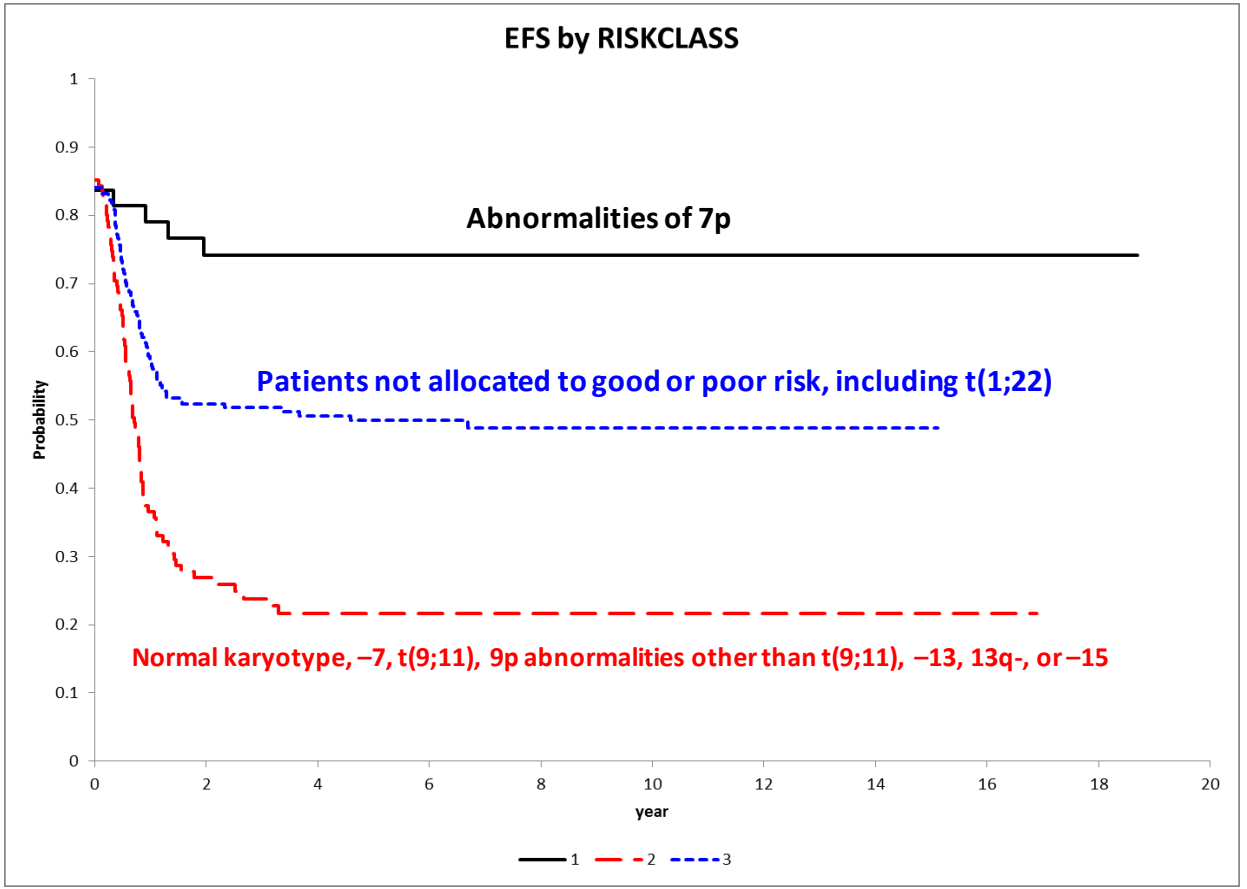






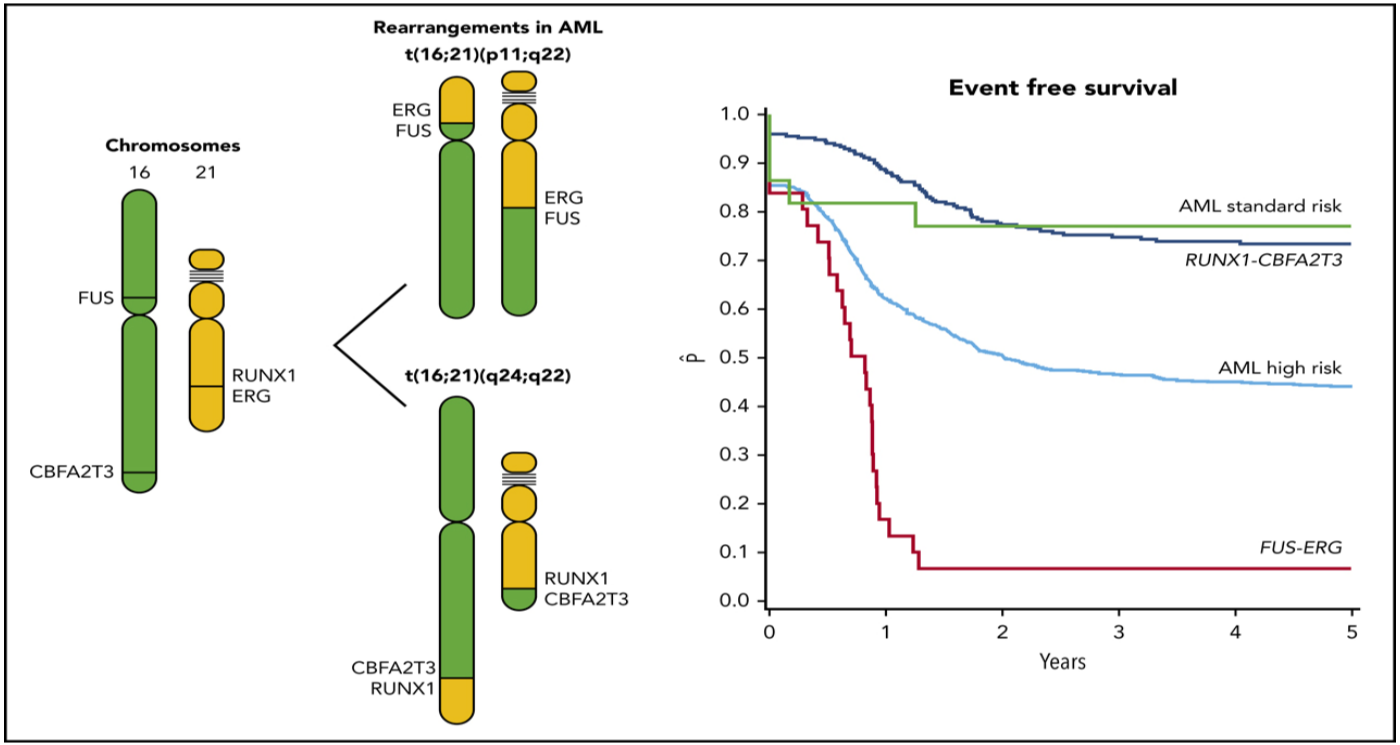
Inaba H, et al. *Blood.* 2015.

Outcome of Patients With M7-AML



Inaba H, et al. *Blood.* 2015.

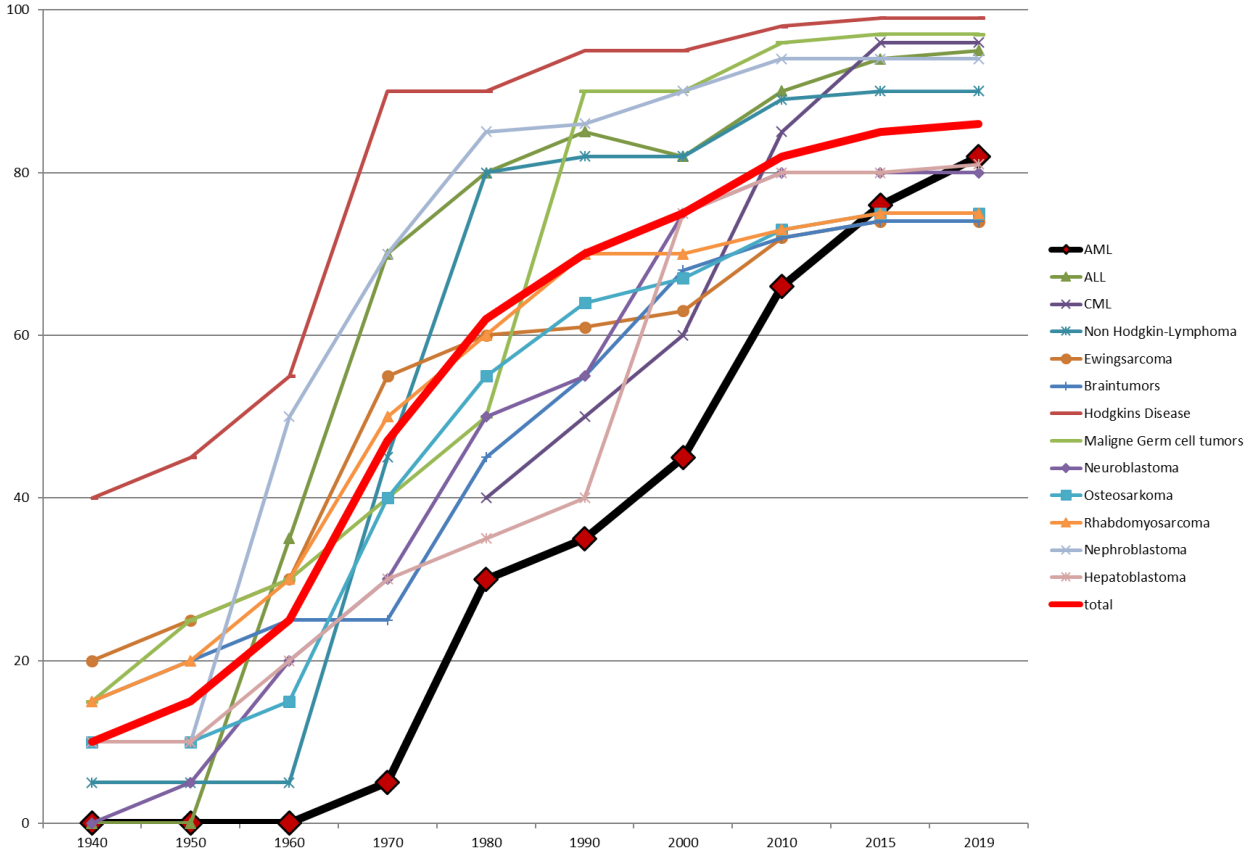
Prognostic Impact of t(16;21)(p11;q22) and t(16;21)(q24;q22) in Pediatric AML: A Retrospective Study by the I-BFM Study Group



Noort S, et al. *Blood.* 2018;132(15):1584-1592.

Improvement of Survival in Pediatric Hematology/Oncology
Impact of Clinicals Trials by Cooperative Study Groups

Example for developed countries



Study Group	Study	Patients (n)	EFS (%)	OS (%)	Relapse (%)	Source
AIEOP	AML2002/01 (2002–2011)	482	8-yr 55.0 ± 2.6	8-yr 67.7 ± 2.4	24	Pession, et al. 2013
BFM-SG	AML-BFM 2004 (2004–2010)	521	5-yr 55 ± 2	5-yr 74 ± 2	29	Creutzig, et al. 2013
COG	AAML03P1 (2003–2005)	340	3-yr 53 ± 6	3-yr 66 ± 5	33 ± 6	Cooper, et al. 2012
	AAML0531 (2006–2010)	1022 (0–29 years)	3-yr 53.1 vs 46.9	3-yr 69.4 vs 65.4	32.8 vs 41.3	Gamis, et al. 2014
JACLS	AML99 (2000–2002)	240	5-yr 61.6 ± 6.5	5-yr 75.6 ± 5.3	32.2	Tsukimoto, et al. 2009
JPLSG	AML05 (2006–2010)	443	3-yr 54.3 ± 2.4	3-yr 73.2 ± 2.3	30.3	Tomizawa, et al. 2013
MRC	MRC AML12 (1995–2002)	564	10-yr 54	10-yr 63	32	Gibson, et al. 2011
NOPHO	NOPHO AML 2004 (2004–2009)	151	3-yr 57 ± 5	3-yr 69 ± 5	30	Abrahamsson, et al. 2011 & Hasle, et al. 2012
PPLLSG	PPLLSG AML-98 (1998–2002)	104	5-yr 47 ± 5	5-yr 50 ± 5	24	Dluzniewska, et al. 2005
SJCRH	AML02 (2002–2008)	216	3-yr 63	3-yr 71	21	Rubnitz, et al. 2010

Zwaan CM, et al. *J Clin Oncol.* 2015;33(27):2949-2962.

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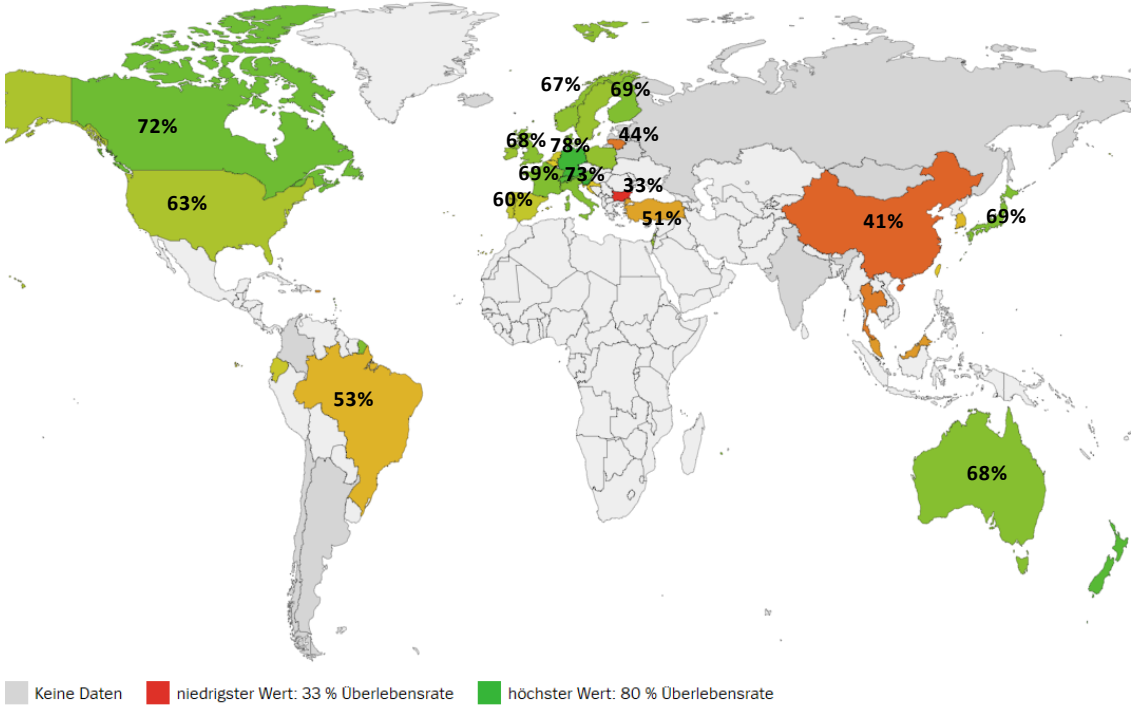
AML BFM Study Group

Lymphatische Leukämie | Akute Myeloische Leukämie

AML

Blutkrebs-Überlebensrate von Kindern

Survival rates in children



http://www.spiegel.de/gesundheit/diagnose/blutkrebs-in-deutschland-haben-kinder-die-besten-ueberlebenschancen-a-1143652.html

Worldwide comparison of survival from childhood leukaemia for 1995–2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries

*Audrey Bonaventure, Rhea Harewood, Charles A Stiller, Gemma Gatta, Jacqueline Clavel, Daniela [illegible] Rafael Marcos-Gragera, Rafael Peris-Bonet, Marion Piñeros, Milena Sant, Claudia E Kuehni, Micha Claudia Allemani, and the CONCORD Working Group**

Lancet Haematol 2017; 4: e202–17

Cooperative Groups Chemotherapy Background

Common principles

- **5 (4) elements of intensive, cytarabine/anthracycline-based chemotherapy**

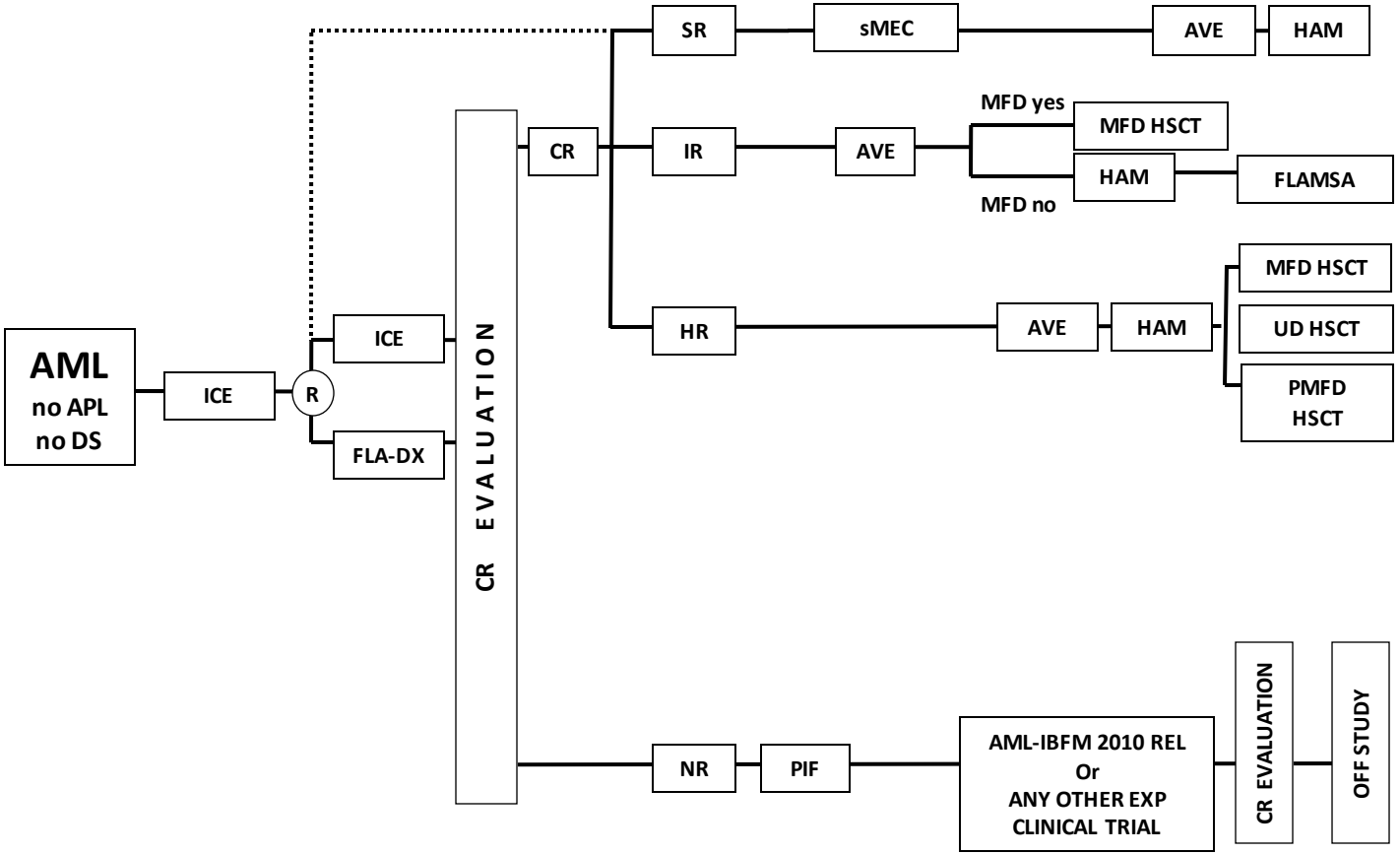
- **Stratification according to risk-groups (according to genetics and/or response)**
  - ***Standard (favorable) risk***
  - ***Intermediate risk***
  - ***High risk***

- **AlloHSCT (CR1) in high risk**

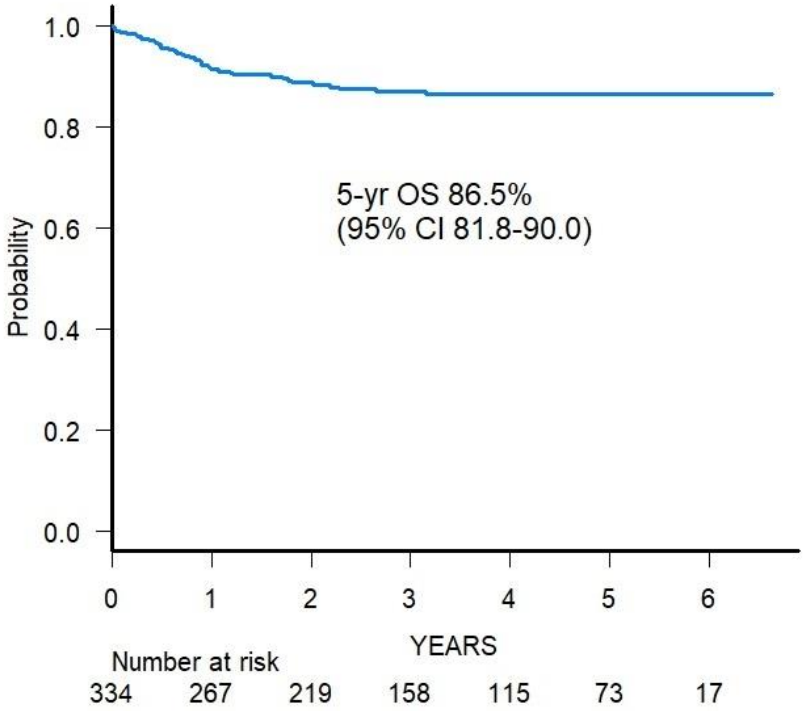
Patient Stratification in the AIEOP LAM 2013 Trial

STANDARD RISK (SR) **20%–22%**	• CBFβ anomalies after 1° induction course and MRD <.1% at TP1 – t(8;21)(q22;q22)/[inv(16)(p13q22)/t(16;16)(p13;q22) • Patients with normal karyotype and mutated NPM-1 and MRD <.1% at TP1
INTERMEDIATE RISK (IR) **35%**	• Normal karyotype – t(9;11)(p22;q23) without other cytogenetic aberrations – t(1;11)(p32;q23) without other cytogenetic aberrations – t(11;19) (p13;q23) – t(16;21)(p11;q22)FUS-ERG, t(3;5)(q25;q34) • Other cytogenetic aberrations. • M7 with t(1;22), irrespectively of patient's age • Other patients not eligible to SR and HR treatment • MRD TP1 >0.1% AND <1%
HIGH RISK (HR) **40%–45%**	• Cytogenetic aberrations associated with dismal outcome – Complex karyotype (≥3 either numeric or structural aberrations) – Monosomal Karyotype (-7, -5) – t(9;11)(p22;q23) associated with other cytogenetic aberrations – Cytogenetic aberrations involving' 11q23 other than those included in the IR: t(11;17)(q23;q21), t(10;11)(p12;q23), t(4;11)(q21;q23), t(6;11)(q27;q23), t(x;11) – Rare cytogenetic aberrations: t(6;9)(p23;q34), t(8-16)(p11;p13), t(9;22)(q34;q11) t(5;11)NUP98/NSD1, t(4;11)MLL/ArgBP2 • FLT3-ITD • Patients with CN AML and CBFA2T3-GLIS2 fusion transcript • FAB M6, M7 without t(1;22), • Patients not in CR at the end of the 1° induction course • MRD >1% at TP1 or >0.1% at TP2 • Patients with non-SR criteria and WBC >100.000/mL

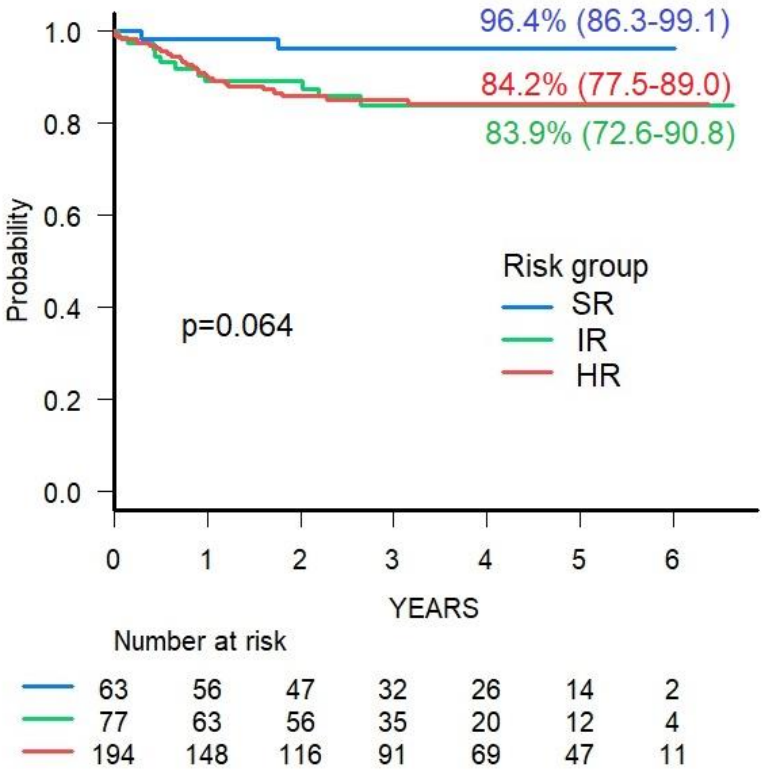
AML WP-Protocol LAM 2013



Overall Survival



Overall Survival by Risk



AIEOP-BFM AML 2020

INTERNATIONAL MULTICENTER, OPEN-LABEL CLINICAL TRIAL FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA IN CHILDREN AND ADOLESCENTS

PROTOCOL CODE:	AIEOP-BFM-AML 2020
EudraCT NUMBER:	2020-005634-15
VERSION NUMBER:	1.4
DATE OF ORIGINAL FINAL VERSION:	07.12.2021
SPONSOR NAME/ADDRESS:	German Pediatric Oncology Group GPOH gGmbH registered at: Chausseestraße 128/129 GERMANY – 10115 Berlin Sponsor´s Office: Holsterhauser Platz 2 GERMANY – 45147 Essen

AIEOP

AML BFM study group

INTERNATIONAL MULTICENTER, OPEN-LABEL CLINICAL TRIAL FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA IN CHILDREN AND ADOLESCENTS

Coordinating Investigator

Prof. Dr. Franco Locatelli, MD PhD
Sapienza, University of Rome
Department of Pediatric Hematology and Oncology
IRCCS Ospedale Pediatrico Bambino Gesù
Piazza Sant'Onofrio, 4
00165 Rome
Italy
Phone: +39 06 68592678/2129
Fax: +39 06 68592292
E-Mail: franco.locatelli@opbg.net

Coordinating Investigator

Prof. Dr. Dirk Reinhardt, MD
University Hospital of Essen
Pediatrics III
Hufelandstraße 55
45147 Essen
Germany
Phone.: +49 201 723 3755
Fax: +49 201 723 5386
E-Mail: Dirk.Reinhardt@uk-essen.de

Biometrics

Mag. Ulrike Pötschger
St. Anna Kinderkrebsforschung e.V.
CCRI - CHILDREN'S CANCER RESEARCH INSTITUTE
Zimmermannplatz 10
1090 Vienna, Austria
Phone.: +43 1 40470 0
FAX: +43 1 40470 7150
E-Mail ulrike.poetschger@ccri.at

International Data Management

Central Data Management GPOH
ZDM-GPOH
Carl-Neuberg-Straße 1
30625 Hannover
Phone: +49 511 532 6717
E-Mail: ZDM-GPOH@mh-hannover.de

Pharmacovigilance

Pediatric Research Network gGmbH

Holsterhauser Platz 2, 45147 Essen Germany
Phone: +49 201 7494 96-0
Fax: +49 201 8777 5484
E-Mail: waack.katharina@aml-bfm.de

Regulatory Affairs & Monitoring

Pediatric Research Network gGmbH

Holsterhauser Platz 2, 45147 Essen Germany
Phone: +49 201 7494 96-0
Fax: +49 201 8777 5484
E-Mail: waack.katharina@aml-bfm.de

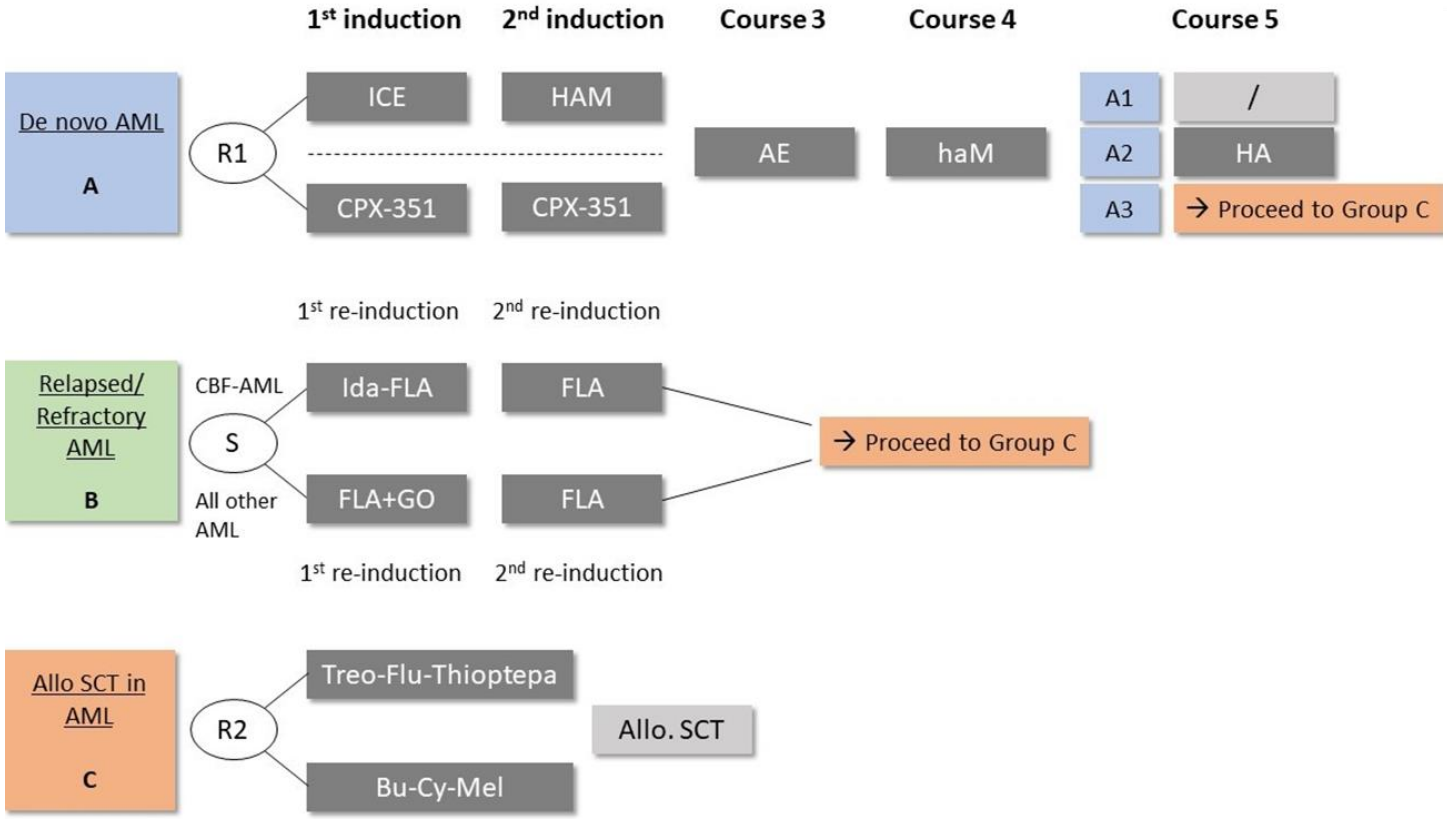
RISK GROUP	GENETIC RISK CRITERIA	RESPONSE CRITERIA

STANDARD RISK (SR)	• CBFβ abnormalities
	  • t(8;21)(q22;q22) with adequate (≥ 2 log) reduction by qPCR at IND 2
	  • inv(16)(p13q22)/t(16;16)(p13;q22)
	• Biallelic CEBPα aberrations
	• t(16;21) *CBFA2T3/RUNX1*
	
	and FLT3-ITD negative
		Genetic standard risk and
		• MRD <0.1% at IND 2
		
		t(8;21) and
		• MRD > 2 log reduction at IND 2 (qPCR)

INTERMEDIATE RISK (IR)	• NON SR and NON HR patients	Genetic standard or intermediate risk and • MRD at IND 1 ≥ 0.1% and < 1% and MRD at IND 2 < 0.1%

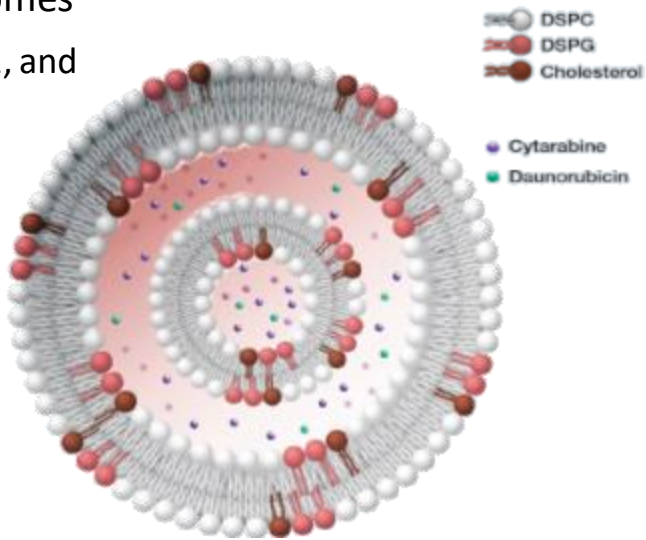
HIGH RISK (HR)	• Complex karyotype (≥ 3 aberrations including at least one structural aberration) *excluding those with recurrent translocations*
	• Monosomal Karyotype, i.e. -7, -5/del(5q)
	• 11q23/*KMT2A* rearrangements involving:
	  • t(4;11)(q21;q23) KMT2A/AFF1
	  • t(6;11)(q27;q23) KMT2A/AFDN
	  • t(10;11)(p12;q23) KMT2A/MLLT10
	• t(16;21)(p11;q22) FUS/ERG
	• t(9;22)(q34;q11.2) BCR/ABL1
	• t(6;9)(p22;q34) DEK/NUP214
	• t(7;12)(q36;p13) MNX1/ETV6
	• inv3(q21q26)/t(3;3)(q21;q26) RPN1/MECOM
	• 12p abnormalities
	• *FLT3-ITD* with AR ≥ 0.5 not in combination with other recurrent abnormalities or NPM1 mutations
	• *WT1* mutation and *FLT3-ITD*
	• *inv(16)(p13q24) CBFA2T3/GLIS2*
	• *t(5;11)(q35;p15.5) NUP98/NSD1 and t(11;12)(p15;p13) NUP98/KDM5A*
	
	• Pure Erythroid leukemia
		• MRD ≥ 1% at IND 1 or ≥ 0.1% at IND 2 or (only if FLOW-result not available/informative) blast count ≥5% at IND 1

- If Isolated t(8;16) and/or t(11;16) occur in patients below 1 month of age a watch and wait strategy is recommended
- GATA 1 screening will be performed in all patients and if mutations leading to exclusive GATA1s expression are found, these patients will be treated according to the Down Syndrome AML Protocol


1st induction
2nd induction
Course 3
Course 4
Course 5
De novo AML
A
R1
ICE
HAM
CPX-351
CPX-351
AE
haM
A1
/
A2
HA
A3
→ Proceed to Group C
1st re-induction
2nd re-induction
Relapsed/ Refractory AML
B
CBF-AML
S
All other AML
Ida-FLA
FLA
FLA+GO
FLA
→ Proceed to Group C
1st re-induction
2nd re-induction
Allo SCT in AML
C
R2
Treo-Flu-Thioptepa
Bu-Cy-Mel
Allo. SCT

CPX-351 (VYXEOS™)

- CPX-351 is a liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio within 100-nm diameter liposomes
  - Ratiometric dosing: Cytarabine/daunorubicin molar ratios of 1:1, 5:1, and 10:1 shown to be synergistic[1]
  - Fixed molar ratio maintained in human plasma for at least 24 hours after final dose[2]
  - Median half-life 31.1 hrs (cytarabine) and 21.9 hrs (daunorubicin)[2]
  - Drug exposure maintained for 7 days[2]
  - Evidence for selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice[3]
  - 1 unit: 1 mg cytarabine, 0.44 mg dauno



DSPC, desaturated phosphatidylcholine; DSPG, distearylphosphatidylglycerol.

Adapted from Lancet et al. EHA 2017 (P556).

1. Mayer LD, et al. *Mol Cancer Ther.* 2006;5(7):1854-1863; 2. Feldman EJ, et al. *J Clin Oncol*. 2011;29(8):979-985; 3. Lim WS, et al. *Leuk Res*. 2010;34(9):1245-1223.

AAML0431 Trial

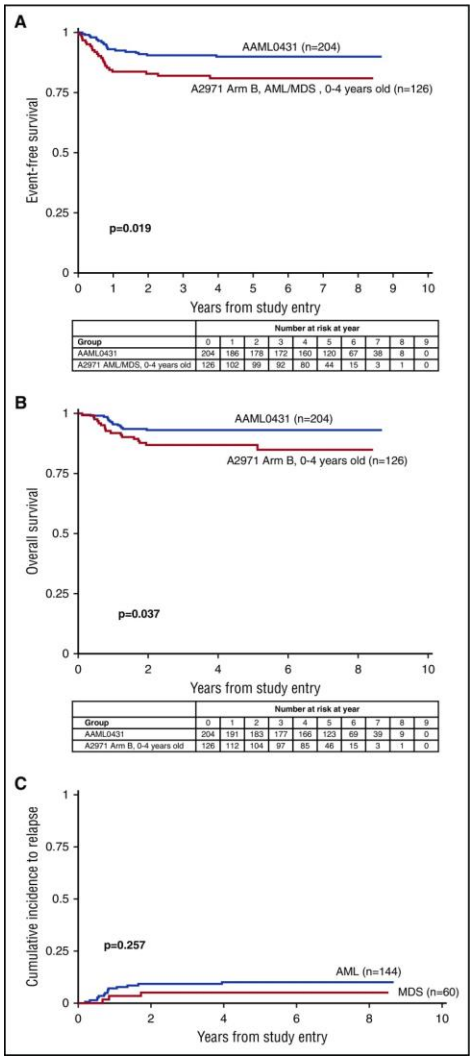
205 children (106 girls, 99 boys) with DS or DS mosaicism
March 2007–December 2011

Induction cycles I, III, and IV
continuous-infusion araC 6.7 mg/kg per day for 4 days
continuous-infusion daunorubicin 0.67 mg/kg per 24 hours for 4 days
oral 6-thioguanine 1.65 mg/kg twice daily for 4 days.

Induction cycle II
AraC 100 mg/kg every 12 hours for 4 doses on days 1, 2, 8, 9
Escherichia coli asparaginase (200 U/kg) days 2 and 9.

Intensification cycles I and II
continuous-infusion AraC 3.3 mg/kg per 24 hours for 7 days
etoposide 4.2 mg/kg per dose for 3 days.

5-year **EFS 89.9%**
5-year **OS 93.0%**
5-year OS for 17 patients with refractory/relapsed leukemia 34.3%

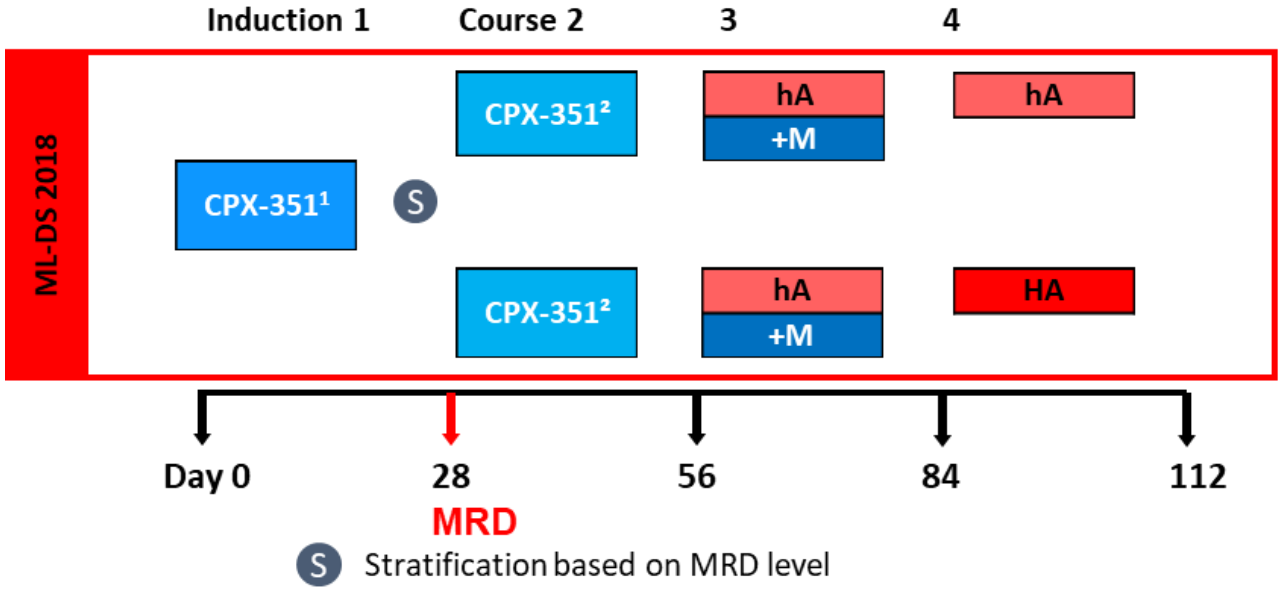


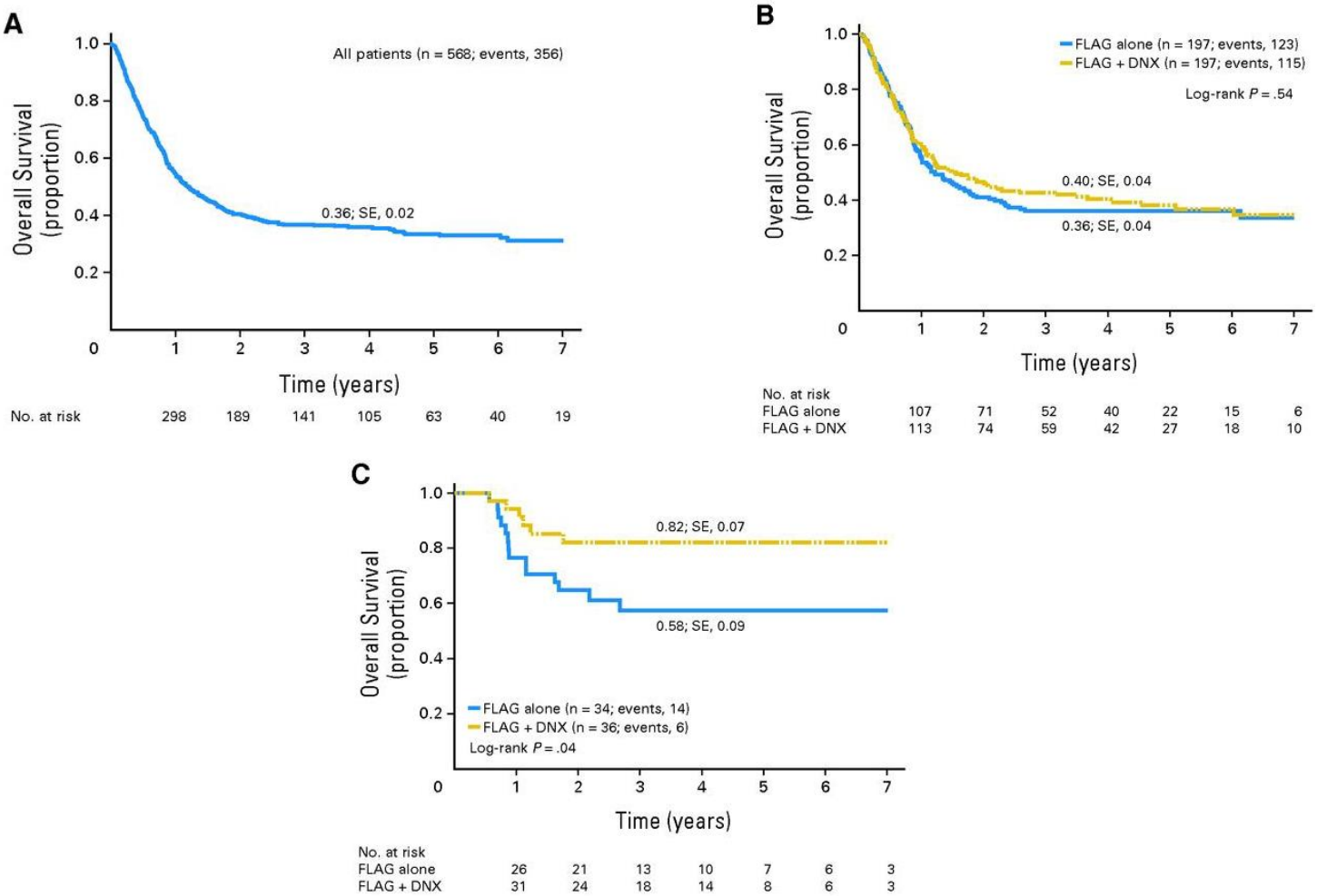
Taub JW, et al. *Blood*. 2017; 129(25):3304-3313.

Clinical Trial Protocol

Treatment of **M**yeloid **L**eukemia
in Children with **D**own **S**yndrome **2018**

ML-DS 2018

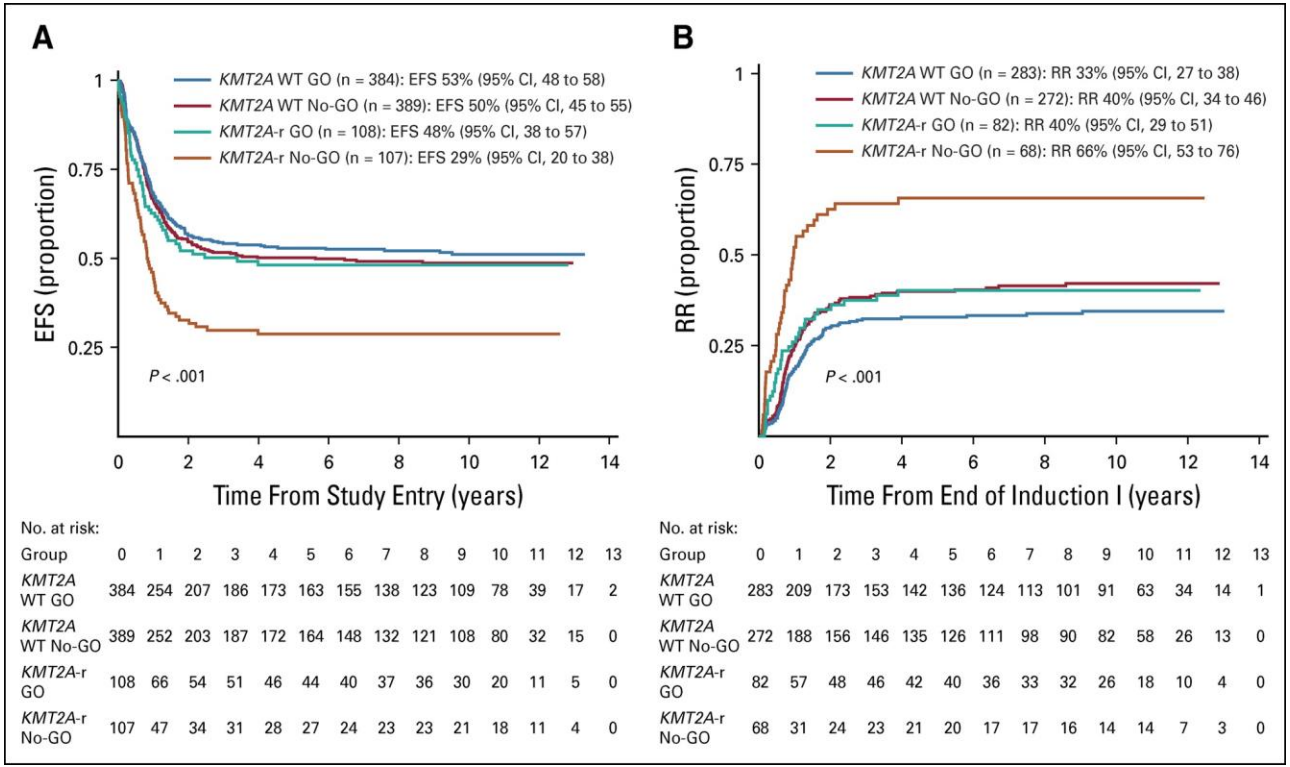




Kaspers GJL, et al. *J Clin Oncol.* 2013;31(5):599-607.

New Agents in Childhood AML

Gemtuzumab ozogamicin (Mylotarg)	Anti-CD33 –calicheamicin	First line (MyeChild/COG)
CPX-351 (Vyeos)	Liposomal cytarabin/daunorubicin	First line (COG, ML-DS, AIEOP-BFM)
Midostaurin (Rydapt)	Tyrosine kinase-inhibitor (FLT-3)	First line (PKC412-AML)
Gilteritinib (Xospata)	FLT3-inhibitor	First line (COG) and R/R AML
Quizartinib	FLT3-inhibitor	R/R AML
Enasidenib (AG-221)	IDH2 inhibitor	R/R AML
Venetoclax (Venclyxto)	BCL2 inhibitor	R/R AML
IMGN632	Anti-CD123 ADC	R/R AML



Outcomes for patients with KMT2A-r versus KMT2A WT outcome by GO exposure. (A) Five-year EFS from study entry and (B) 5-year RR from CR.

CR, complete remission; EFS, event-free survival; GO, gemtuzumab ozogamicin; KMT2A-r, KMT2A-rearranged; No-GO, not receiving GO; RR, relapse risk; WT, wild-type.

Pollard JA, et al. *J Clin Oncol.* 2021;39(28):3149-3160.

blood

613. ACUTE MYELOID LEUKEMIA: CLINICAL STUDIES| NOVEMBER 13, 2019

Clinical Profile of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate (ADC), in Patients with Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) or Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

Naval G. Daver, MD, Pau Montesinos, MD PhD, Daniel J. DeAngelo, MD, Eunice S. Wang, MD, Nikolaos Papadantonakis, MDPhDMSc, Eric Deconinck, MD PhD, Harry P. Erba, MD PhD, Naveen Pemmaraju, MD, Andrew A. Lane, MD PhD, David A. Rizzieri, MD, Kendra L. Sweet, MD, Giovanni Martinelli, Corrado Tarella, MD, Elisabetta Todisco, MD PhD, Marina Y Konopleva, MD PhD, Callum M. Sloss, PhD, Kerry Culm-Merdek, PhD, Patrick A. Zweidler-McKay, MD PhD, Hagop M. Kantarjian, MD

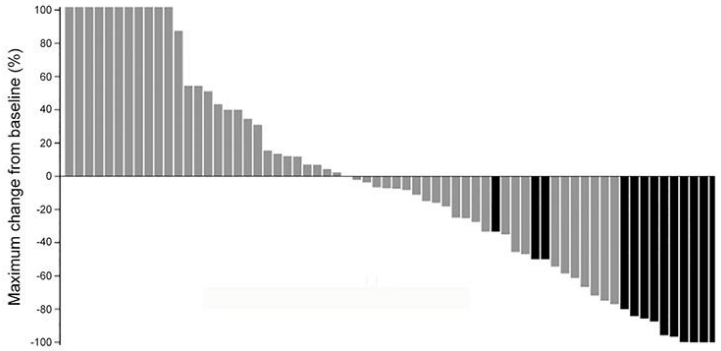
Adult patients with CD123-positive R/R AML or R/R BPDCN with no more than 3 prior lines of therapy.
Median age of patients: 69 years (range 33–83)

IMGN632 was given in 2 schedules: A) dosing day 1 and B) fractionated dosing on days 1, 4, and 8, both on a 21-day cycle.
74 patients (67 AML, 7 BPDCN) have received IMGN632 across 9 dose-escalation cohorts on 2 schedules, with dosing escalated from .015–.45 mg/kg on schedule A (n = 61) and .015-.06 mg/kg on days 1, 4, and 8 on schedule B (n = 13).

In the assessable **AML population** (n = 66)

- 37 (55%) had a reduction in bone marrow blasts
- 13 (20%) achieved an objective response (3 CR, 8 CRi, 2 MLFS) across a wide range of doses (.045 to .3 mg/kg)

Of note, the majority of responders (77%) had failed prior intensive therapies (including 3 with prior transplant), 62% had adverse ELN risk classification (including complex karyotype, ASXL1, RUNX1, and *FLT3*-ITD mutations), and 23% were primary refractory.



Maximum % decrease in bone marrow blasts from baseline. Objective responses (CR, CRi, or MLFS) are shown in black.

Take-home Messages

- Outcome of pediatric patients with AML is progressively improving over time
- Patient stratification is becoming more and more sophisticated, being based on the detection of recurrent genetic lesions and MRD level at the end of induction therapy
- Treatment intensity, including indications to allogeneic HSCT, is modulated according the risk profile of the patients
- Outcome of patients with relapsed/refractory disease is still unsatisfactory and novel, more efficacious agents are warranted
- International cooperation is key in such a rare disease

Question 1

The outcome of patients with KMT2A-rearranged AML is influenced by the partner gene. Which of the following statements is wrong?

a) Patients with translocation t(6;11) have a dismal outcome
b) Patients with translocation t(1;11) have an excellent/good outcome
c) Patients with translocation t(10;11) have a dismal outcome
d) Patients with translocation t(1;11) have a poor outcome

Question 2

Which of the following statements is correct?

a) Gemtuzumab ozogamicin (GO) improves the outcome of patients with KMT2A translocations

b) Gemtuzumab ozogamicin (GO) doesn't influence the outcome of patients with KMT2A translocations

c) Gemtuzumab ozogamicin (GO) worsens the outcome of patients with KMT2A translocations

d) There are no data on the effect of Gemtuzumab ozogamicin (GO) on the outcome of patients with KMT2A translocations

Global Leukemia Academy

Case 1: Pediatric AML

Luisina Peruzzo

APTITUDE HEALTH

SAHOP
Sociedad Argentina de Hemato-Oncología Pediátrica

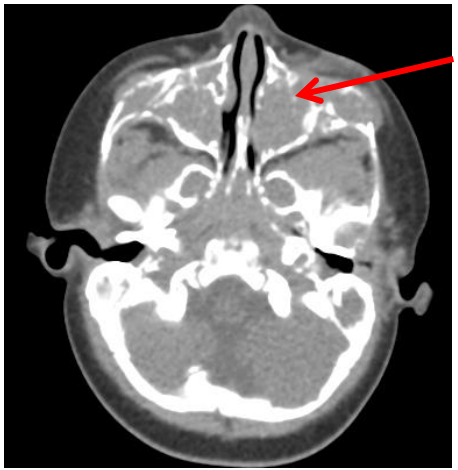
Hospital de Pediatría
Garrahan

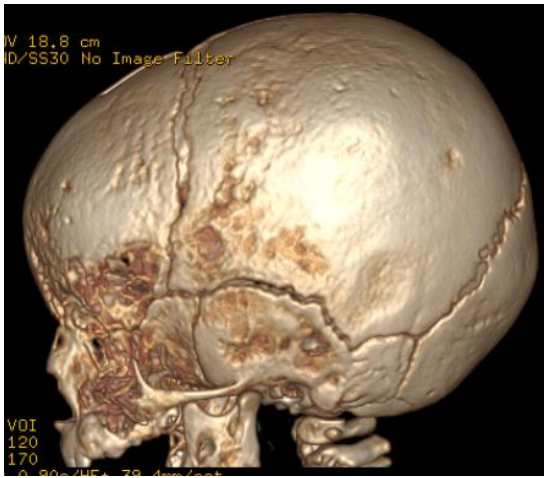
Report of Cases

Luisina Peruzzo, MD
Hematology Oncology Department
Buenos Aires, Argentina

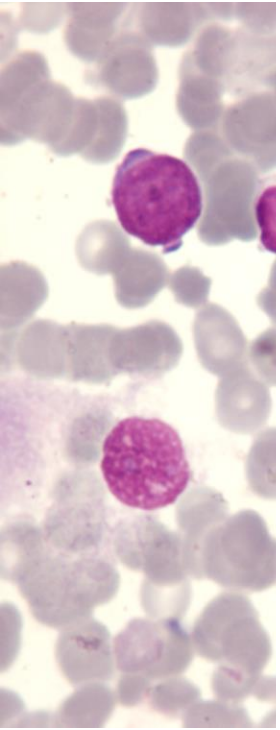
CLINICAL CASE 1

- A female patient, 6 months old, twin sibling
- No relevant antecedents
- Physical examination: Peripheral facial paralysis, no liver or spleen enlargement
- Pancytopenia: WBC 5,220/mm^3 - Hb 9.9 g/dl- platelets 47,000/mm^3





CLINICAL CASE 1: Bone Marrow Aspiration

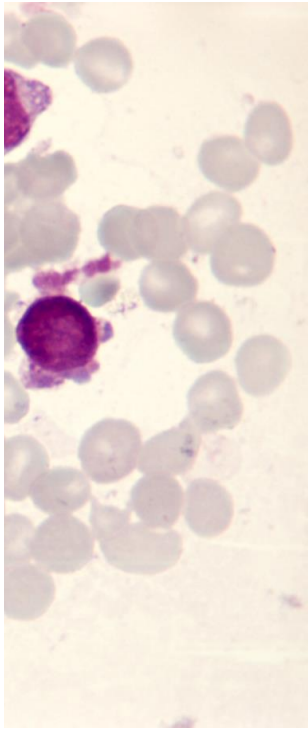


- Flow-cytometry: CD42a, CD41, CD61, and CD34 positive
- G-banding: t(1;22)(p13;q13)
- RT-PCR: *OTT::MAL* or *RBM15::MKL*
- CNS compromise

ACUTE MEGAKARYOBLASTIC LEUKEMIA

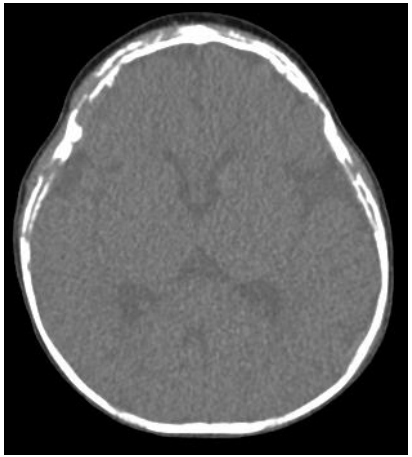
⇓

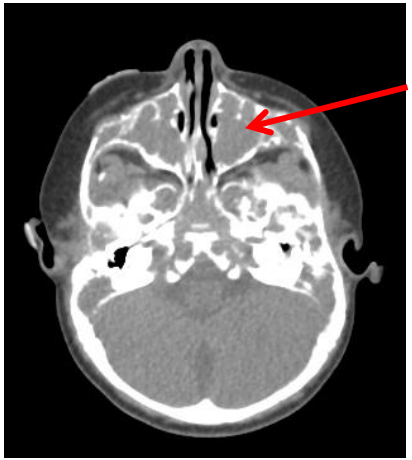
AML-BFM–based 07 PROTOCOL



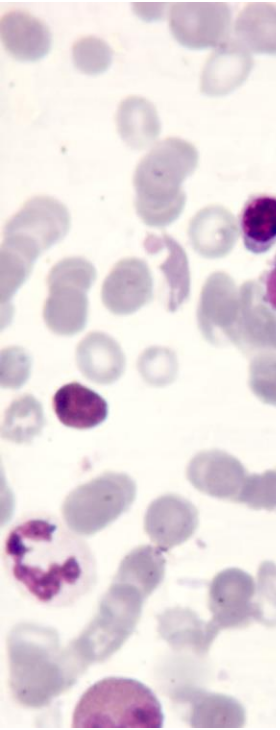
CLINICAL CASE 2

- Her twin sibling, female, 7 months old (19 days later)
- No relevant antecedents
- Physical examination: Supraciliary nodular lesion, no liver or spleen enlargement
- Bi-cytopenia: WBC 8,300/mm^3 (immature elements 11%) - Hb7 g/dl - platelets 60,000/mm^3





CLINICAL CASE 2: Bone Marrow Aspiration

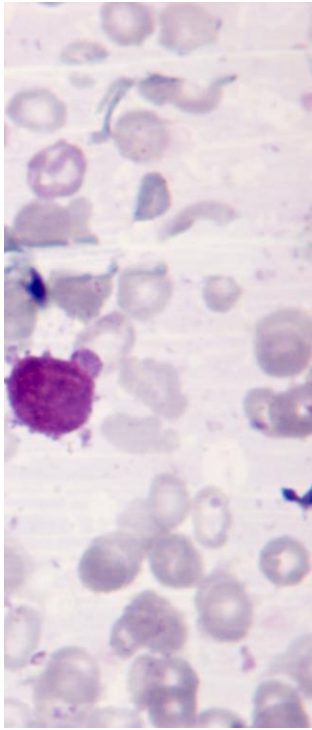


- Flow-cytometry: CD42a, CD41, CD61, and CD34 positive
- G-banding: t(1;22)(p13;q13)
- RT-PCR: *OTT::MAL* or *RBM15::MKL*
- No CNS compromise

ACUTE MEGAKARYOBLASTIC LEUKEMIA

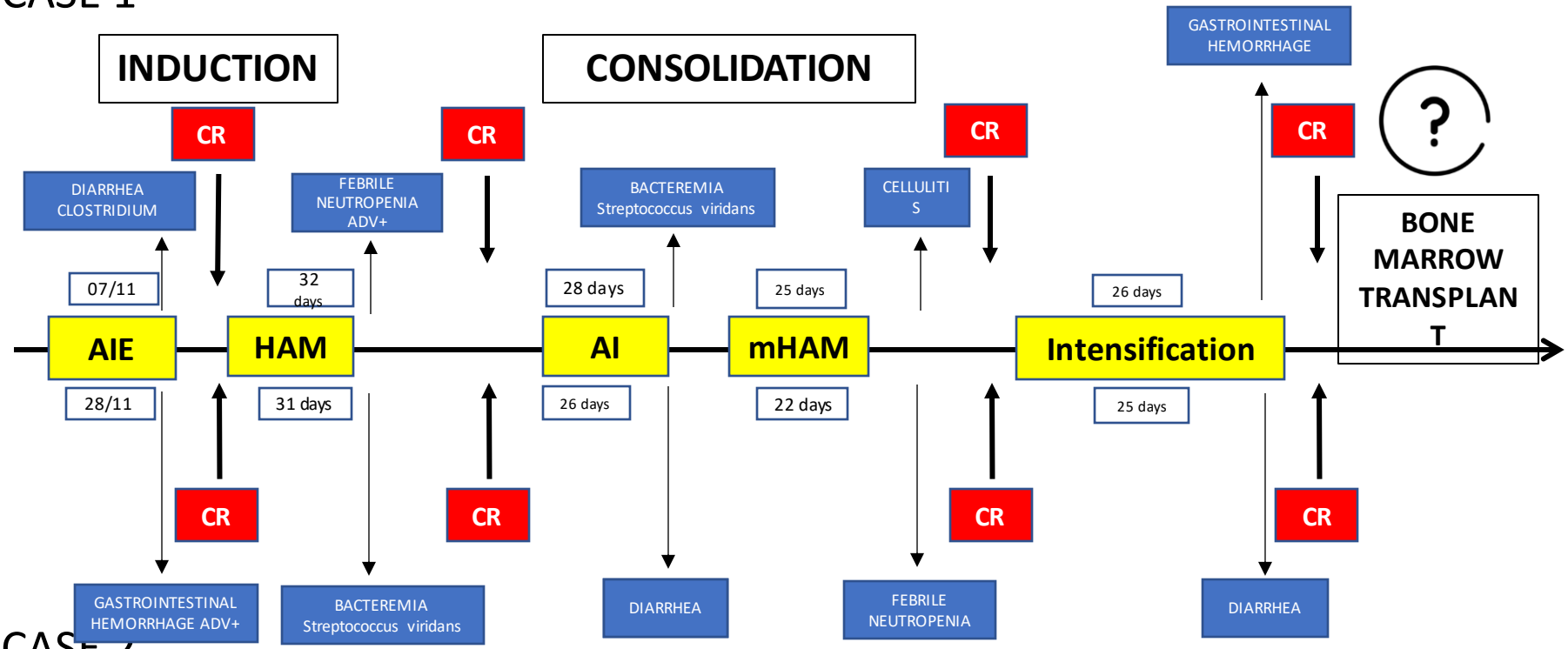
⇓

AML-BFM–based 07 PROTOCOL



EVOLUTION AML 07 – BFM-Based Protocol Treatment

CASE 1



CASE 2

CONSIDERING . . .

- Twin siblings <1 year old – without bone marrow related donor
- M7 AML - t(1;22)(p13;q13) - *OTT::MAL* or *RBM15::MKL*
- Complete remission after first induction block
- Good treatment tolerance

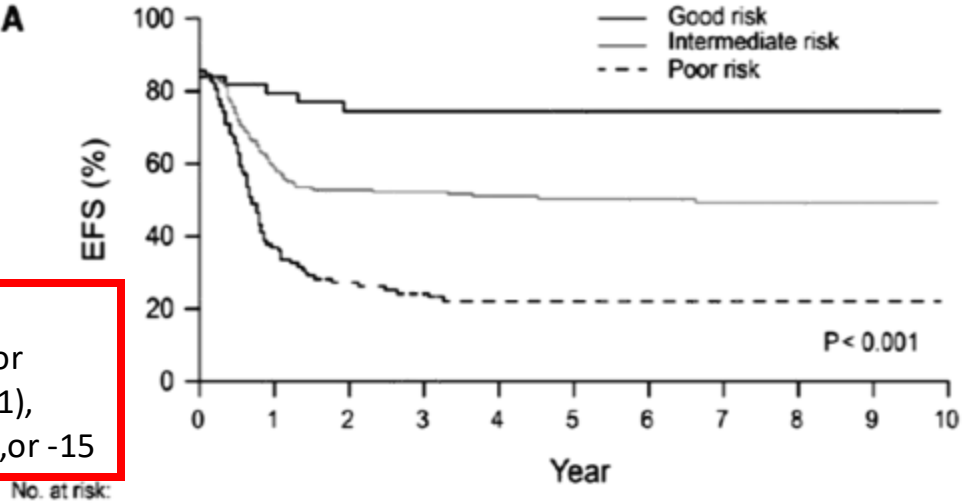
WOULD YOU CONSIDER MUD HSCT OR OTHER ALTERNATIVE DONOR AS TREATMENT CONSOLIDATION?

1. YES
2. NO

Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study

Hiroto Inaba,[1] Yinmei Zhou,[1] Oussama Abla,[2] Souichi Adachi,[3,4] Anne Auvrignon,[5] H. Berna Beverloo,[6,7] Eveline de Bont,[7,8] Tai-Tsung Chang,[9,10] Ursula Creutzig,[11,12] Michael Dworzak,[13] Sarah Elitzur,[14] Alcira Fynn,[15,16] Erik Forestier,[17,18] Henrik Hasle,[18,19] Der-Cherng Liang,[10,20] Vincent Lee,[21,22] Franco Locatelli,[23,24] Riccardo Masetti,[24,25] Barbara De Moerloose,[26,27] Dirk Reinhardt,[12,28] Laura Rodriguez,[2] Nadine Van Roy,[26,27] Shuhong Shen,[29] Takashi Taga,[4,30] Daisuke Tomizawa,[4,31] Allen E. J. Yeoh,[32] Martin Zimmermann,[11,12] and Susana C. Raimondi[1]

Figure 4. Kaplan-Meier curves for EFS (A) and overall survival (OS) (B) for 372 patients with good-, poor-, and intermediate-risk abnormalities. Good risk: abnormalities of 7p; poor risk: normal karyotype, −7, t(9;11), 9p abnormalities other than t(9;11), −13, 13q−, or −15; and intermediate risk: patients not included in good or poor-risk group. A patient with both 7p abnormalities and −15 was included in the good-risk group.



- **Good**: abnormalities 7p
- **Intermediate:** not good or poor
- **Poor**: Normal karyotype, t(9;11), other 9p abnormalities, -13, 13q-,or -15

BLOOD, 24 SEPTEMBER 2015 • VOLUME 126, NUMBER 13

CONSIDERING . . .

- Twin siblings <1 year old – without bone marrow related donor
- M7 AML - t(1;22)(p13;q13) - *OTT::MAL* or *RBM15::MKL*
- Complete remission after first induction block
- Good treatment tolerance

WOULD YOU CONSIDER CNS RADIATION THERAPY A TREATMENT STRATEGY FOR THE PATIENT WITH PERIPHERAL FACIAL PARALYSIS?

1. YES
2. NO

Pediatr Blood Cancer 2010;55:414–420

The Presence of Central Nervous System Disease at Diagnosis in Pediatric Acute Myeloid Leukemia Does Not Affect Survival: A Children's Oncology Group Study

Donna L. Johnston, MD,[1]* Todd A. Alonzo, PhD,[2] Robert B. Gerbing, MSc,[3] Beverly J. Lange, MD,[4] and William G. Woods, MD[5]

a superior outcome, but they utilized radiation therapy in over half of these patients [4]. Radiation therapy is known to have significant side effects [17], and its use no longer standard in pediatric patients because of the excellent CNS penetration of high dose cytarbine containing regimens. Given that the patients in this current study

Review article

BLOOD, 18 OCTOBER 2012 • VOLUME 120, NUMBER 16

Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel

*Ursula Creutzig,[1] *Marry M. van den Heuvel-Eibrink,[2] Brenda Gibson,[3] Michael N. Dworzak,[4] Souichi Adachi,[5] Eveline de Bont,[6] Jochen Harbott,[7] Henrik Hasle,[8] Donna Johnston,[9] Akitoshi Kinoshita,[10] Thomas Lehrnbecher,[11] Guy Leverger,[12] Ester Mejstrikova,[13] Soheil Meshinchi,[14] Andrea Pession,[15] Susana C. Raimondi,[16] Lillian Sung,[17] Jan Stary,[18] Christian M. Zwaan,[2] †Gertjan J. L. Kaspers,[19] and †Dirk Reinhardt,[1] on behalf of the AML Committee of International BFM Study Group

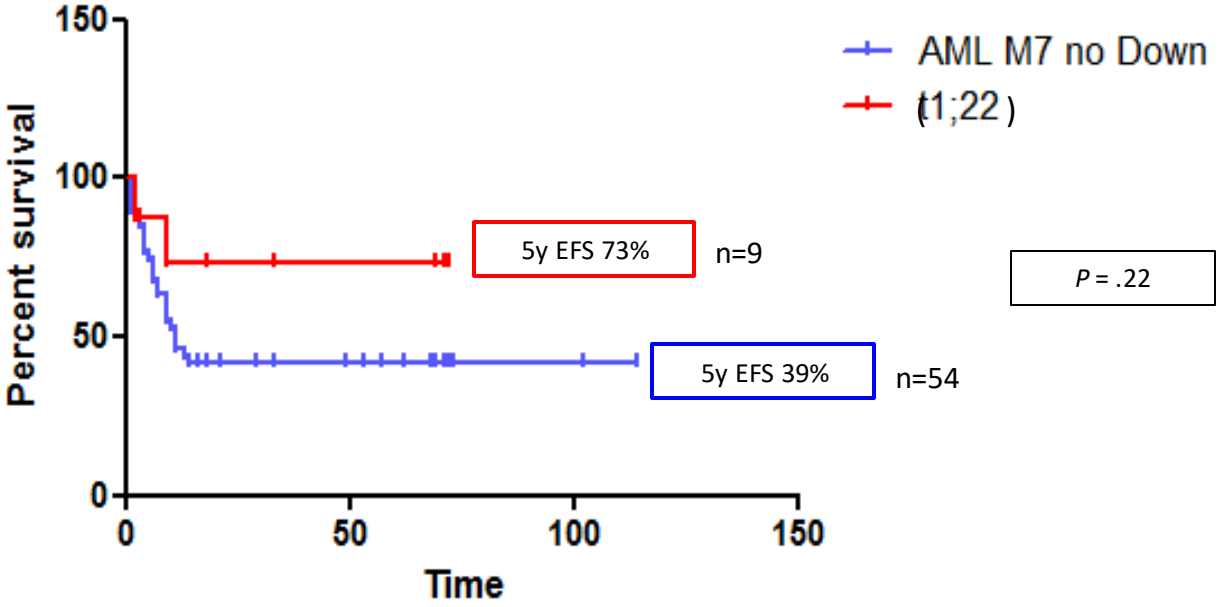
patients with CNS involvement require intensified intrathecal therapy to clear blasts from the CNS fluid. Although most study groups have added CNS irradiation to the regimen of these patients, recent observations suggest that frequent intrathecal chemotherapy combined with intensive systemic chemotherapy may yield similar results.[119,121]

OUTCOME

Both twins are alive, free of disease, and without sequelae at 73 and 72 months from diagnosis.

HPG-SAHOP EXPERIENCE

EFS M7 AML vs M7 AML t1;22



THANKS FOR YOUR ATTENTION

Global Leukemia Academy

Case 2: Pediatric AML

Erica Almeida Viana

APTITUDE HEALTH

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

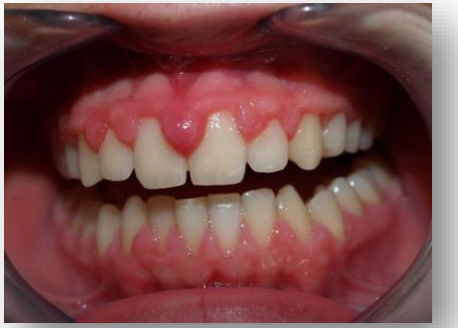
Latin America and Canada

Refractory Acute Myeloid Leukemia

Clinical Case

Speaker Brief:
Érica Almeida Viana
Fellow GRAACC, Sao Paulo, Brazil

Medical History



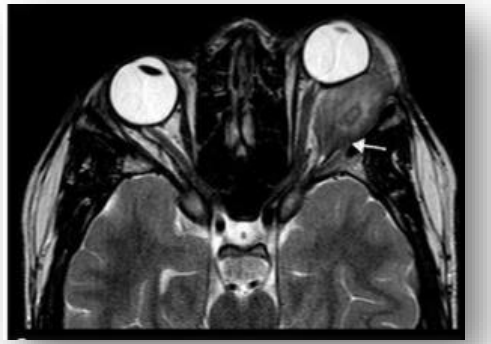
- male, 7 years old
- No prior comorbidities
- Gingival hypertrophy and low fever for about 1 week
- Conjunctival hyperemia and eyelid edema
- Epistaxis, pallor, petechiae, and hematomas

Medical History

Hb 5.9 g/dL | WBC: 465,000/mm^3 (90% blasts) | Plt: 22.000

Flow cytometry → acute myelomonocytic leukemia

- Karyotype: 46,XY [20]
- Molecular biology: negative for *FTL3*, CBFB-MyH11 and *NPM1*
- CSF: 1 RBC 0 WBC
- Considered CNS 3 due to
  - Orbital chloroma



Therapeutic Options

1. BFM Protocol 2004
2. Cytoreduction with hydroxyurea
3. AML NOPHO Protocol 2012
4. GELMAI

6.2. INDUÇÃO I – **MAG I**

Todos os pacientes devem iniciar o tratamento com esquema de baixas doses – MAG I com as seguintes medicações:

a) Mitoxantrone: 5mg/m²/dia, IV (D1 a D3). Infusão em 15 a 30 min.

b) Citarabina: 10mg/m², SC, a cada 12 h (D1 a D10), total de 20 doses.

c) GCSF: 5mcg/kg/dia, SC ou IV, (D1 a D10).

d) Intratecal: de acordo com idade.

Tabela 1: Dose dos quimioterápicos administrados por via intratecal

Idade	MTX	Hidrocortisona	Ara-C	Volume
< 1 ano	6 mg	12 mg	18 mg	6 ml
1 - 2 anos	8 mg	16 mg	24 g	8 ml
2 - 3 anos	10 mg	20 mg	30 mg	10 ml
> 3 anos	12 mg	24 mg	36 mg	12 ml

Tabela 2 – Doses acumuladas para grupo de baixo risco – MAG I e MAG II

Quimioterápico	Indução I MAG	Indução II MAG	Intensificação I ARAC-VP	Intensificação II MIT-ARAC	Intensificação III FLAG	Dose Total
Mitoxantrone	15mg/m²	15mg/m²		20mg/m²		**50mg/m²**
Citarabina	200mg/M²	200mg/M²	12.000mg/m²	9.000mg/m²	10.000mg/m²	**31.400mg/m²**
Etoposideo			750mg/m²			**750mg/m²**
Fludarabina					150mg/m²	**150mg/m²**

Dose total de antraciclinas convertidas para DOXORRUBICINA: 200mg/m²

Tabela 3 – Doses acumuladas para grupo de baixo risco – MAG I e ADE

Quimioterápico	Indução I MAG	Indução II ADE	Intensificação I ARAC-VP	Intensificação II MIT-ARAC	Intensificação III FLAG	Dose Total
Mitoxantrone	15mg/m²			20mg/m²		**35mg/m²**
Daunorrubicina		150mg/m²				**150mg/m²**
Citarabina	200mg/M²	2.000mg/m²	12.000mg/m²	9.000mg/m²	10.000mg/m²	**33.200mg/m²**
Etoposideo		500mg/m²	750mg/m²			**1250mg/m²**
Fludarabina					150mg/m²	**150mg/m²**

Dose total de antraciclinas convertidas para DOXORRUBICINA: 290mg/m²

Pacientes com critérios para risco intermediário seguirão exatamente as mesmas orientações para a indução que os pacientes de baixo risco.

Therapy

BFM 2004 HR Protocol

- D15: 5.6%
- Post-AIE ≥ 17.6% blasts
- Post-HAM ≥ MRD: 0.19%
- Post-AI ≥ MRD: negative
- Post-hAM ≥ MRD: 0.47%
- Post-HAE ≥ MRD 0.60%

 # CNS 1

Allo-SCT ?

Refractory AML Therapies

1. BFM REZ 2010
2. IDA-FLAG
3. Venetoclax + Citarabine
4. Venetoclax + Azacitidina
5. ICE (Ifosfamide + Carboplatin + Etoposide)

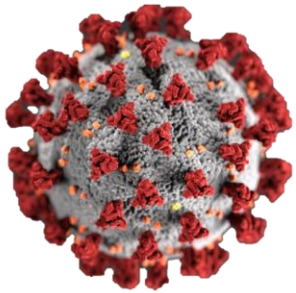
Therapies

FLAG + MADIT

- Post-FLAG: MRD 0.93%
- CNS 1
- Allo-SCT despite persistent MRD

COVID: transplant delayed twice

- No chemotherapy
- BMA (2 mo later): 60% blasts
- Cytogenetics: 46XY[20]
- And now?

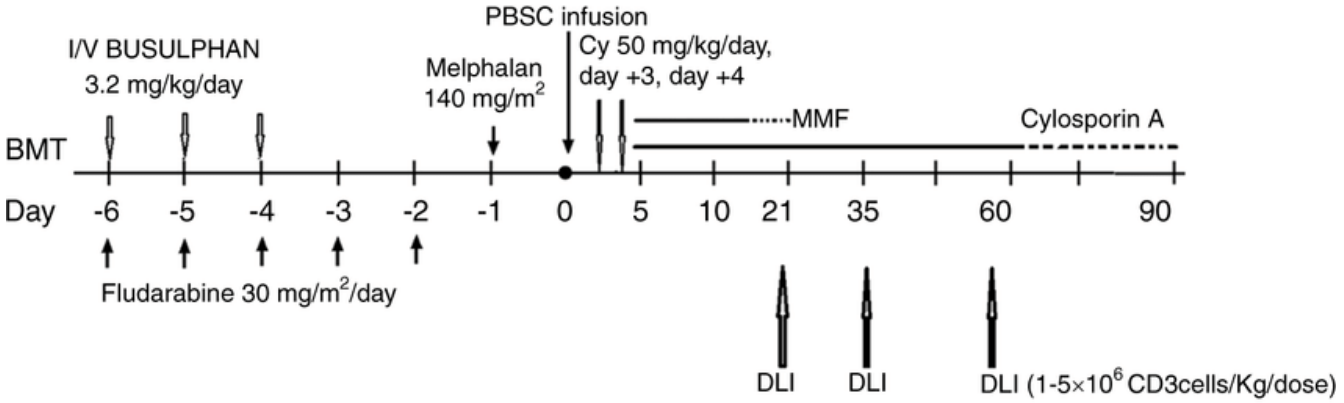


Can My Patient Undergo SCT in Relapse?

1. Prognosis
2. Toxicity
3. Transplantation strategies
4. Post-transplant prophylaxis

Jaiswal SR, et al. **CTLA4Ig-primed donor lymphocyte infusions following haploidentical transplantation improve outcome with a distinct pattern of early immune reconstitution as compared to conventional donor lymphocyte infusions in advanced hematological malignancies.** *Bone Marrow Transpl*. 2021;**56**:185-194.

Haplo SCT – Jaiswal



- Mother, ABO matched, PBSC
- Engraftment: D +15
- DLI on D +21 → 1×10^6 CD3/kg

Post-SCT

- Other DLIs suspended due to acute GVHD
  - Skin on D +25 → increased liver enzymes
  - Prednisone
  - Not able to suspend immunesuppression
- 10 mo post-SCT
  - Prednisone on alternate days
  - Tacrolimus
  - Bone marrow reassessments
    - D +21 (pre-DLI): remission/full donor chimerism
    - D +60: remission/mixed chimerism (6.2% autologous cells)
    - D +80: full donor chimerism
    - D +100: remission/full donor chimerism
    - 6 mo: full donor chimerism
    - 9 mo: full donor chimerism

Would You Use Any Others Post-SCT Prophylaxis?

1. Venetoclax
2. Azacitidine + Venetoclax
3. Azacitidine + DLI
4. Others


O tratamento contra o **câncer**
não pode esperar a
pandemia passar
GRAACC

Thank you!

Global Leukemia Academy

AML case-based panel discussion

Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla




APTITUDE HEALTH

Global Leukemia Academy

Session close

Franco Locatelli

APTITUDE HEALTH

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

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

Question 3

Which assertion is correct for children with AML?

a) Treatment of patients is based only on the presence of recurrent molecular alterations

b) Treatment of patients is based only on the level of MRD after induction therapy

c) Both the presence of recurrent molecular alterations and MRD level after induction therapy influence the post-remission treatment choice

d) Neither the presence of recurrent molecular alterations, nor MRD level after induction therapy influence the post-remission treatment choice

Global Leukemia Academy

Closing remarks

Franco Locatelli

APTITUDE HEALTH

Thank you!

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

THANK YOU!

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Emerging and Practical Concepts and Controversies in Leukemias

APTITUDE HEALTH