Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

24 September 2022

Virtual Breakout: Pediatric ALL

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Franco Locatelli

APTITUDE HEALTH

FACULTY

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

CHAIR

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

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

Virtual Breakout – Pediatric ALL Sessions (Day 2)

24 September 2022, 10.00 – 12.45 CEST

Chair: Dr Franco Locatelli

Time (CEST)	Title	Speaker
10.00 – 10.10	**Session Open**	Franco Locatelli
10.10 – 10.30	**How to Use MRD and Genetics for Stratification and Therapy Guidance in First-Line Therapy of Childhood ALL**	Rob Pieters
10.30 – 10.55	**Optimizing First-Line Therapy in Pediatric ALL: How to Balance Cure and Long-Term Risks?**	Rob Pieters
10.55 – 11.15	**ALL Case-Based Panel Discussion** • Balancing Cure and Toxicity Risks	Moderator: Franco Locatelli Janine Stutterheim All faculty
11.15 – 11.25	***Break***	
11.25 – 11.55	**Current Treatment Options for High-Risk ALL in Children**	Christina Peters
11.55 – 12.35	**ALL Case-Based Panel Discussion** • Relapsed/Refractory Setting (Part 1) • Toxicity Management (Part 2)	Moderator: Franco Locatelli Hannah von Mersi Anna Cvrtak All faculty
12.35 – 12.45	**Session Close**	Franco Locatelli

Global Leukemia Academy

Introduction to the Voting System

Franco Locatelli

APTITUDE HEALTH

Question 1

Which of the following subsets of first-relapse ALL patients can be considered as very high risk?

1. All patients with B-ALL relapsing within 18 months from diagnosis
2. All patients with hypodiploidy
3. All patients with t(17;19) or t(1;19)
4. Each of the 3 previous subsets

Question 2

Which assertion is correct for children with B-ALL?

1. Inotuzumab is approved by EMA for induction treatment of relapsed B-ALL in childhood
2. Inotuzumab recommended dosage is 3 mg/m^2
3. Blinatumomab is approved for consolidation treatment before HSCT in children with high-risk first relapse B-ALL
4. None of the patients experiencing relapse later than 6 months after treatment discontinuation should be transplanted

Global Leukemia Academy

How to Use MRD and Genetics for Stratification and Therapy Guidance in First-Line Therapy of Childhood ALL

Rob Pieters

APTITUDE HEALTH

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

Rob Pieters
Chief Medical Officer

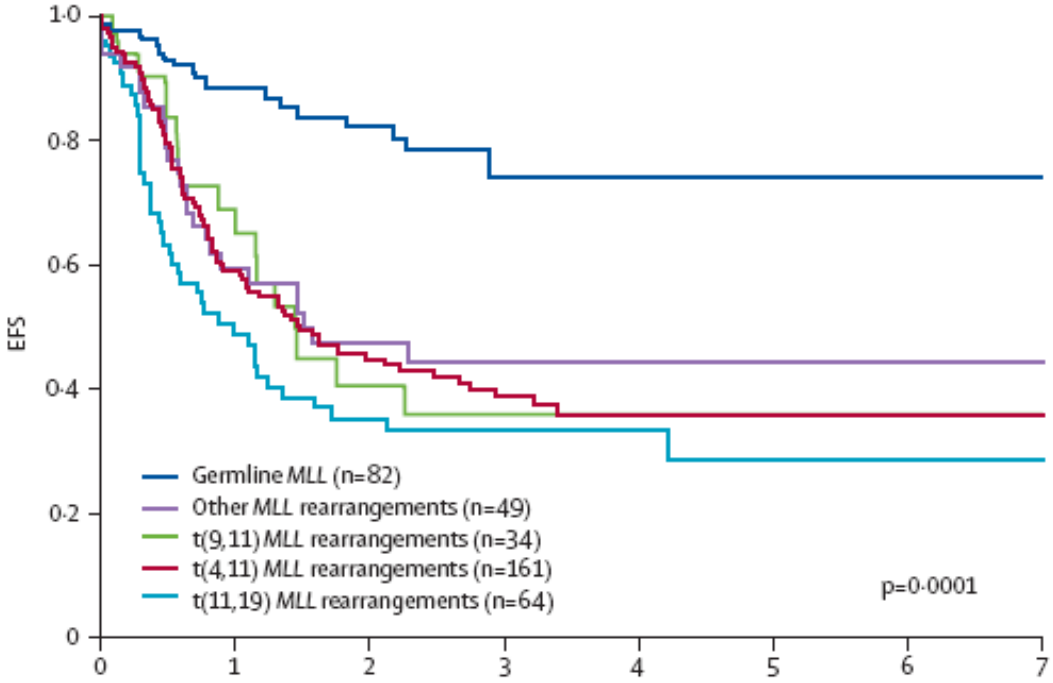
MRD and genetics to guide stratification and therapy

- 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 1: 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 a 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

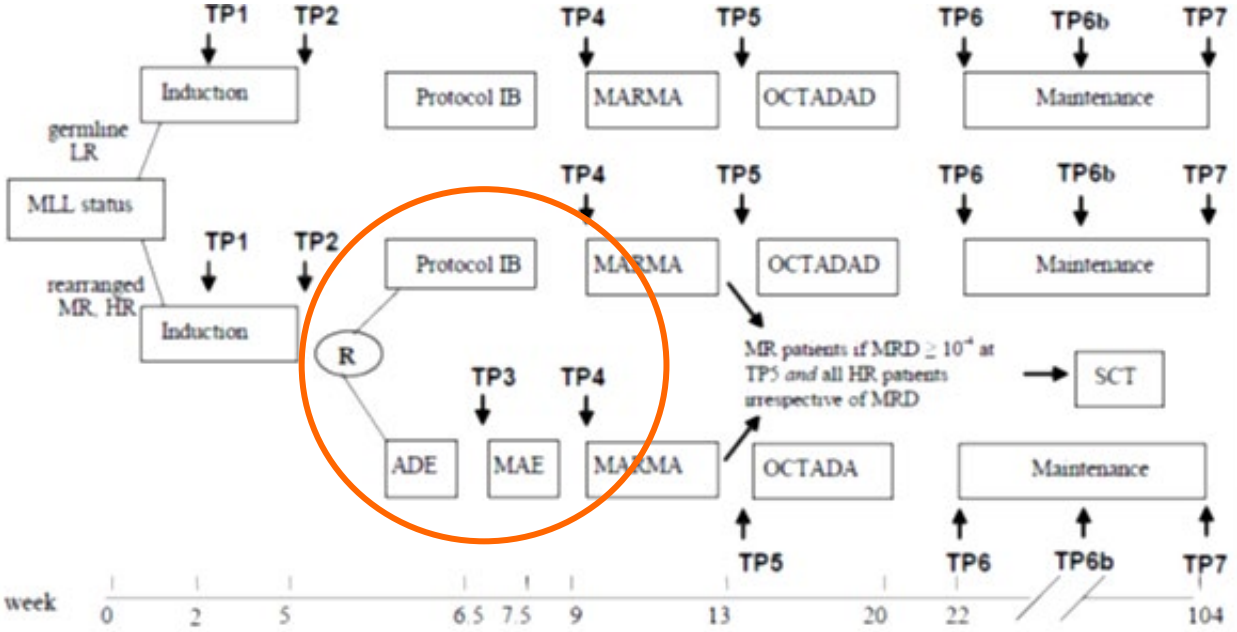


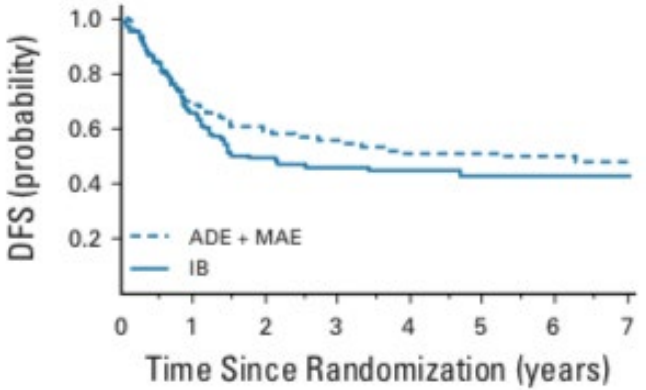
KMT2A germline

KMT2A rearranged

Pieters R, et al. *Lancet*. 2007;370(9583):240-250.

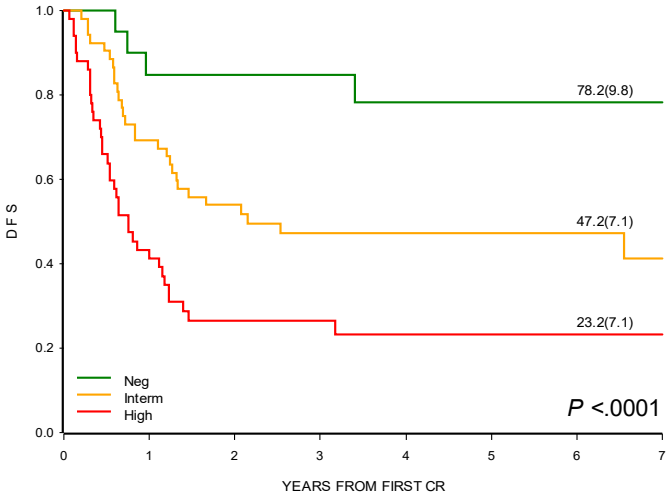
Interfant-06 treatment schedule





Prognostic value of MRD at EOI depends on consolidation treatment given

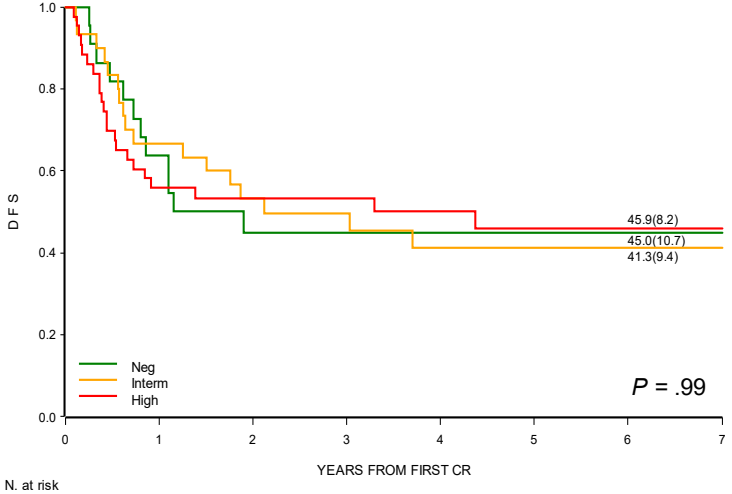
Patients treated with lymphoid IB consolidation



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

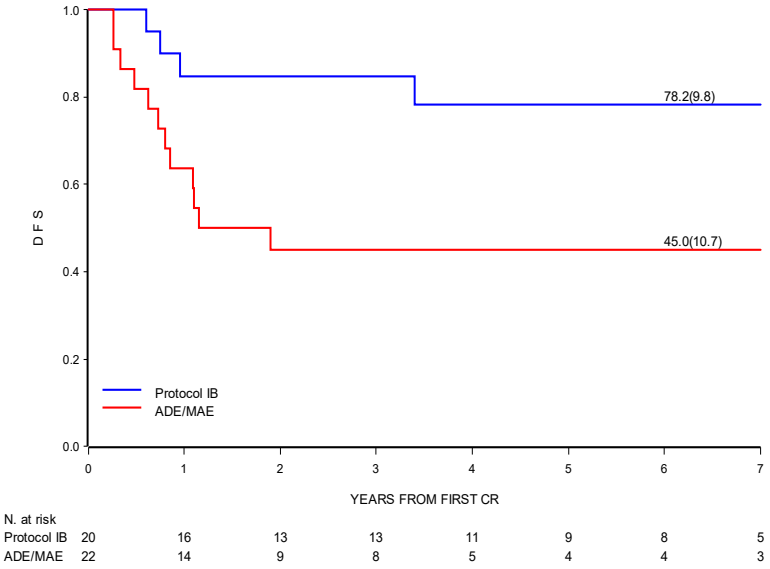


N. at risk

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

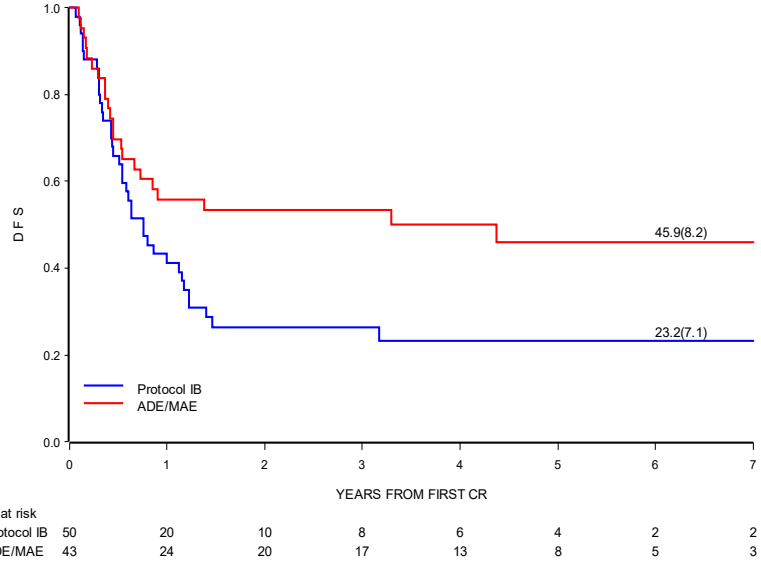
Patients with negative MRD at end of induction



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??

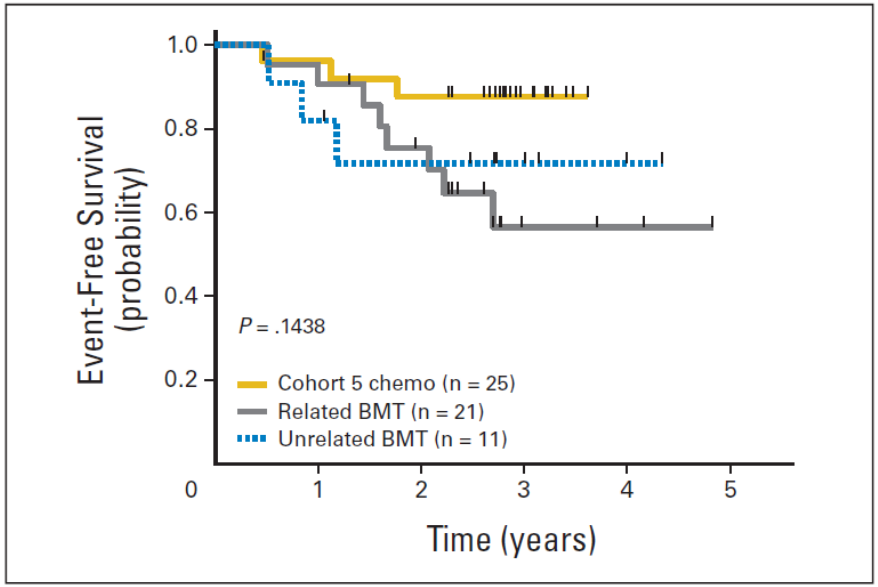
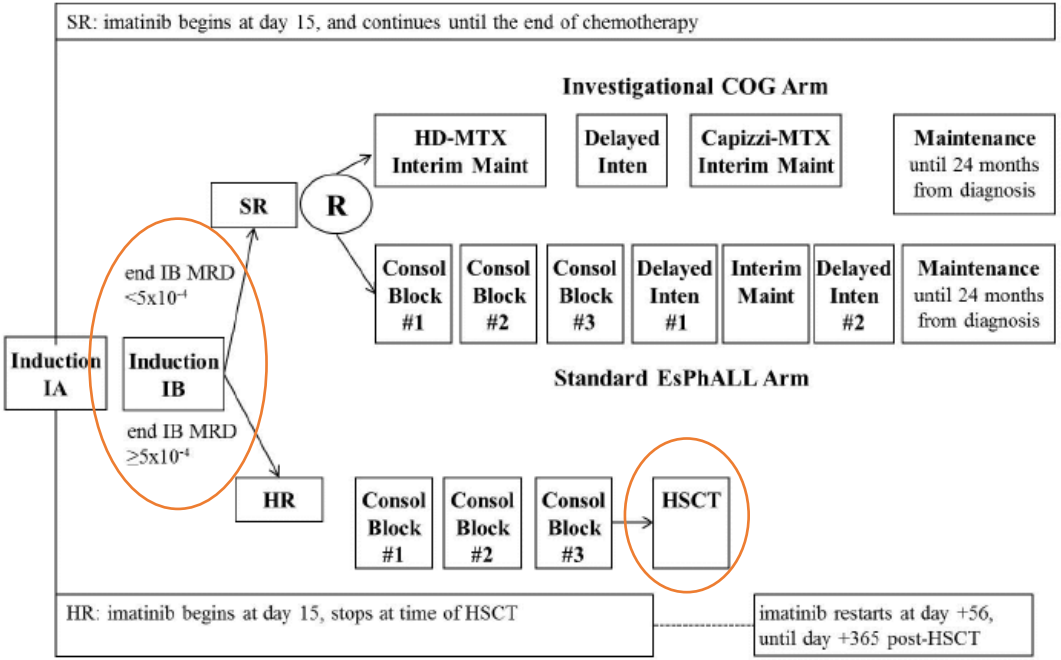


Fig 4. Comparison of event-free survival (EFS) for Cohort 5 chemotherapy only versus related-donor bone marrow transplantation (BMT) versus unrelated-donor BMT. Cohort 5 patients were compared with human leukocyte antigen (HLA) –identical sibling BMT (8 of 39 in cohorts 1-4; 13 of 44 in cohort 5) and 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.

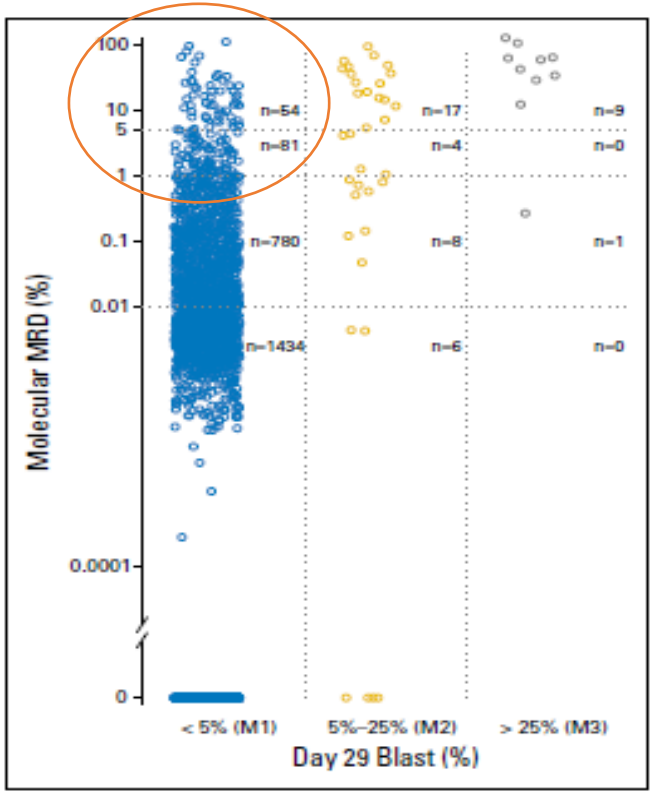
Schultz KR, et al. *J Clin Oncol*. 2009;27(31):5175-5181.

EsPhALL2017/COGAALL1631

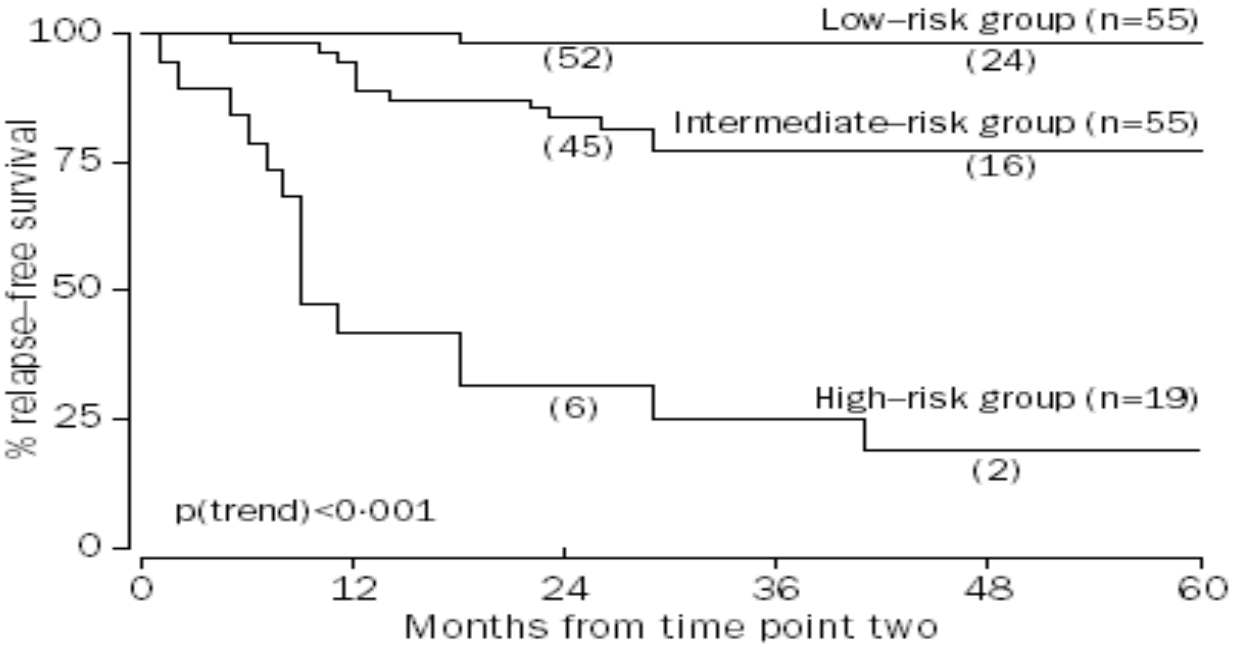


Note. MRD: Minimal Residual Disease, SR:Standard Risk, HR: High Risk, R: Randomization, HD-MTX: High Dose Methotrexate, Maint: Maintenance, Inten: Intensification, Consol: Consolidation, HSCT: Hematopoietic Stem Cell Transplant

Morphologic vs molecular detection of MRD at end of induction

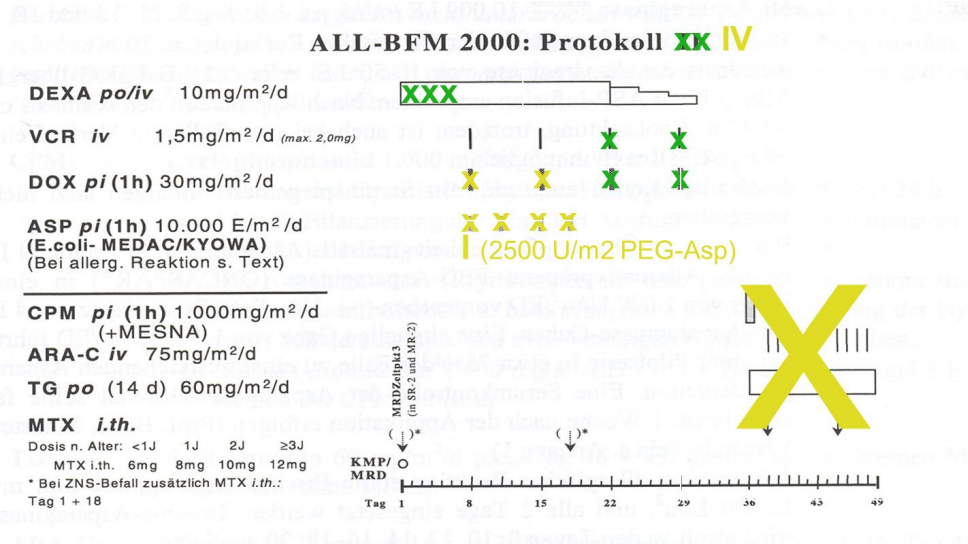


Minimal residual disease and outcome in ALL



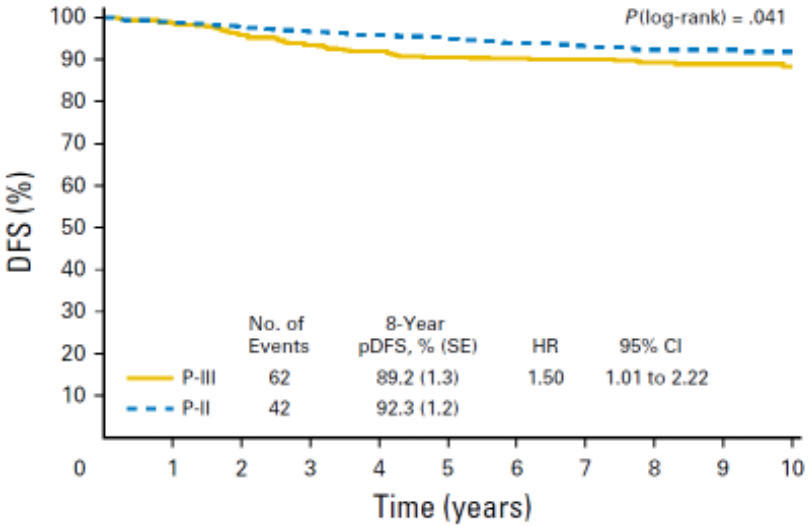
Relapse-free survival of the 3 MRD-based risk groups, as defined by MRD information at time points 1 and 2

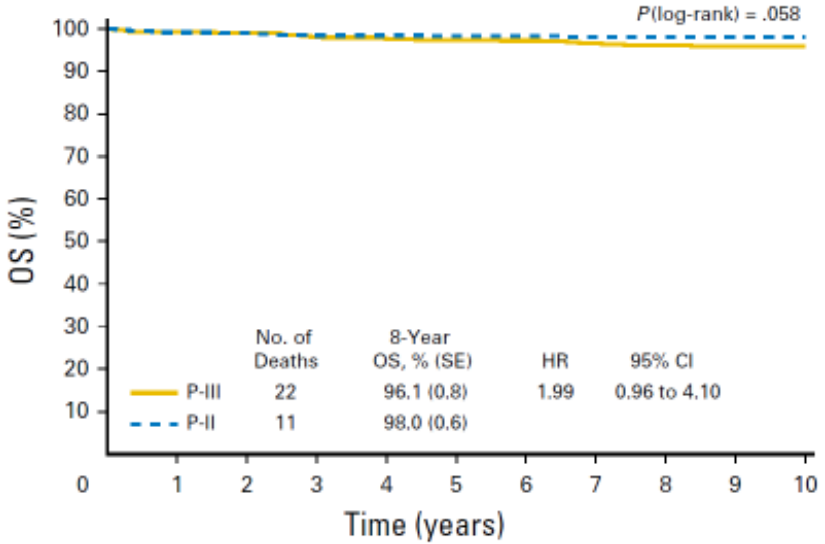
Therapy reduction in MRD-negative patients: BFM-II vs BFM-III vs DCOG-IV



	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





Schrappe M, et al. *J Clin Oncol*. 2018;36(3):244-253.

Study 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%**

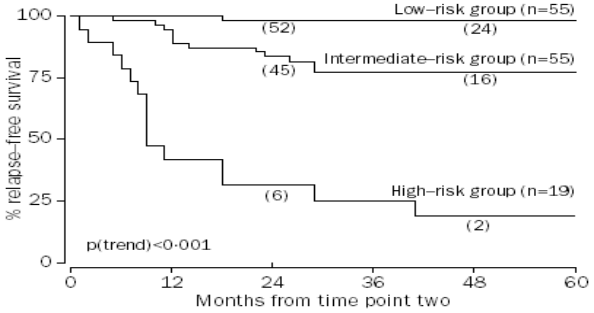
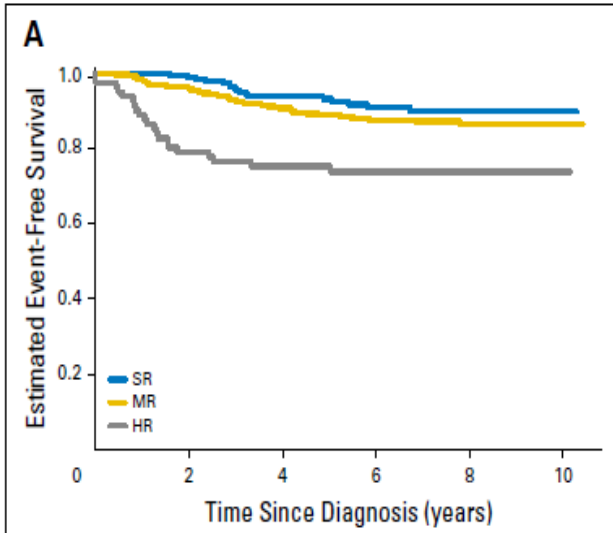
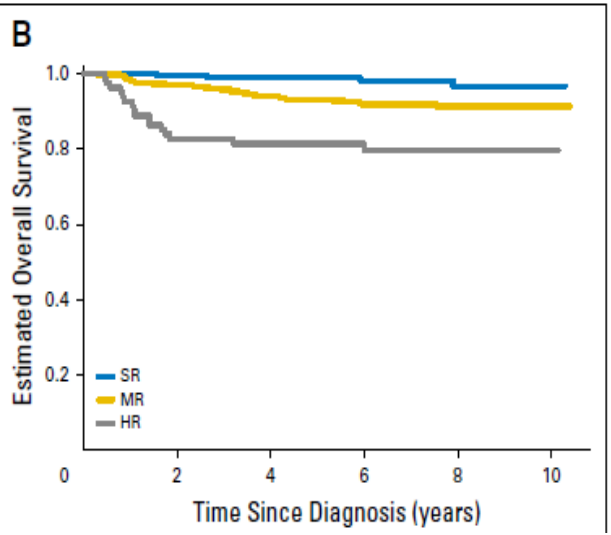


Figure 4: **Relapse-free survival of the three MRD-based risk groups, as defined by MRD information at time points one and two**

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

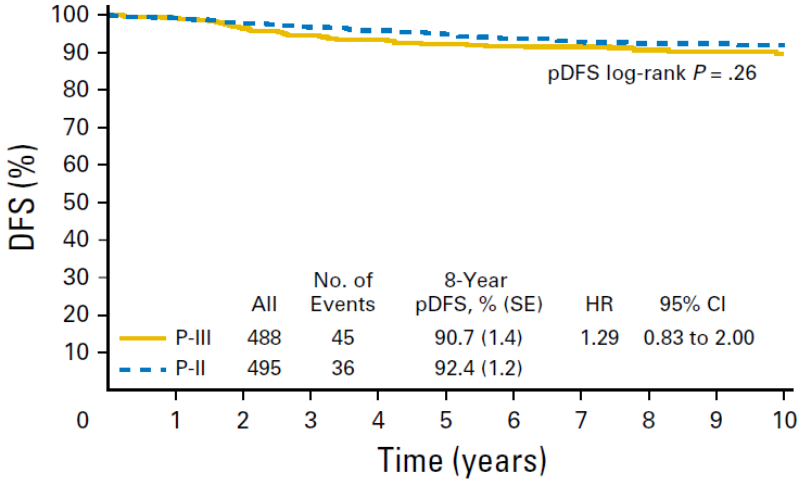
- Decrease of therapy for all MRD low-risk patients: an extra ~4% of them need relapse therapy

OR

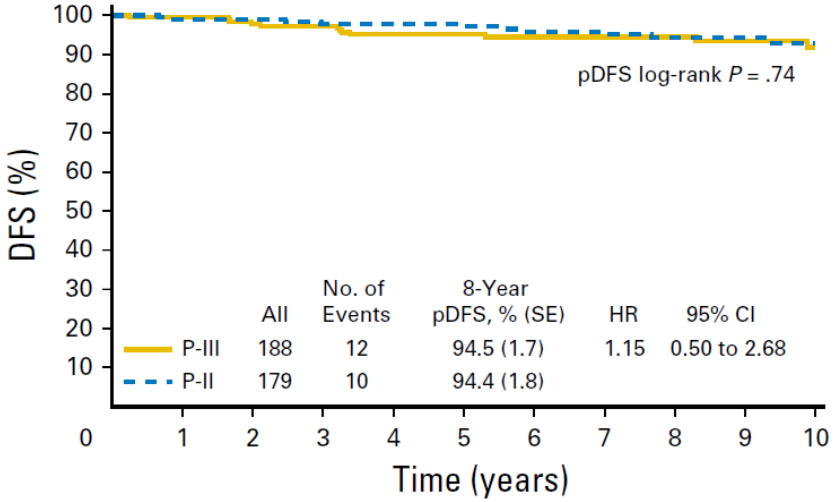
- More intensive therapy for all MRD low-risk patients

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

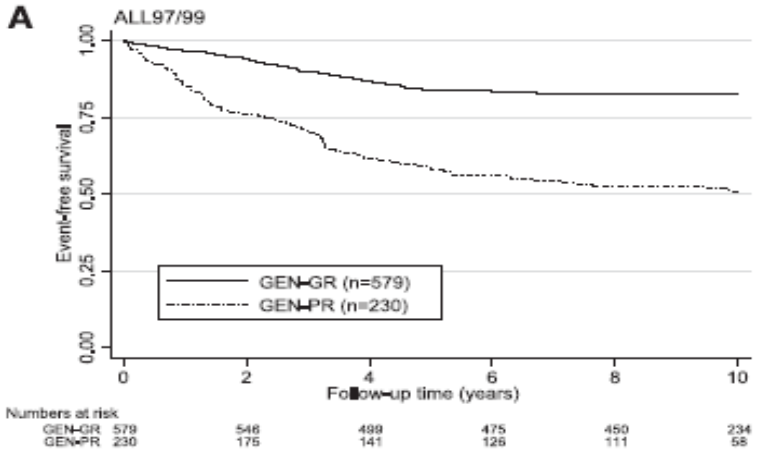
Age 1–9 yr

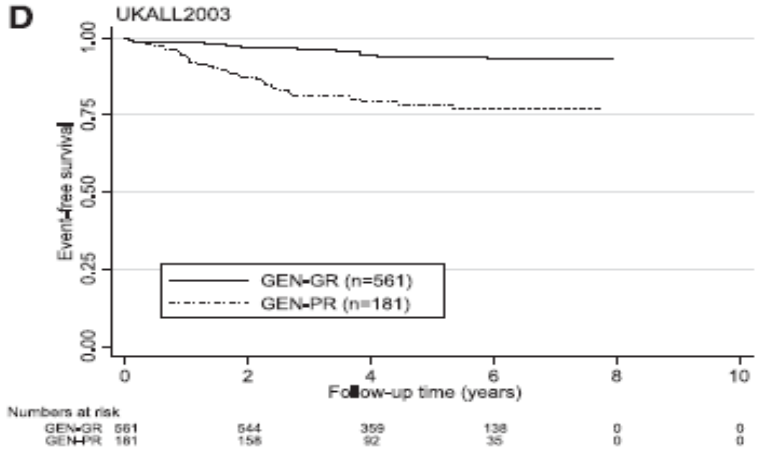


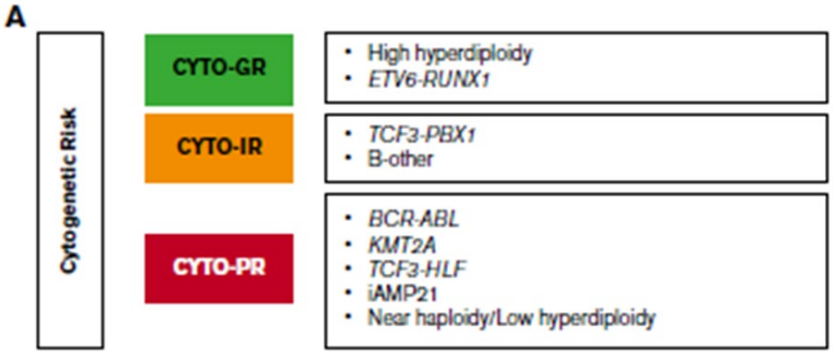
ETV6/RUNX1



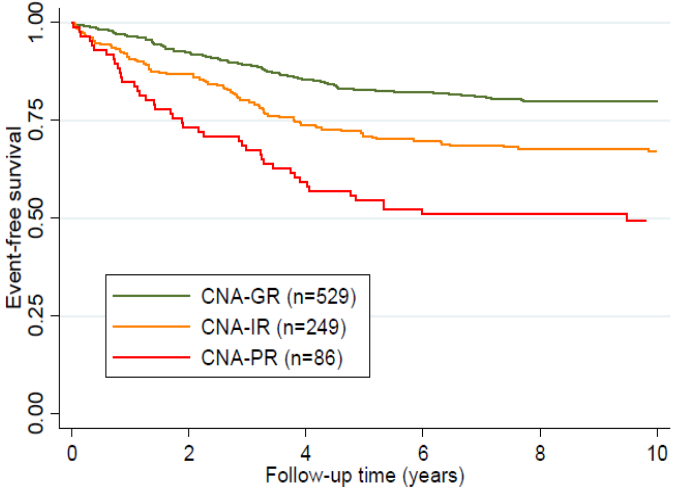
EFS ALL97/99 and UKALL2003 by genetic risk group

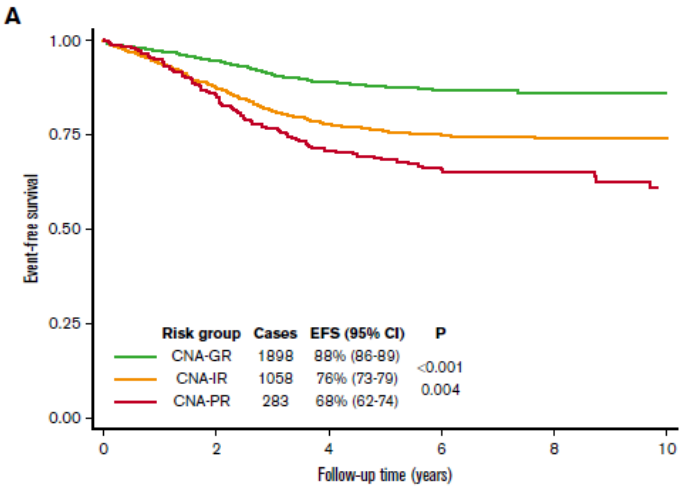






UK copy number alteration (CNA) classifier (by MPLA)





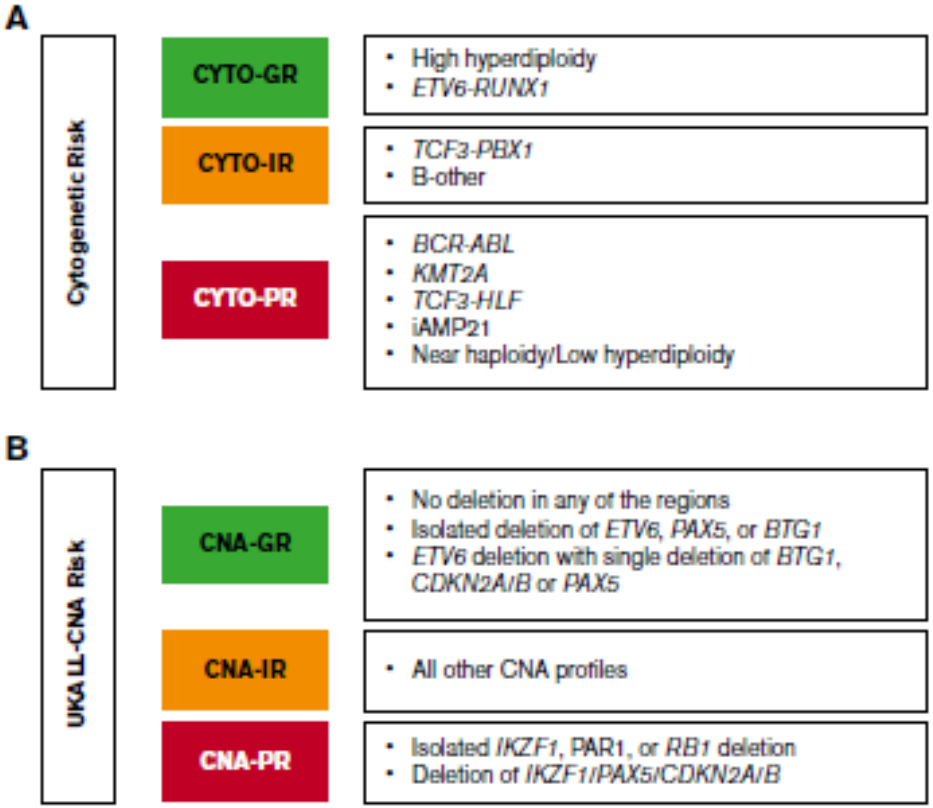
Good risk
- No deletion
- Isolated deletion of *ETV6, PAX5*, or *BTG1*
- *ETV6* deletion + *BTG1, CDKN2A/B* or *PAX5 deletion*

Intermediate risk
- All other CNA profiles

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

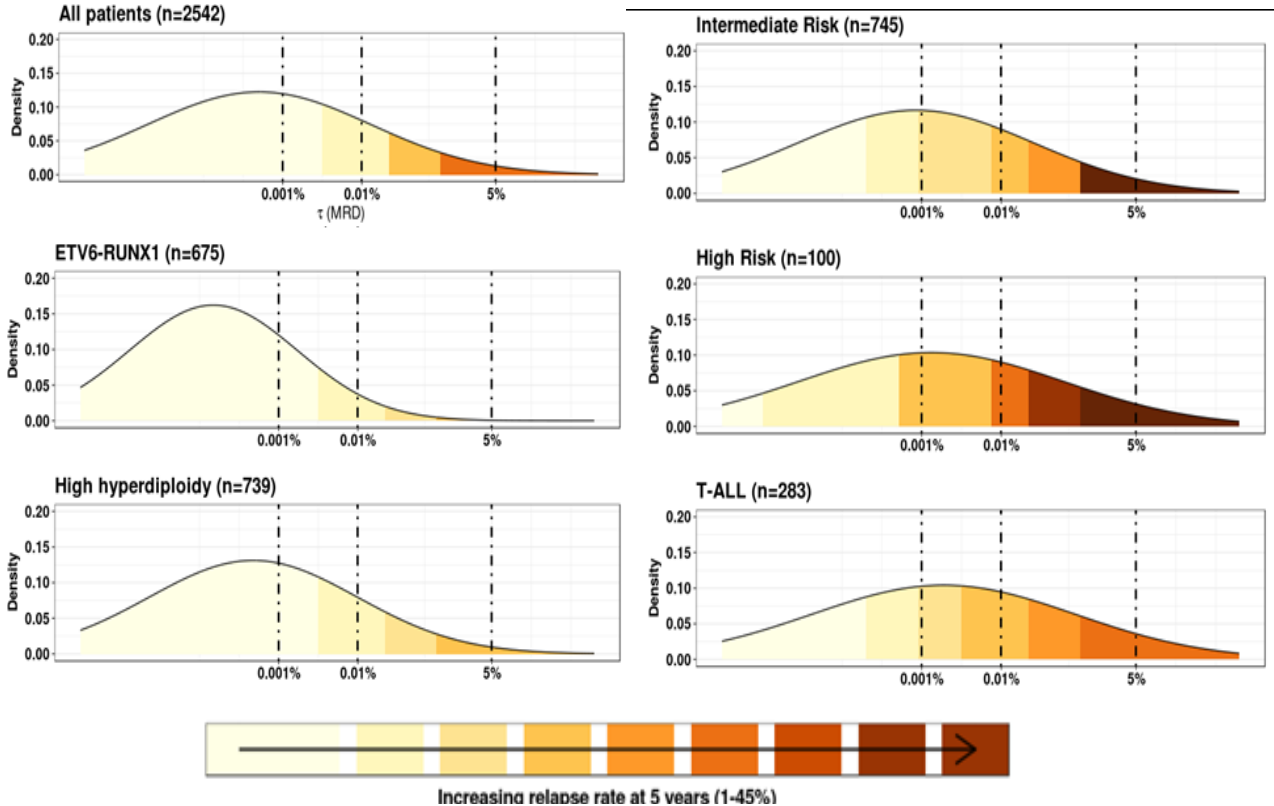
Moorman AV, et al. *Blood.* 2014;124(9):1434-1444; Hamadeh L, et al. *Blood Adv.* 2019;3(2):148-157.

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



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

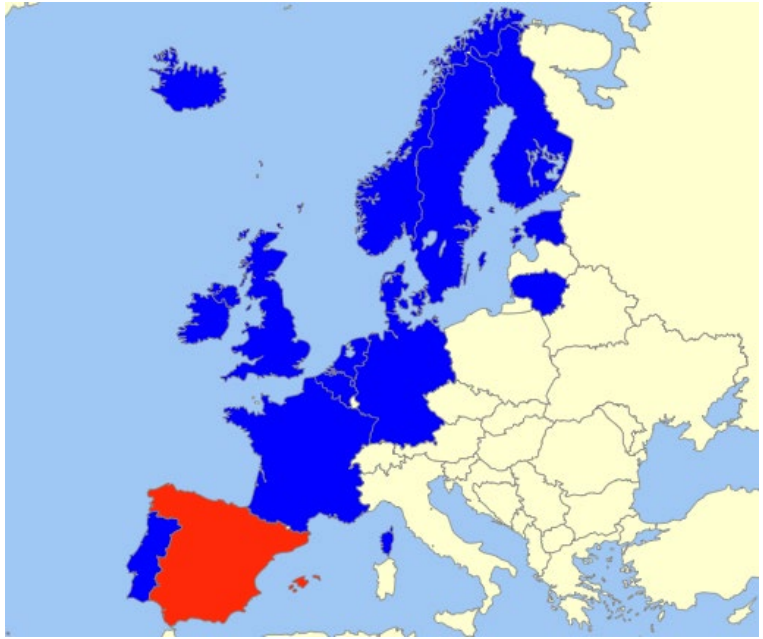
Risk of relapse by MRD value varies by genetic subtype



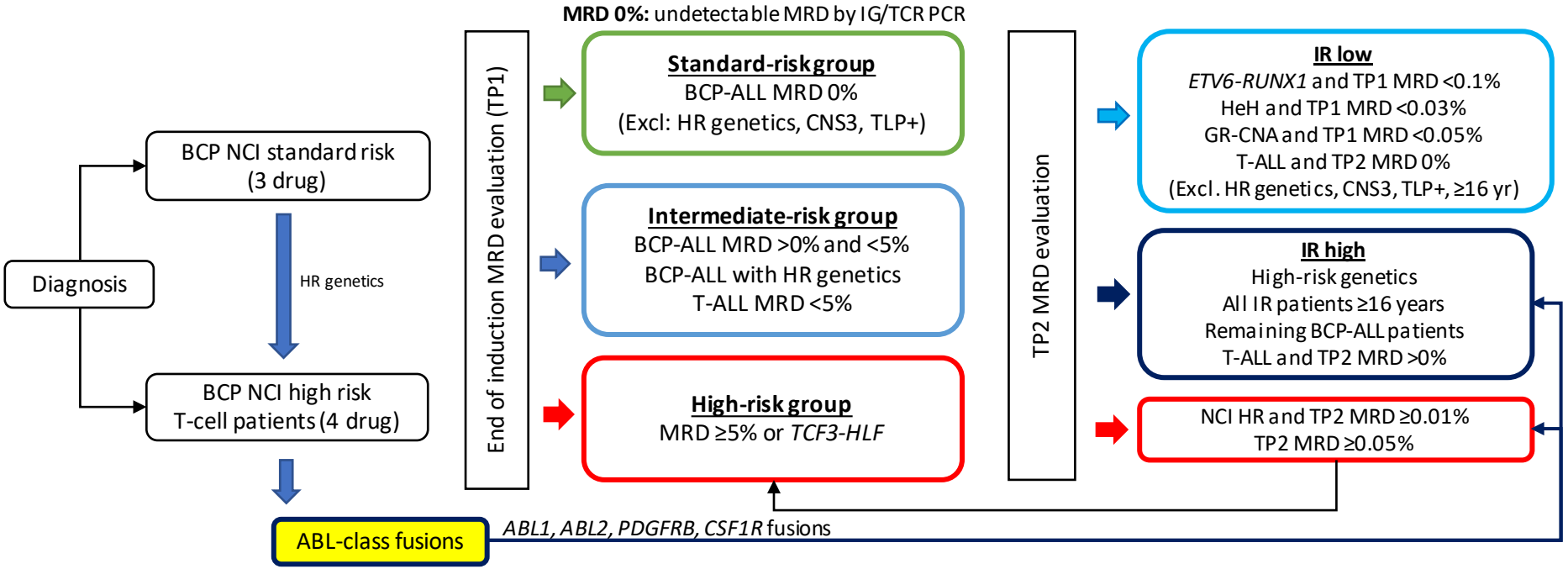
O'Connor D, et al. *J Clin Oncol*. 2018;36(1):34-43.

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 1: 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 a 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

Optimizing First-Line Therapy in Pediatric ALL: How to Balance Cure and Long-Term Risks?

Rob Pieters

APTITUDE HEALTH

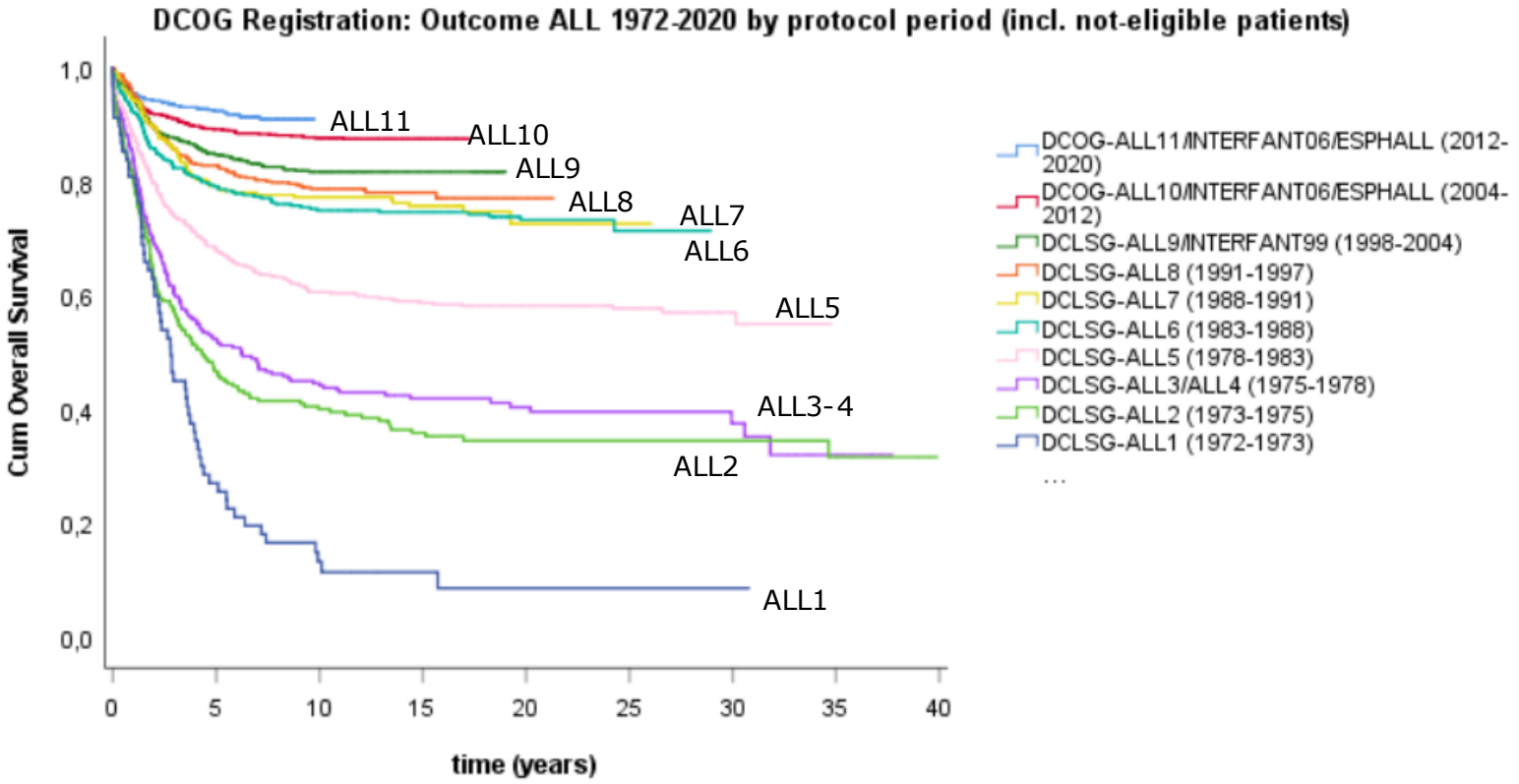
Optimizing First-Line Therapy in ALL: How to Balance Cure and Long-Term Toxicities

Rob Pieters
Chief Medical Officer

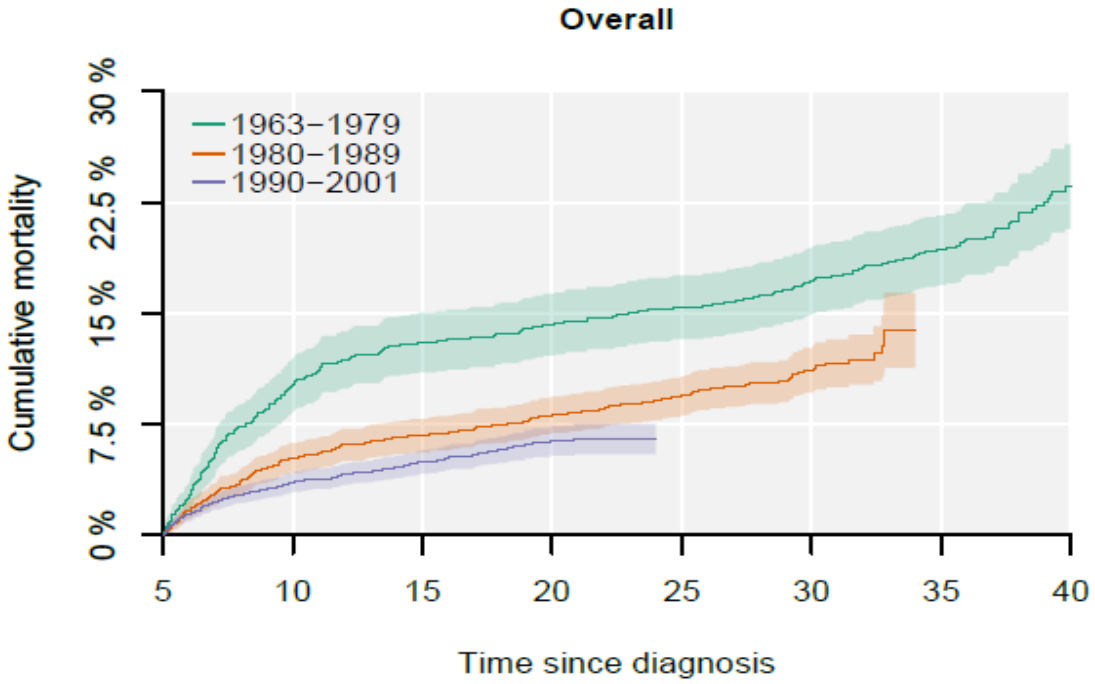
Question 1: Which factor has the lowest probability of causing significant long-term toxicity in pediatric ALL?

1. The anthracyclines daunorubicin and/or doxorubicin in a cumulative dose of >300 mg/m^2 in a child aged 5 years at diagnosis
2. Methotrexate in a cumulative dose of 20,000 mg/m^2 in a child aged 8 years at diagnosis
3. Cranial radiotherapy in a child aged 2 years at diagnosis
4. Dexamethasone in a girl aged 14 years at diagnosis

ALL Survival in the Netherlands: 1972–2020

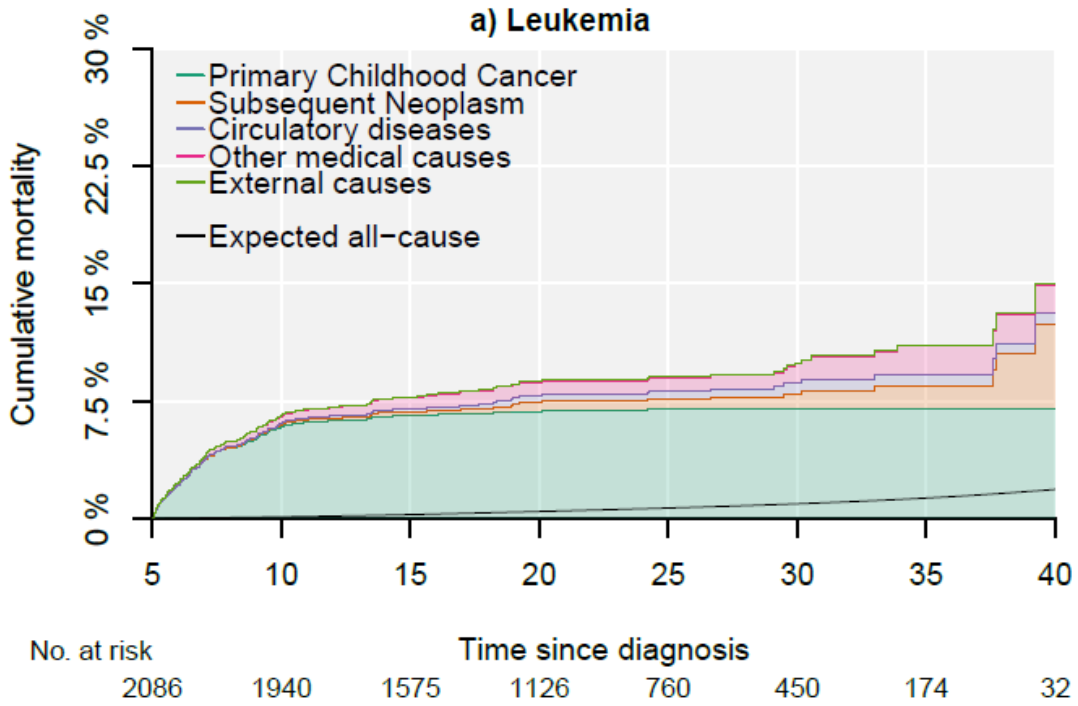


Cumulative Late Mortality of Childhood Cancer Survivors by Year of Diagnosis

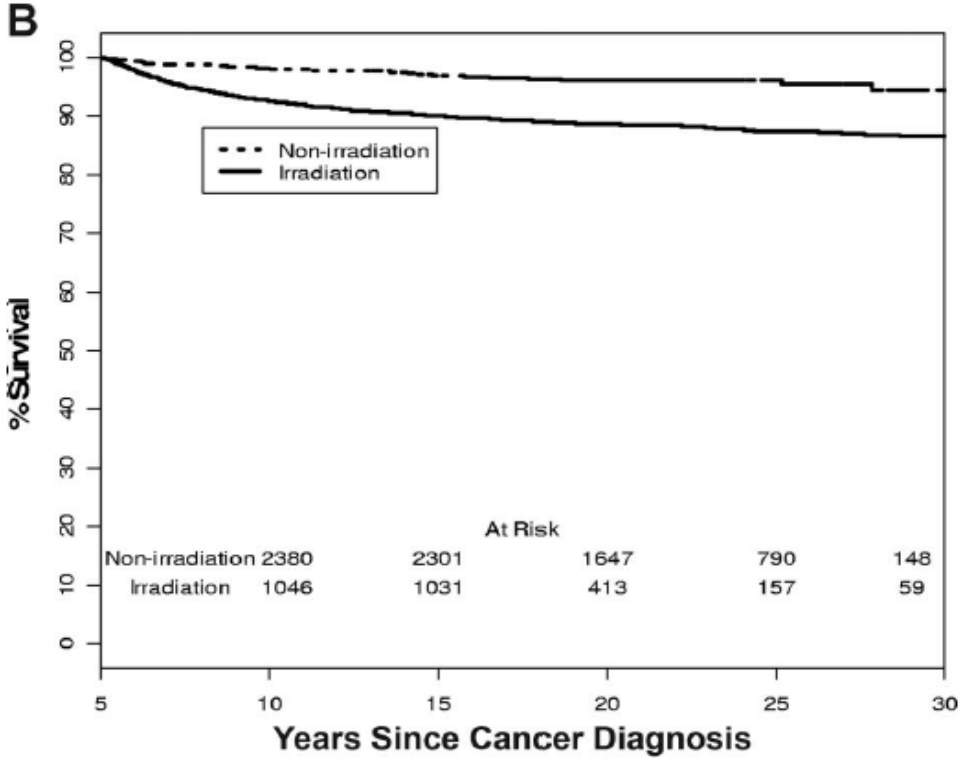


Van Kilsdonk, 2022

Cumulative Late Mortality of Survivors of Childhood Leukemia



Survival of 5-Year ALL Survivors: Irradiated vs Nonirradiated

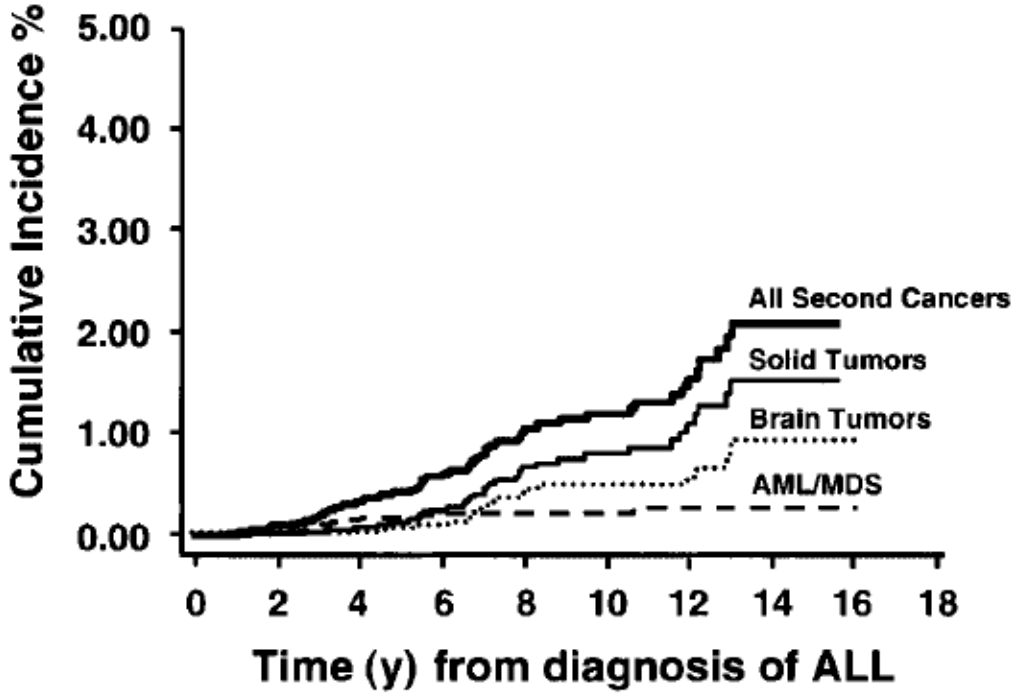


Mody R, et al. *Blood.* 2008;111(12):5515-5523.

Balancing Cure and Toxicity

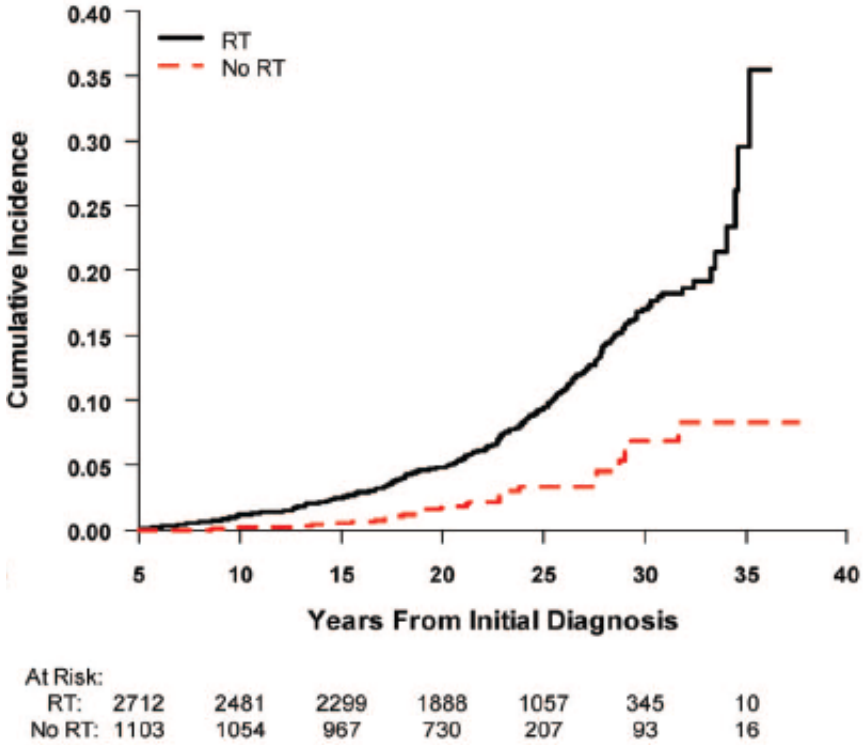
- Second malignancies
- Osteonecrosis
- Neurocognitive sequelae
- Cardiomyopathy
- Insulin-dependent diabetes (pancreatitis)
- Who should be transplanted?
- Late effects of immunotherapies?

Cumulative Incidence of Second Neoplasms in 8831 Children With ALL



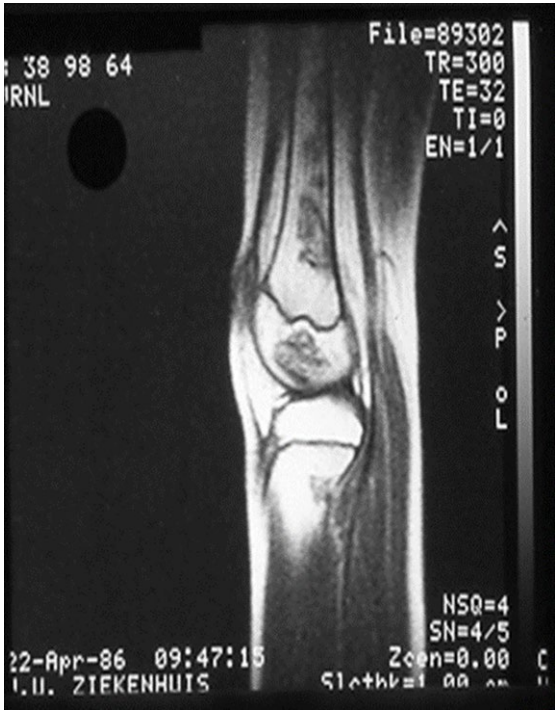
Bhatia S, et al. *Blood*. 2002;99(12):4257-4264.

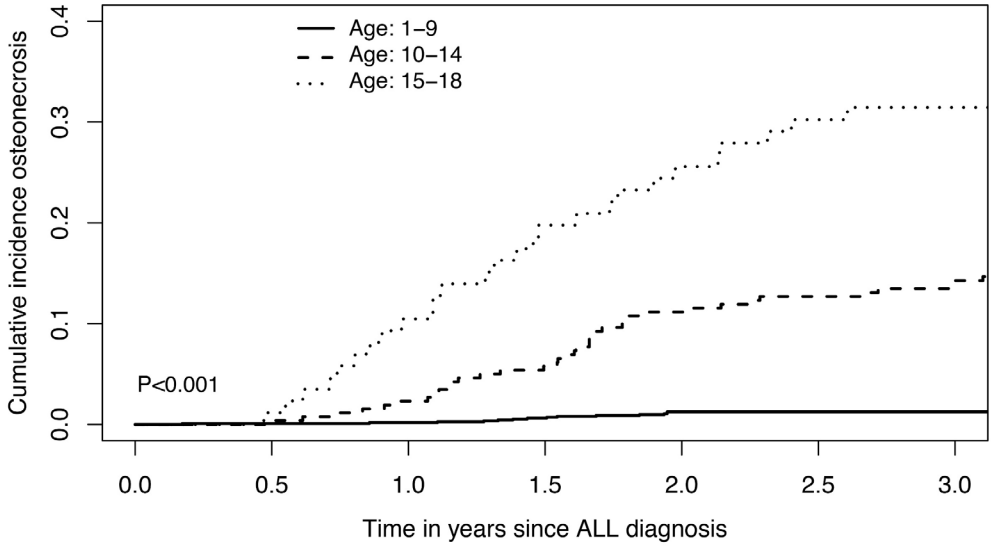
Second Neoplasms Among 5-Year Survivors of Childhood ALL in the CCSS Cohort: Role of Radiotherapy



Robison LL, et al. *Hematology Am Soc Hematol Educ Program*. 2011;2011:238-242.

Cumulative Incidence of Osteonecrosis by Age



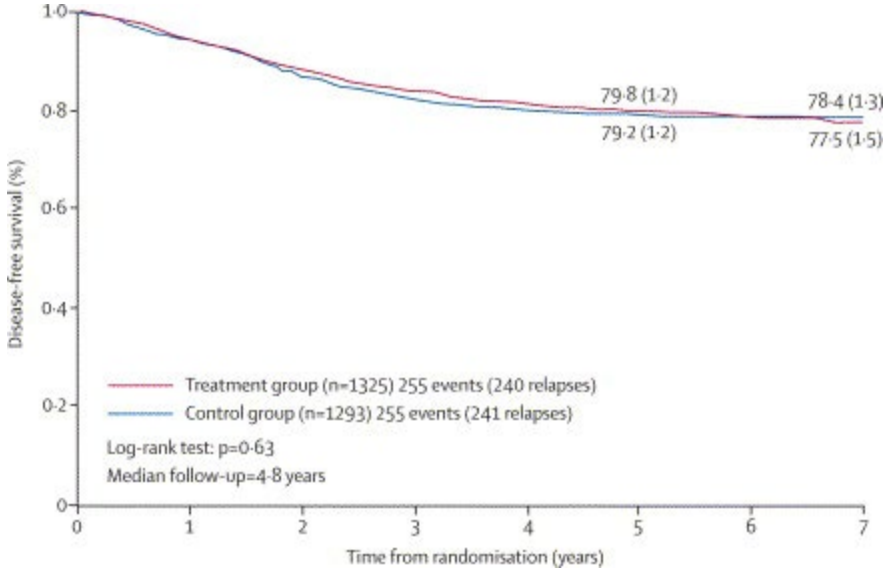


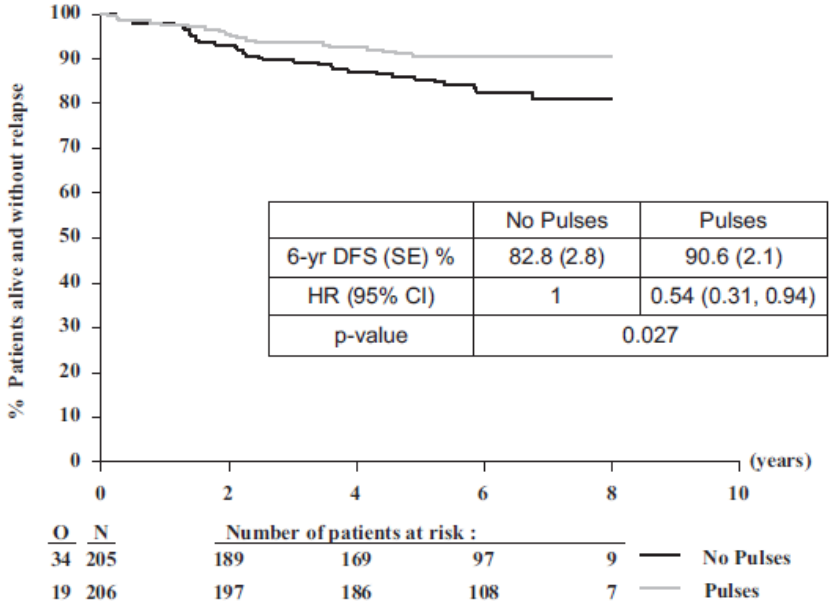
No. at risk

——	1124	1108	1083	1059	1040	1032	983
– –	260	251	229	210	191	179	164
· · · ·	86	84	70	61	53	47	39

Pieters R, et al. *Cancer*. 1987;60(12):2994-3000; Van Atteveld JE, 2020

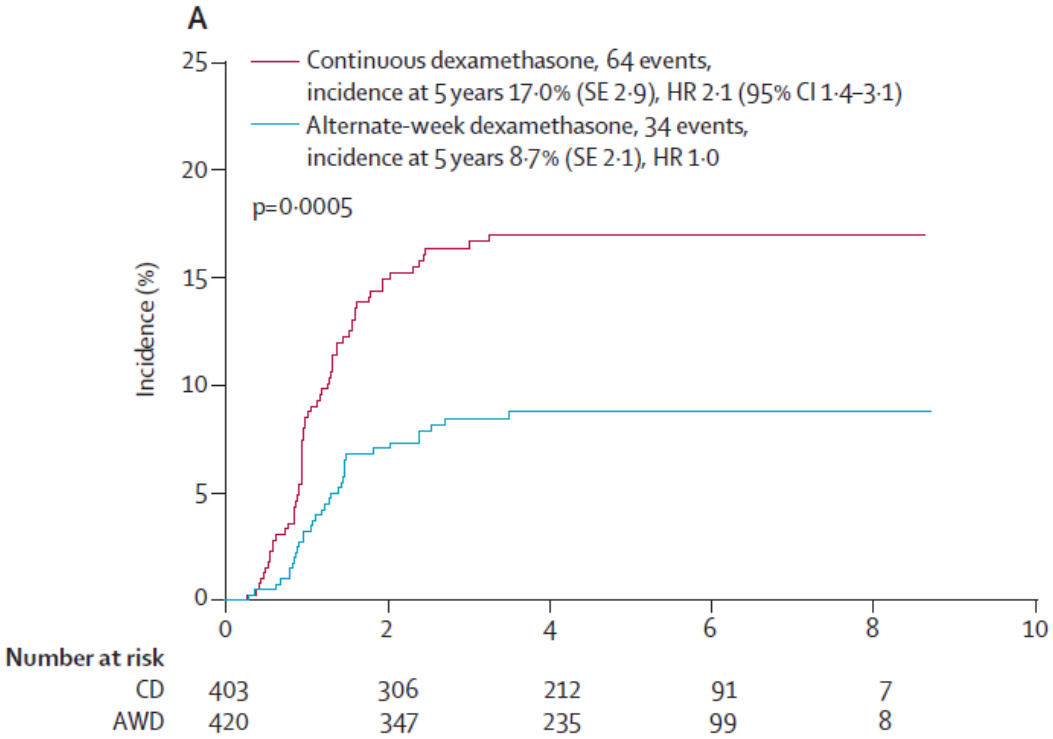
Dexa/VCR Pulses During Maintenance in Average-Risk ALL Patients: Results From AIEOP-BFM and From EORTC





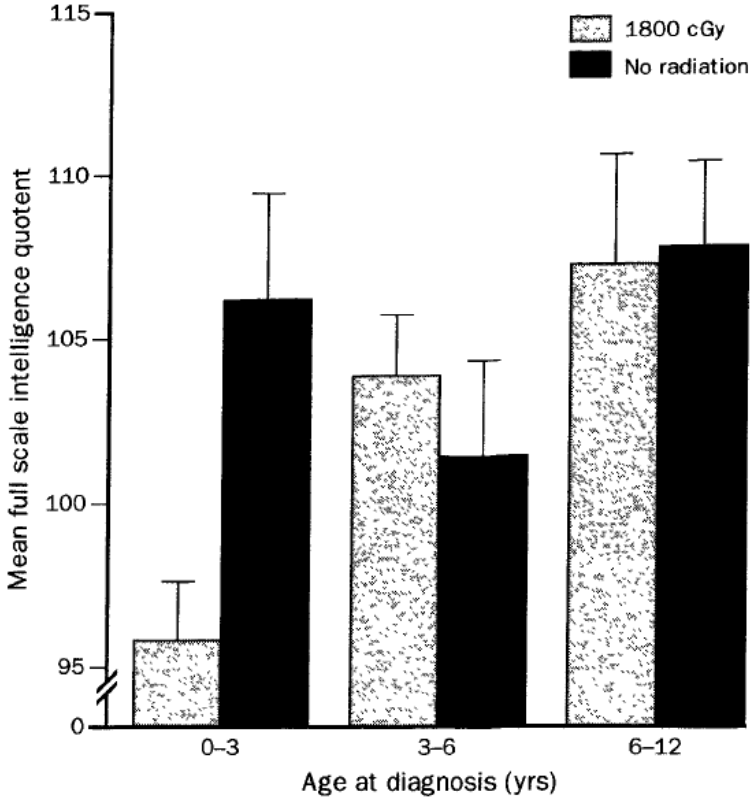
Conter V, et al. *Lancet*. 2007;369(9556):123-131; de Moerloose B, et al. *Blood*. 2010;116(1):36-44.

Osteonecrosis: Continuous vs Alternate-Week Dexamethasone



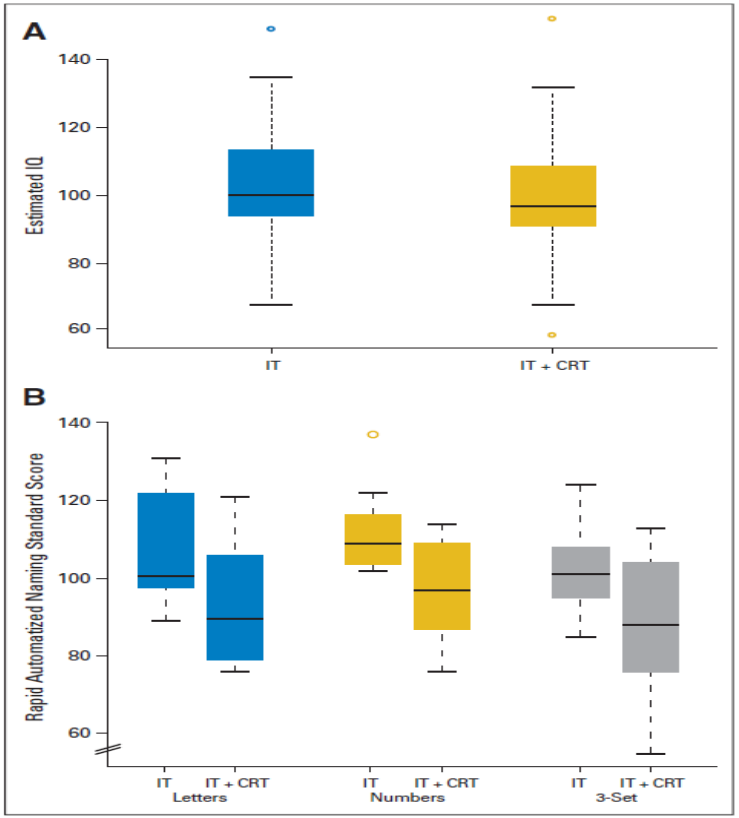
Mattano LA, et al. *Lancet Oncol*. 2012;13(9):906-915.

Effects of 1800 cGy Cranial Radiation on Intellectual Performance by Age



Jankovic M, et al. *Lancet*. 1994;344(8917):224-227.

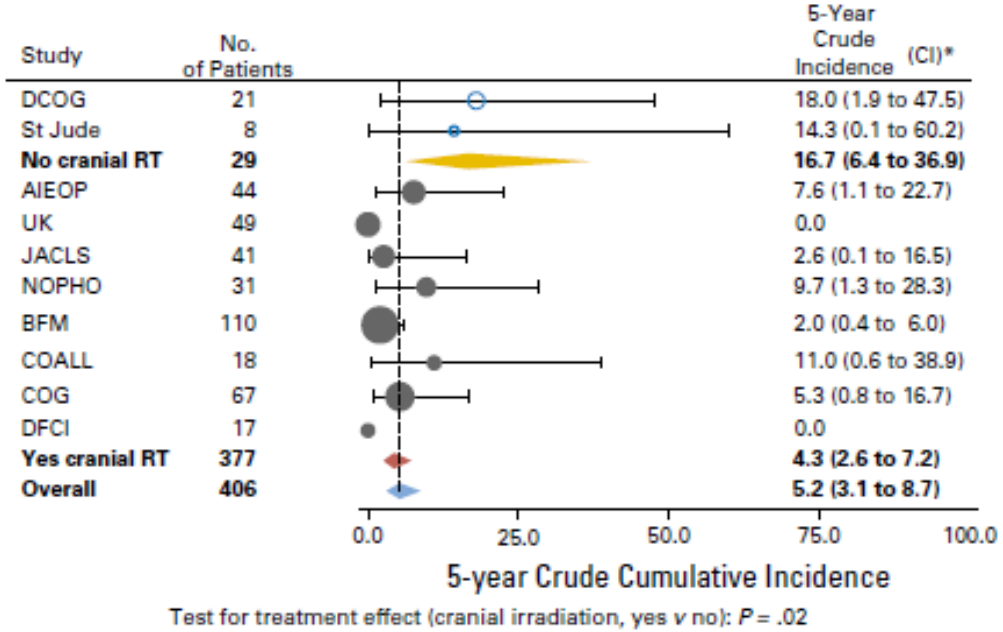
IQ and Rapid Naming Tasks: Intrathecal (IT) vs IT + Cranial Radiation (CRT)



Waber DP, et al. *J Clin Oncol*. 2007;25(31):4914-4921.

5-Year Outcomes to Preemptive Cranial Radiotherapy for ALL With CNS3

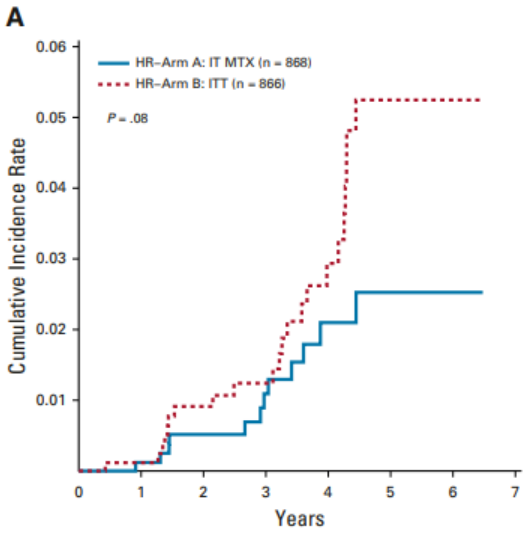
5-yr isolated CNS relapse: 16.7% vs 4.3% (*P* = .02)
5-yr mortality: 22.4% vs 20.6% (*P* = .83)



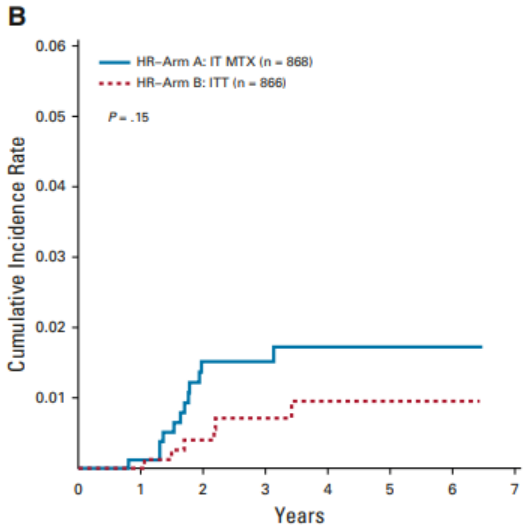
Test for treatment effect (cranial irradiation, yes *v* no): *P* = .02

Cumulative Incidence of Relapse in HR B-ALL: Intrathecal MTX vs Intrathecal Triple Therapy

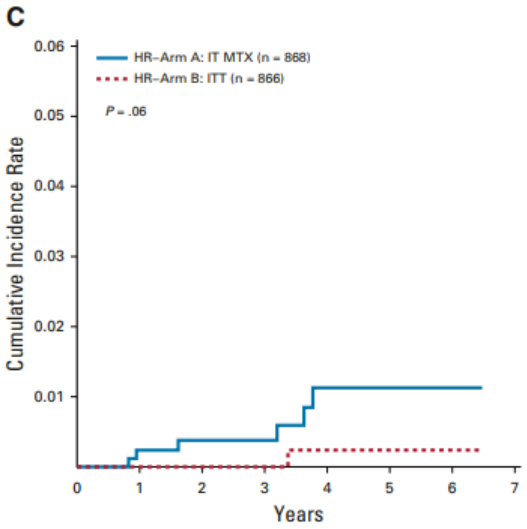
Isolated BM Relapse



Isolated CNS Relapse

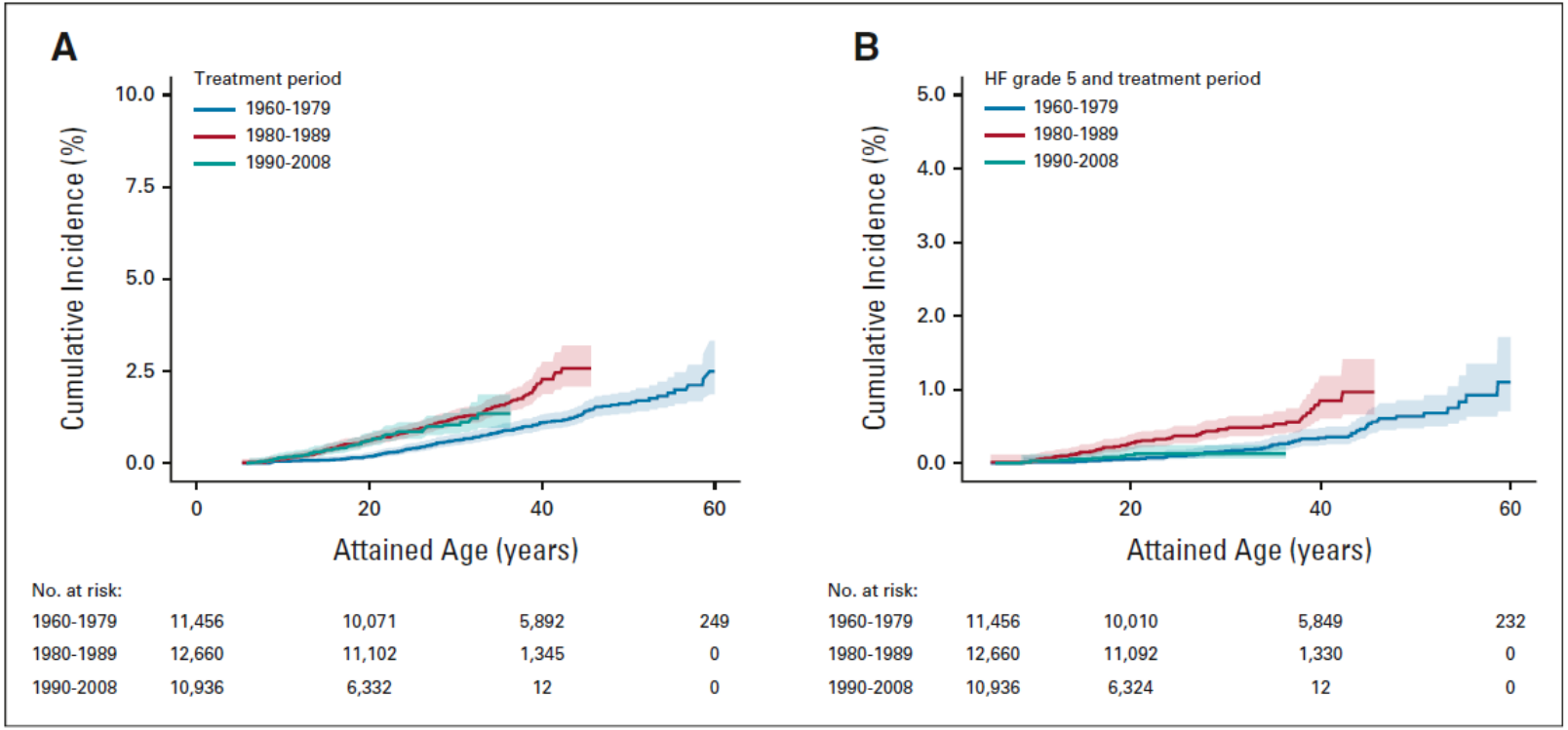


Combined BM + CNS Relapse

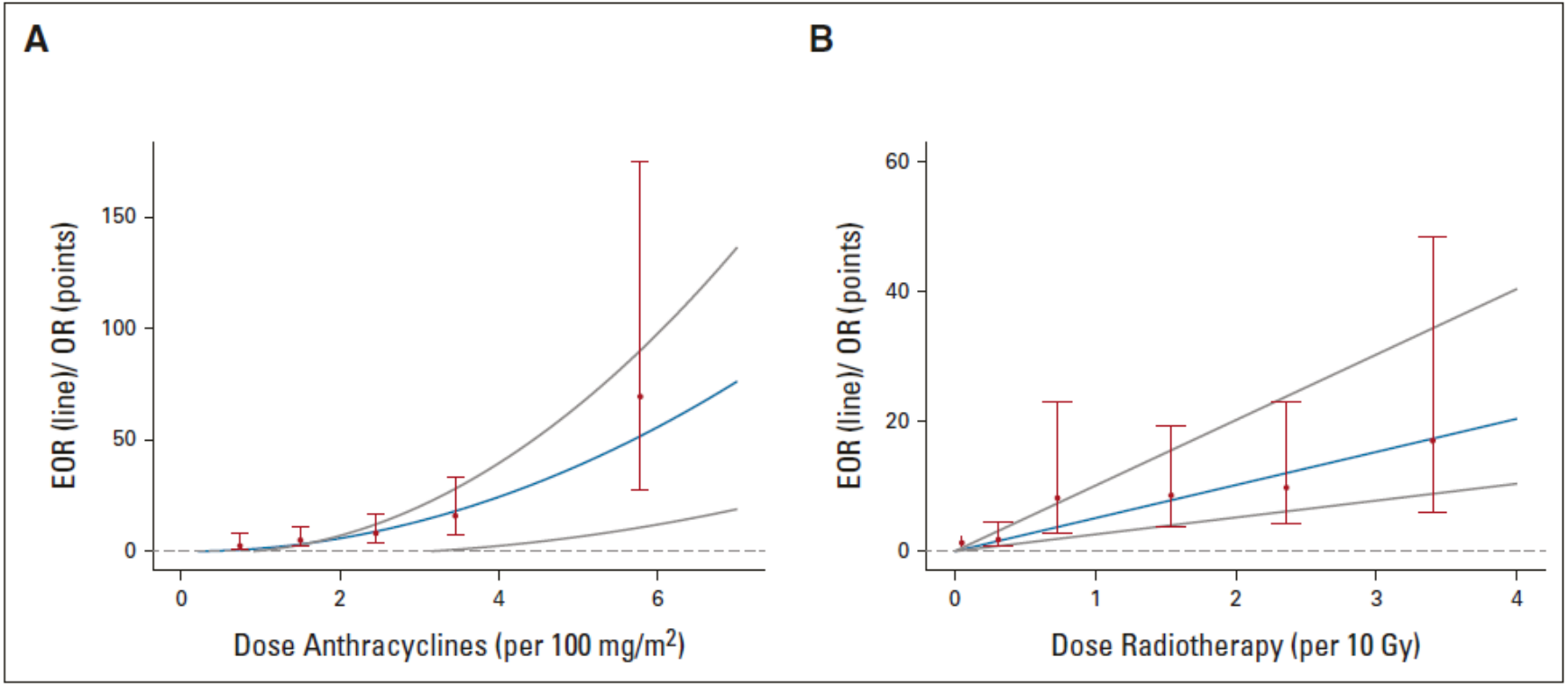


Salzer WL, et al. *J Clin Oncol*. 2020;38(23):2628–2638.

Cumulative Incidence of Heart Failure in Childhood Cancer Survivors

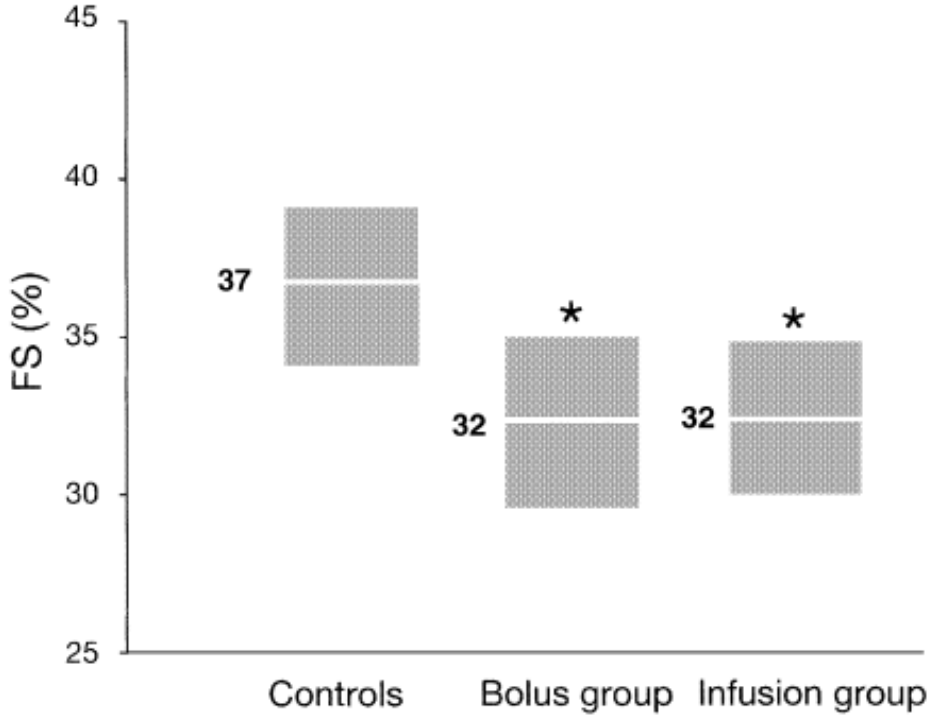


Cumulative Incidence of Heart Failure in Childhood Cancer Survivors

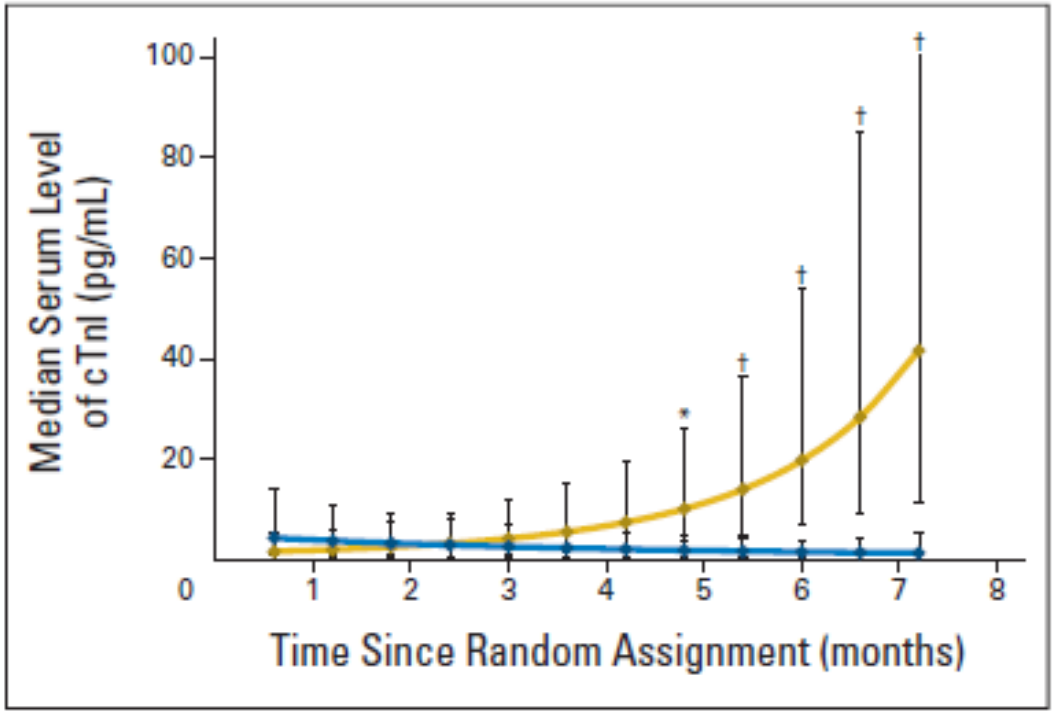


de Baat EC, et al. *J Clin Oncol.* 2022;JCO2102944.

Shortening Fraction by Bolus or 6-Hour Infusion of Daunorubicin

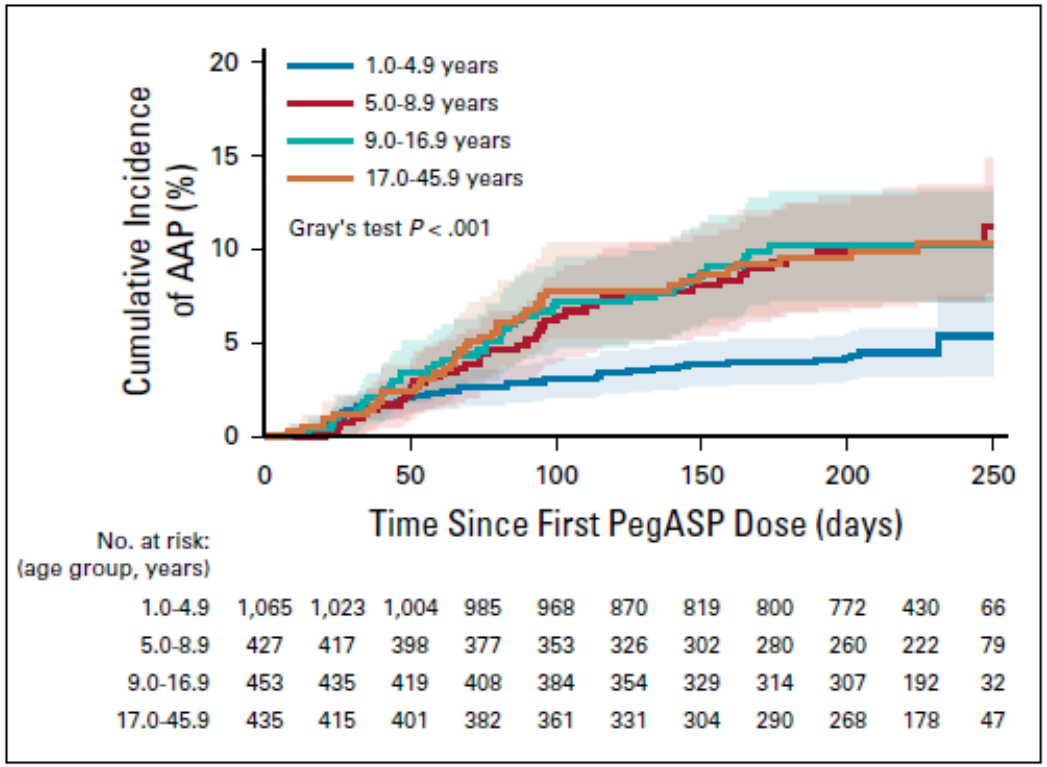


Cardiac Troponin During Doxorubicin Therapy in ALL With (blue) or Without (yellow) Dexrazoxane



Lipshultz SE, et al. *J Clin Oncol*. 2012;30(10):1050-1057.

Pancreatitis by Age

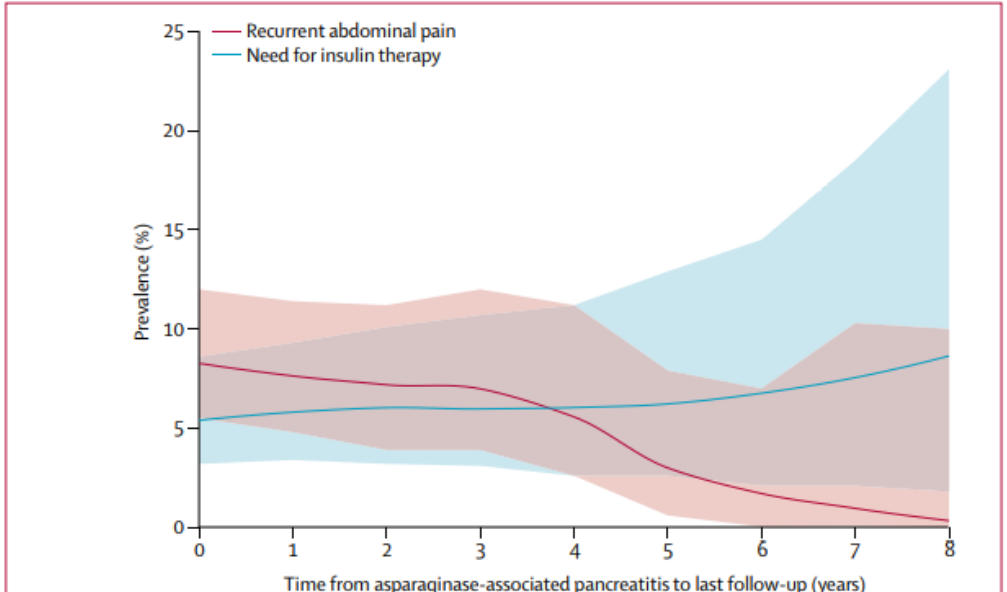


No. at risk:
(age group, years)

1.0-4.9	1,065	1,023	1,004	985	968	870	819	800	772	430	66
5.0-8.9	427	417	398	377	353	326	302	280	260	222	79
9.0-16.9	453	435	419	408	384	354	329	314	307	192	32
17.0-45.9	435	415	401	382	361	331	304	290	268	178	47

Rank CU, et al. *J Clin Oncol*. 2020;38(2):145-154.

Prevalence of Persisting Complications From Asparaginase-Associated Pancreatitis

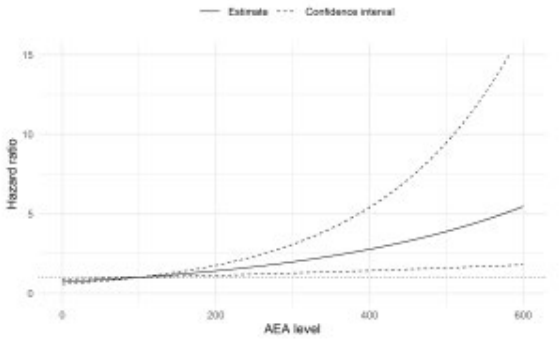


Patients (n)	312	275	216	180	137	108	77	52	35
Need for insulin therapy, n (%)	17 (5%)	16 (6%)	13 (6%)	11 (6%)	8 (6%)	7 (6%)	5 (6%)	4 (8%)	3 (9%)
Recurrent abdominal pain, n (%)	26 (8%)	21 (8%)	15 (7%)	13 (7%)	8 (6%)	3 (3%)	1 (1%)	1 (2%)	0

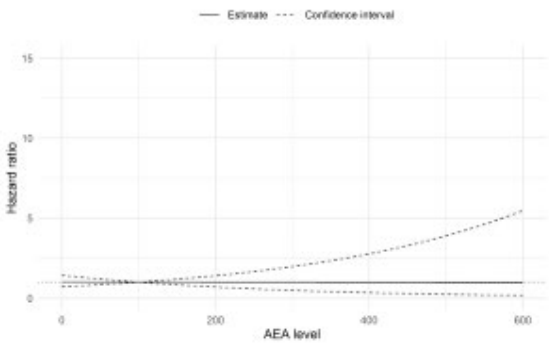
Wolthers BO, 2017

Risk of Toxicity by Median Asparaginase Enzyme Activity

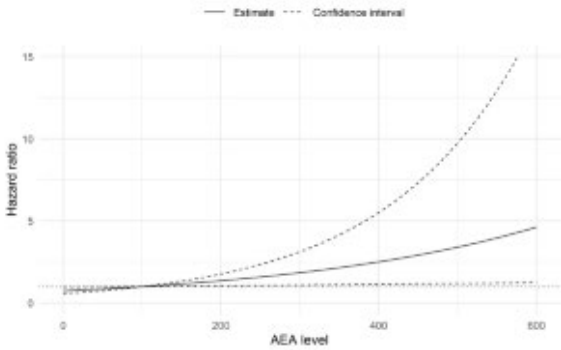
Pancreatitis



Thrombosis

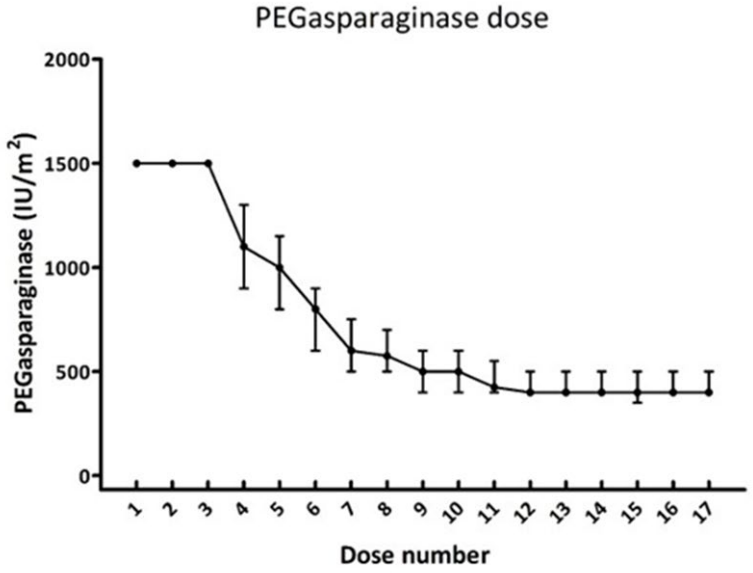


Osteonecrosis

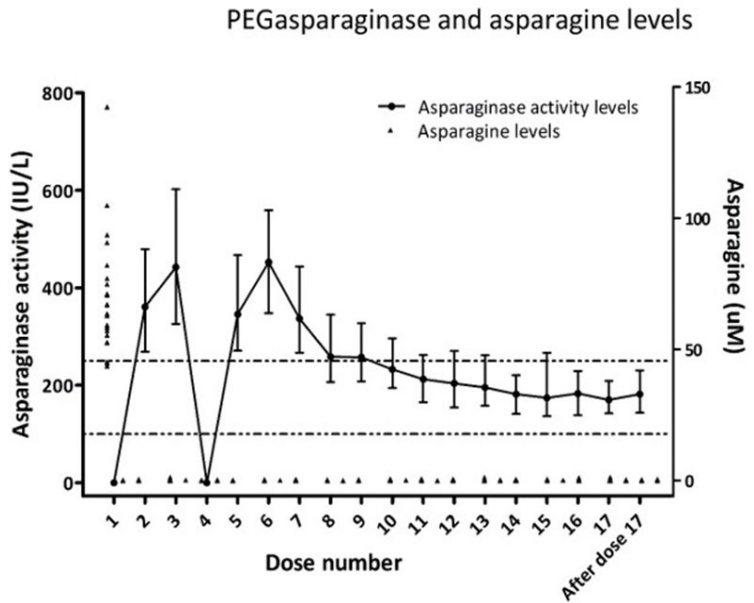


Lynggaard LS, et al. *Blood Advances.* 2022;6(1):138-147.

Therapeutic Drug Monitoring: Target Drug Level 100–250 U/L



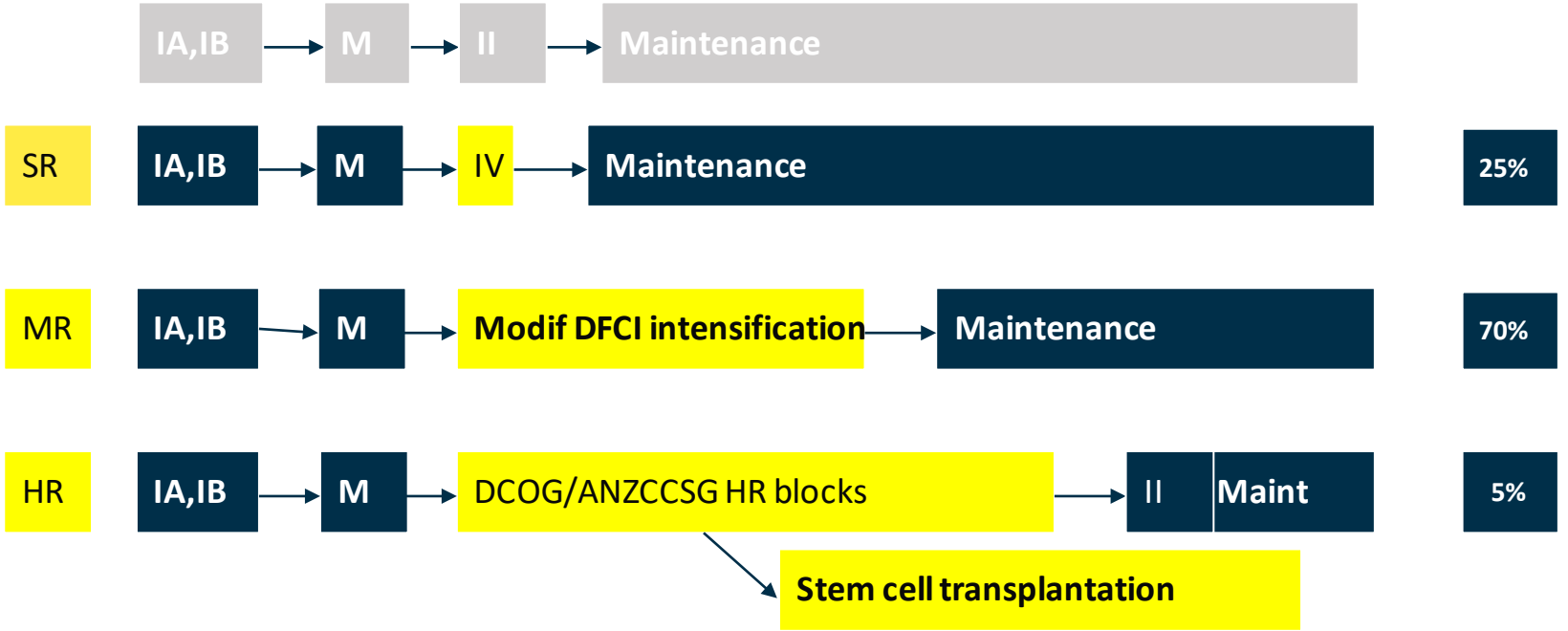
Dose number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Number of patients	323	320	298	283	247	190	183	188	174	170	150	151	130	137	123	115	153



Dose number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	After dose 17
Number of patients	323	319	287	283	247	184	177	187	169	165	144	149	122	129	120	108	148	77

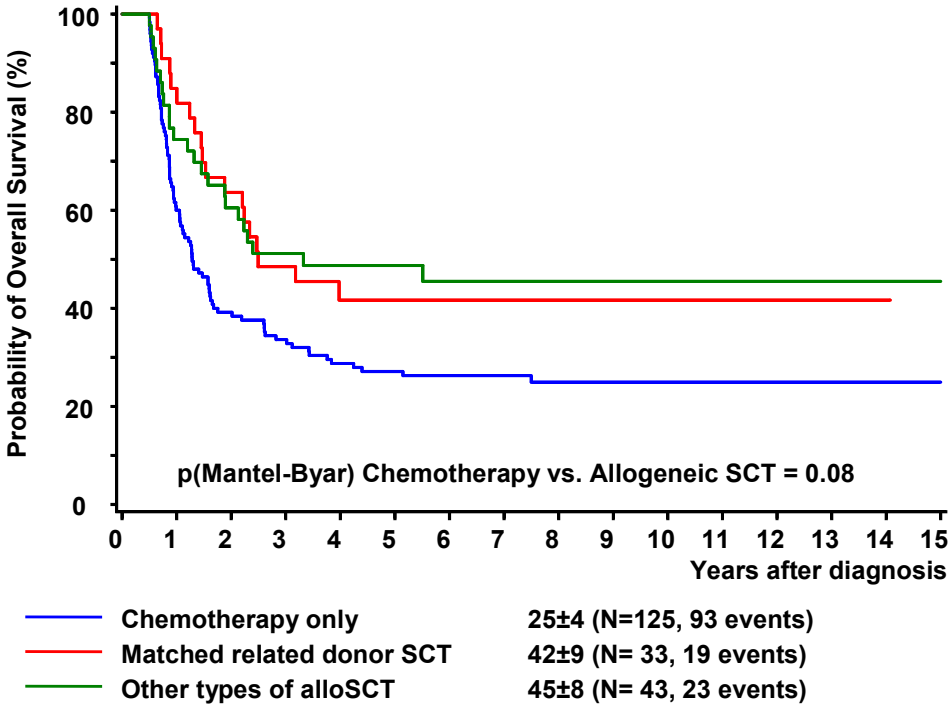
Kloos R, et al. *J Clin Oncol*. 2020;38(7):715-724.

Dutch Childhood Oncology Group (DCOG) Study ALL10 and ALL11 Outlines

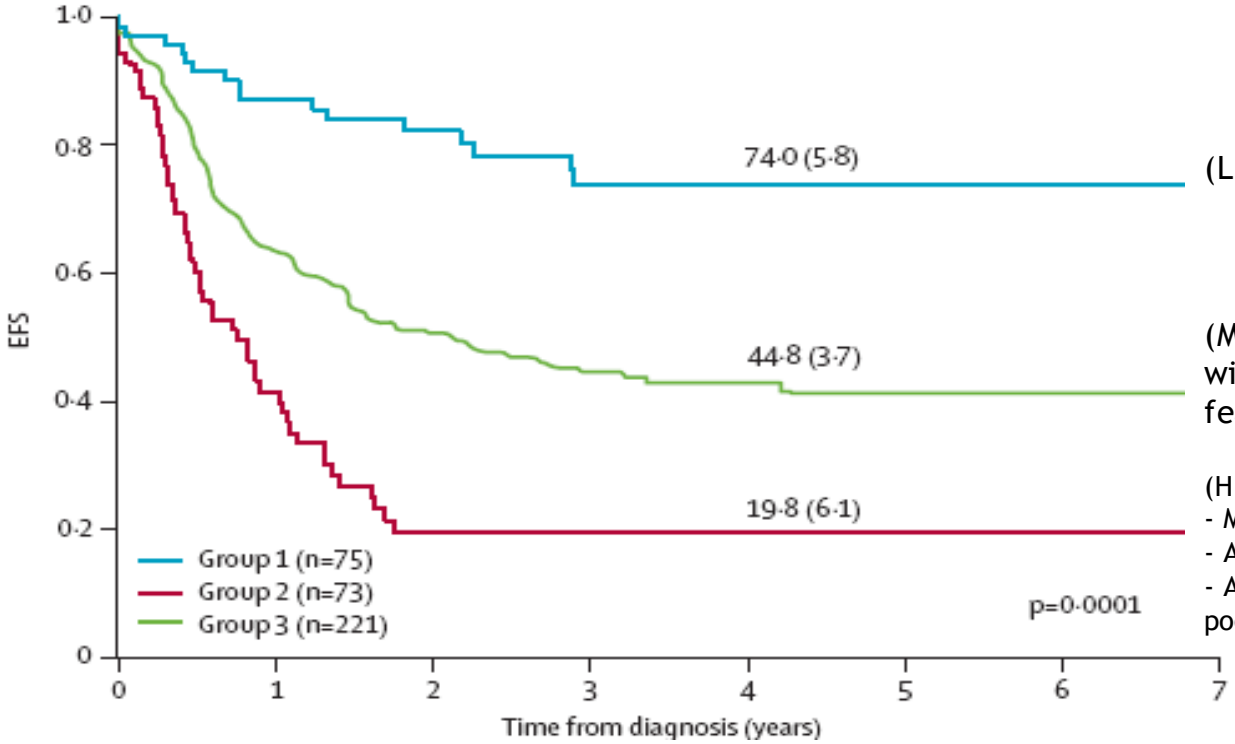


Pieters R, et al. *J Clin Oncol*. 2016;34(22):2591-2601.

No CR After Induction AND T-ALL: Better Survival With AlloSCT



Outcome by MLL Status, Age, and White Blood Cell Count



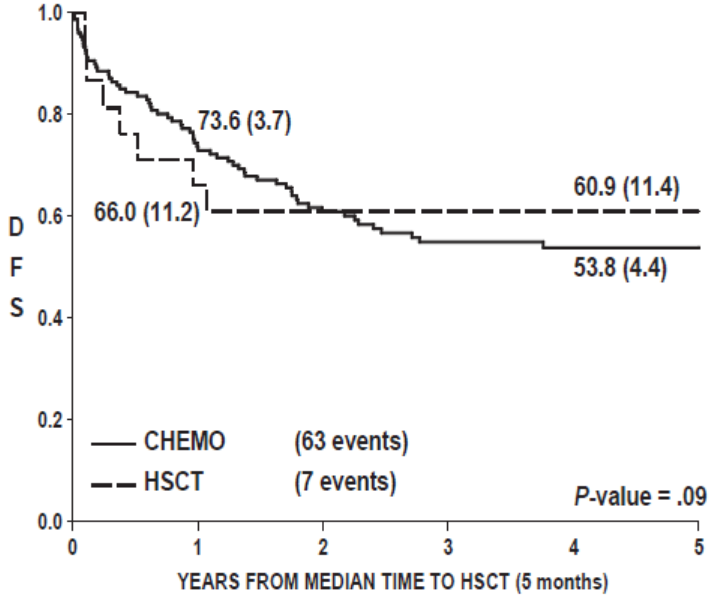
(LR) MLL germline

(MR) MLL rearranged without other HR features

(HR)
- MLL rearranged
- AND age <6 mths
- AND WBC >300 or pred poor resp

Pieters R, et al. *Lancet*. 2007;370(9583):240-250.

AlloSCT in Infant MLL-Rearranged ALL: Interfant-99 MR Patients Adjusted by Waiting Time to SCT



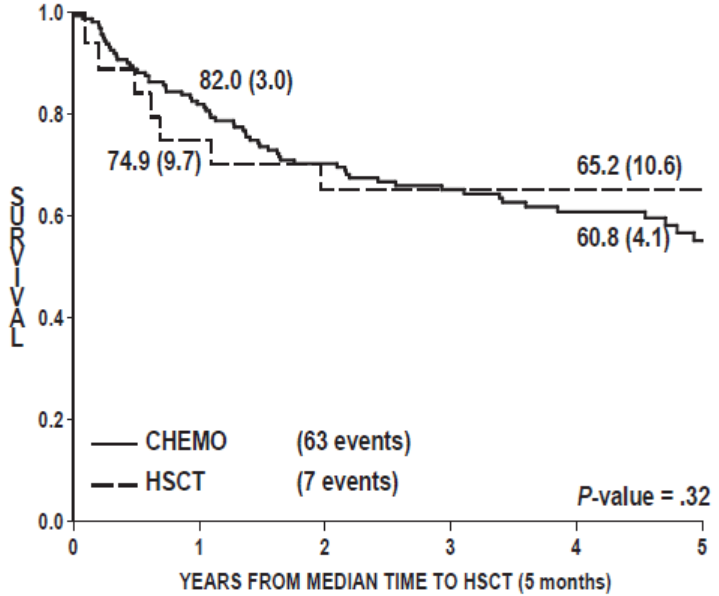
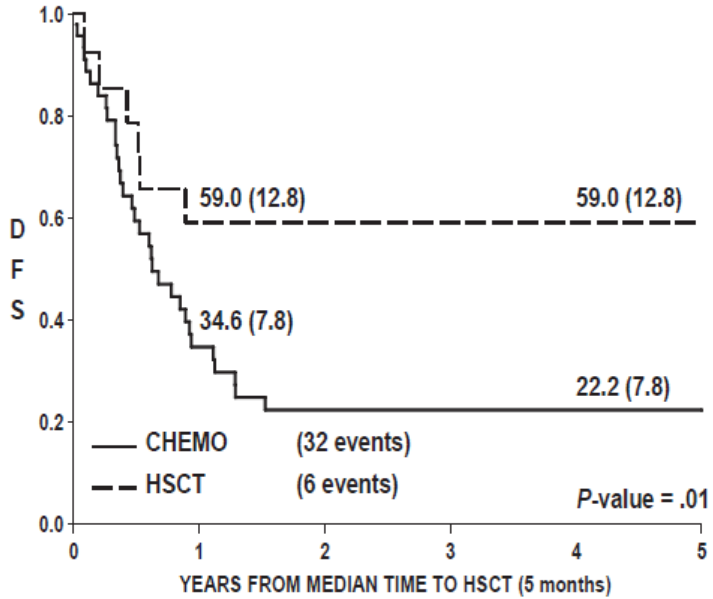


Figure 2. DFS and OS of 188 medium-risk patients with *MLL*+ infant ALL by treatment performed, adjusted by waiting time to HSCT. *P* value is from Cox Model. CHEMO indicates chemotherapy only; and HSCT, hematopoietic stem cell transplantation.

AlloSCT in Infant MLL-Rearranged ALL: Interfant-99 MR Patients Adjusted by Waiting Time to SCT



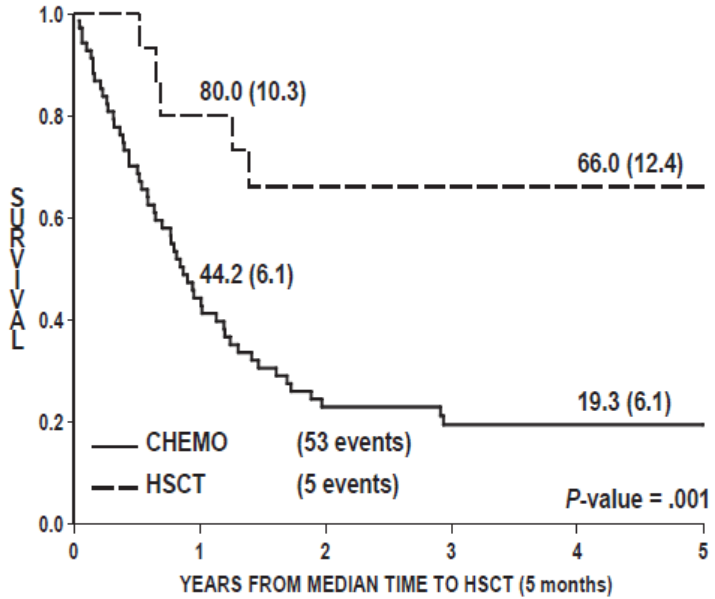


Figure 3. DFS and OS of 97 high-risk patients with *MLL*$^+$ infant ALL by treatment performed, adjusted by waiting time to HSCT. *P* value is from Cox Model. CHEMO indicates chemotherapy only; and HSCT, hematopoietic stem cell transplantation.

TKI in BCR-ABL–Positive ALL: Need for SCT?

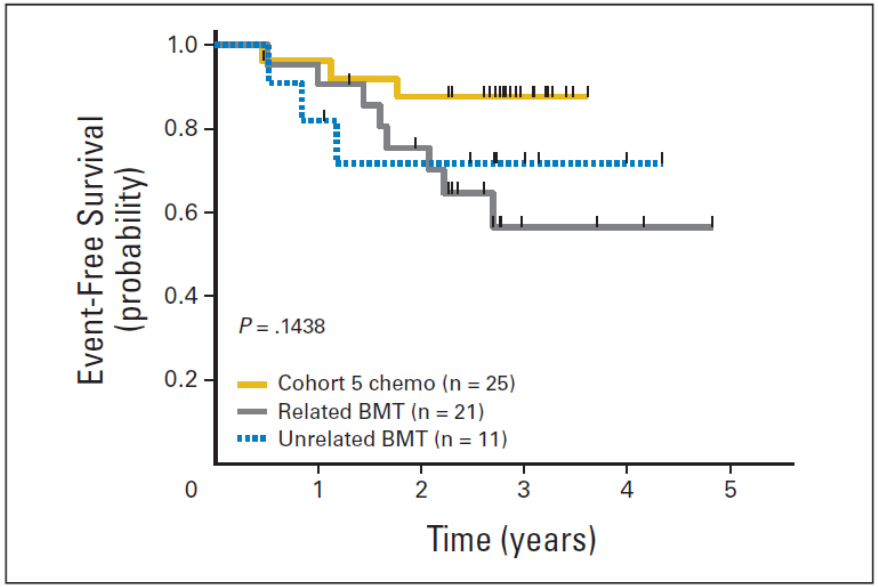
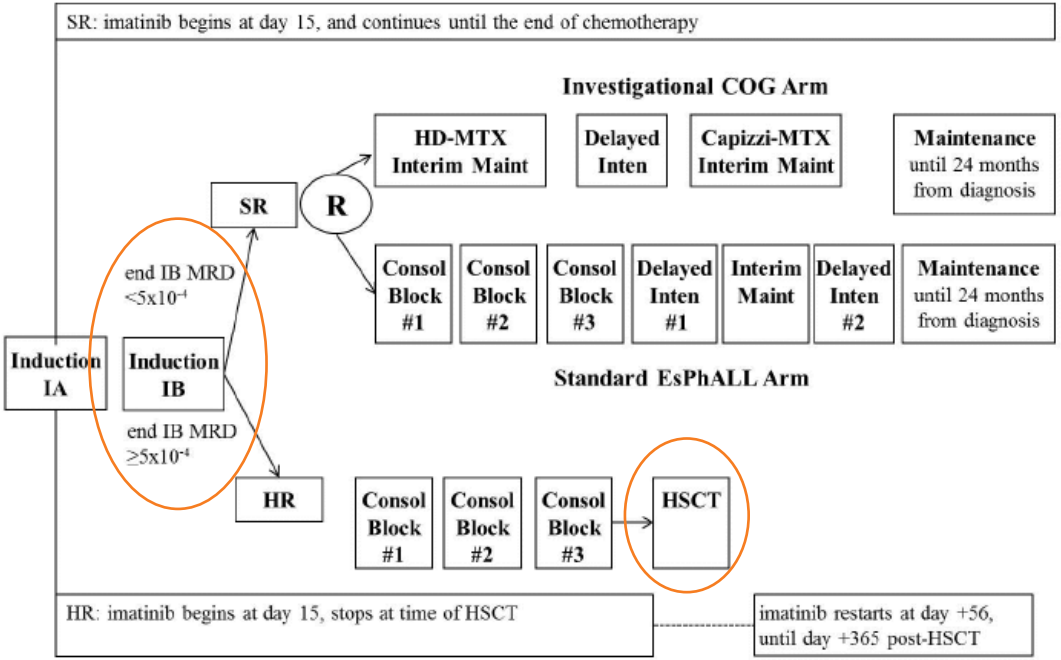


Fig 4. Comparison of event-free survival (EFS) for Cohort 5 chemotherapy only versus related-donor bone marrow transplantation (BMT) versus unrelated-donor BMT. Cohort 5 patients were compared with human leukocyte antigen (HLA) –identical sibling BMT (8 of 39 in cohorts 1-4; 13 of 44 in cohort 5) and 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.

Schultz KR, et al. *J Clin Oncol*. 2009;27(31):5175-5181.

EsPhALL2017/COGAALL1631

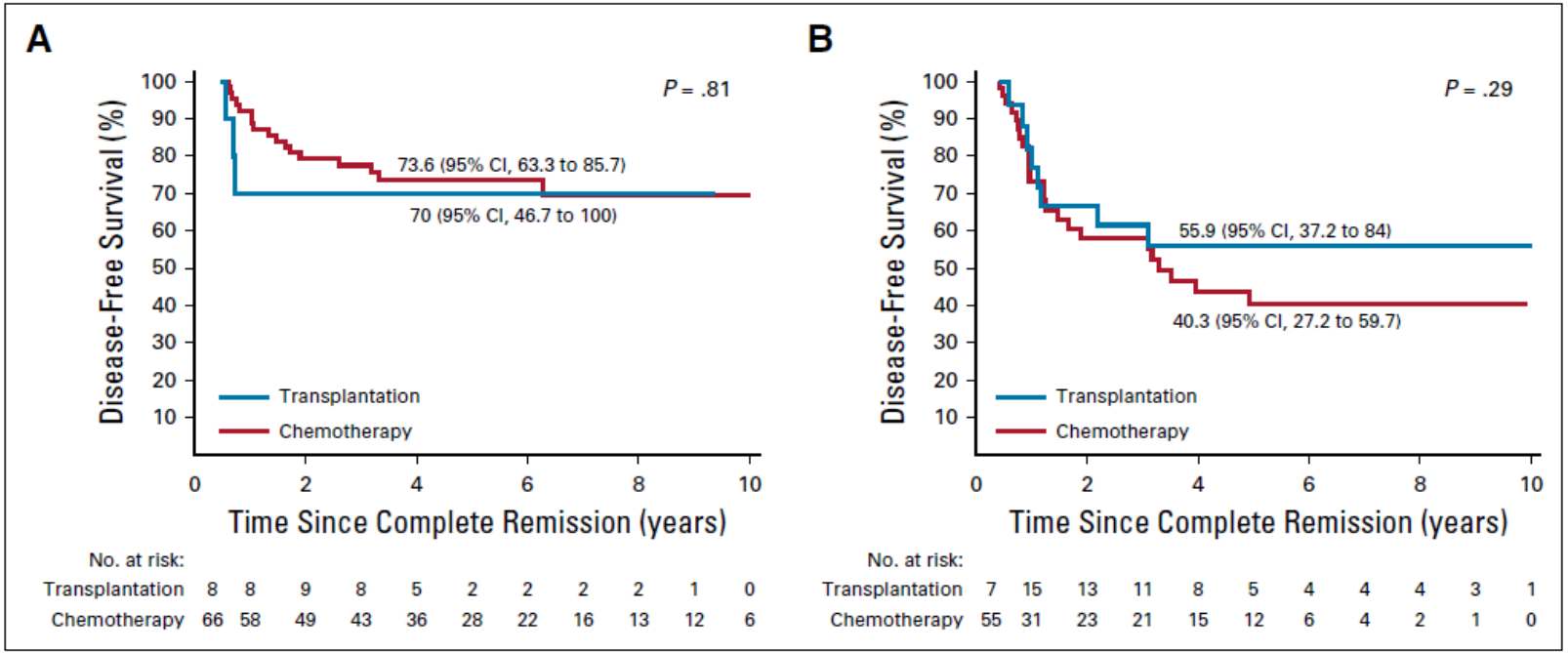


Note. MRD: Minimal Residual Disease, SR:Standard Risk, HR: High Risk, R: Randomization, HD-MTX: High Dose Methotrexate, Maint: Maintenance, Inten: Intensification, Consol: Consolidation, HSCT: Hematopoietic Stem Cell Transplant

DFS of Hypodiploid (<44 chromosomes) ALL With vs Without SCT

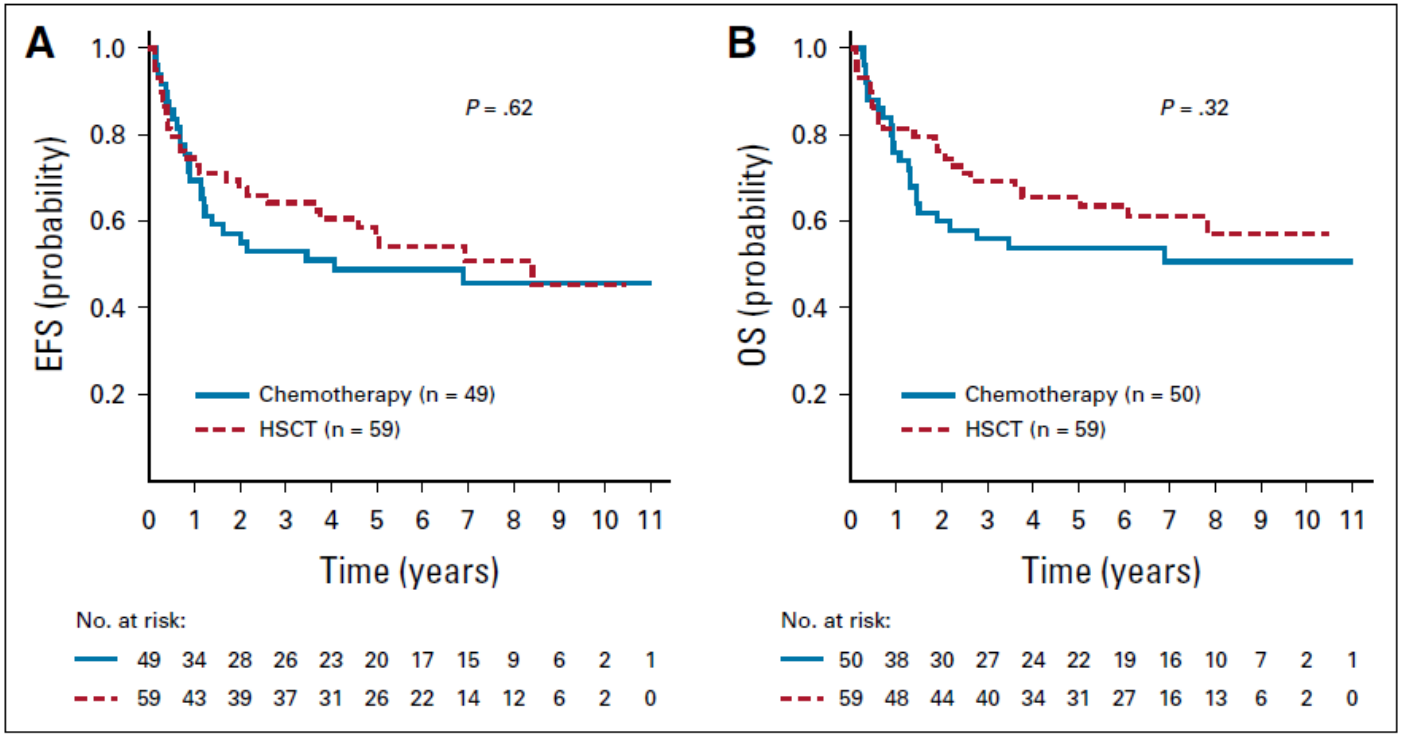
MRD EOI $<10^{-4}$

MRD EOI $>10^{-4}$



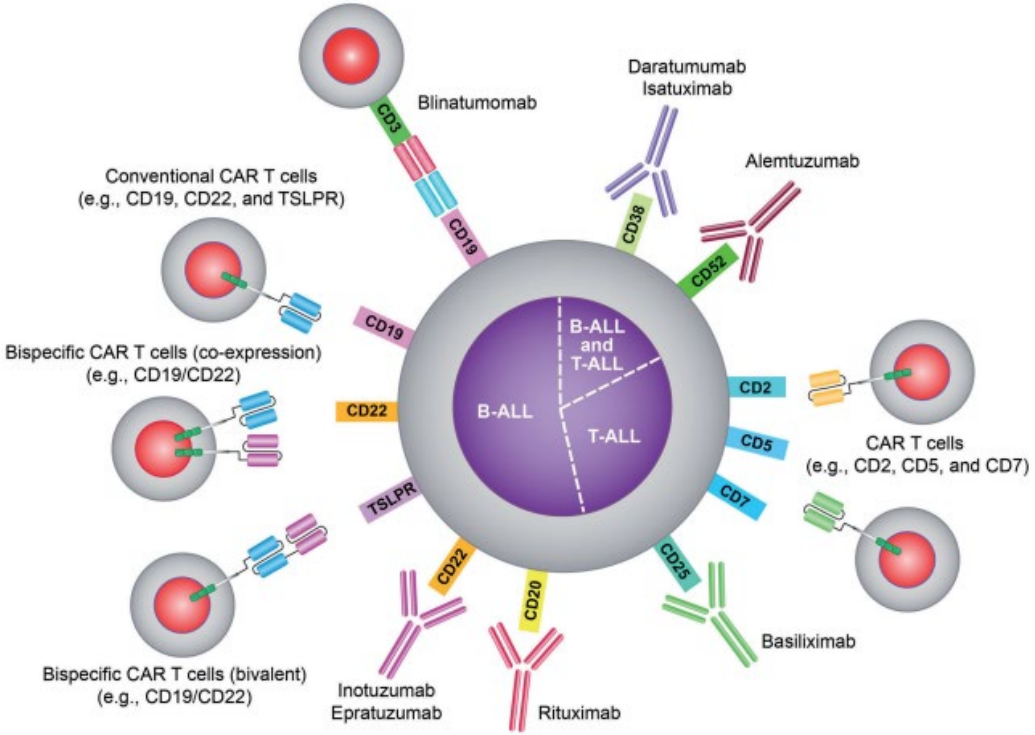
Pui CH, et al. *J Clin Oncol*. 2019;37(10):770-779.

Outcome of Hypodiploid (<44 chromosomes) ALL With vs Without SCT



Loh, J Clin Oncol 2019

Immunotherapy in Acute Lymphoblastic Leukemia



Inaba H, et al. *Haematologica*. 2020;105(11):2524-2539.

Answer to Question 1: Which factor has the lowest probability of causing significant long-term toxicity in pediatric ALL?

1. The anthracyclines daunorubicin and/or doxorubicin in a cumulative dose of >300 mg/m^2 in a child aged 5 years at diagnosis
2. **Methotrexate in a cumulative dose of 20,000 mg/m^2 in a child aged 8 years at diagnosis**
3. Cranial radiotherapy in a child aged 2 years at diagnosis
4. Dexamethasone in a girl aged 14 years at diagnosis

Balancing Cure and Late Toxicity

- Second malignancies
- Osteonecrosis
- Neurocognitive sequelae
- Cardiomyopathy
- Insulin-dependent diabetes (pancreatitis)
- Who should be transplanted?
- Late effects of immunotherapies?

- Large numbers of patients
- Long and structured follow-up
- Feedback to current protocols
- Dedicated late effects outpatient clinics

Late Effects Outpatient Clinic: 16,000 Survivors

Global Leukemia Academy

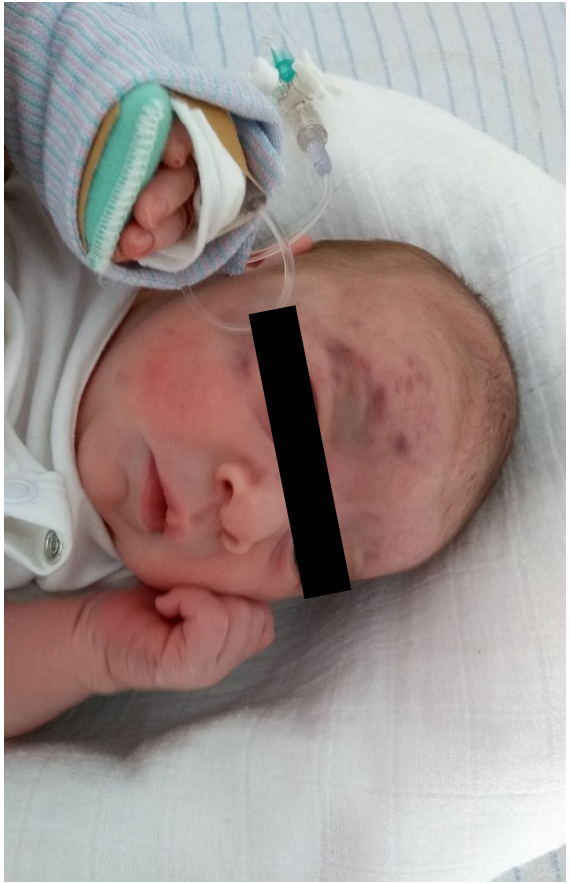
Case 1: Balancing Cure and Toxicity Risks

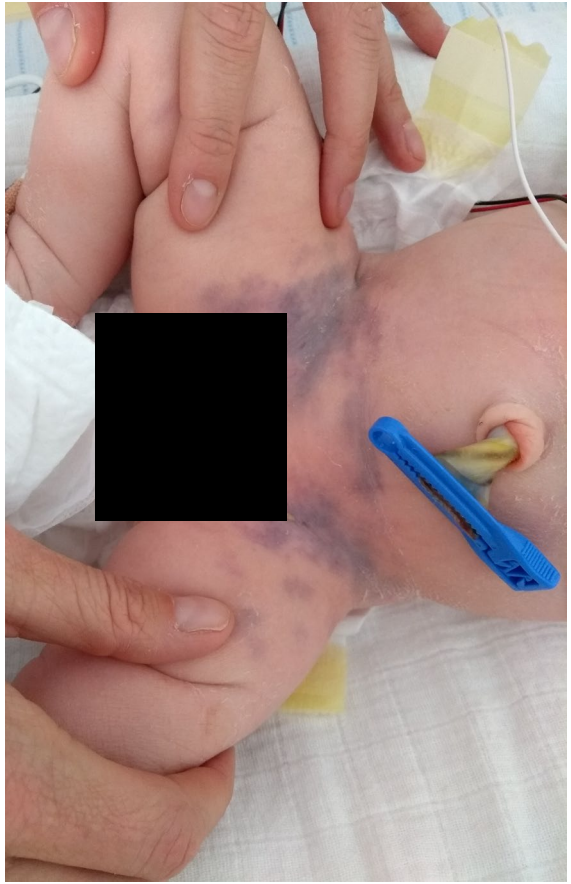
Janine Stutterheim

APTITUDE HEALTH

Case: Bilineage Leukemia (infant)

24-9-2022



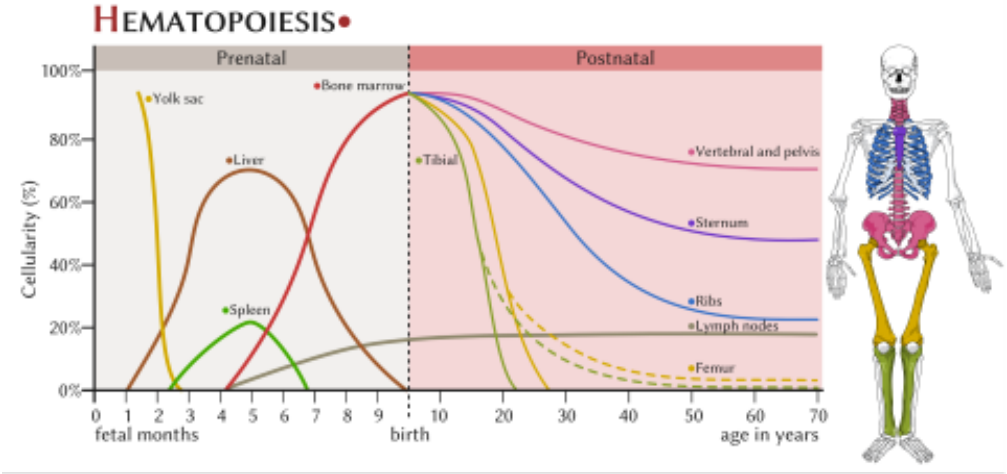


Baby S
41 + 1 weeks GA
3765 g (p50–p90)

- Uncomplicated gravidity
- Normal NIPT test
- Spontaneous parturition APGAR 5/8/9
- Physical exam: blueberry muffin rash

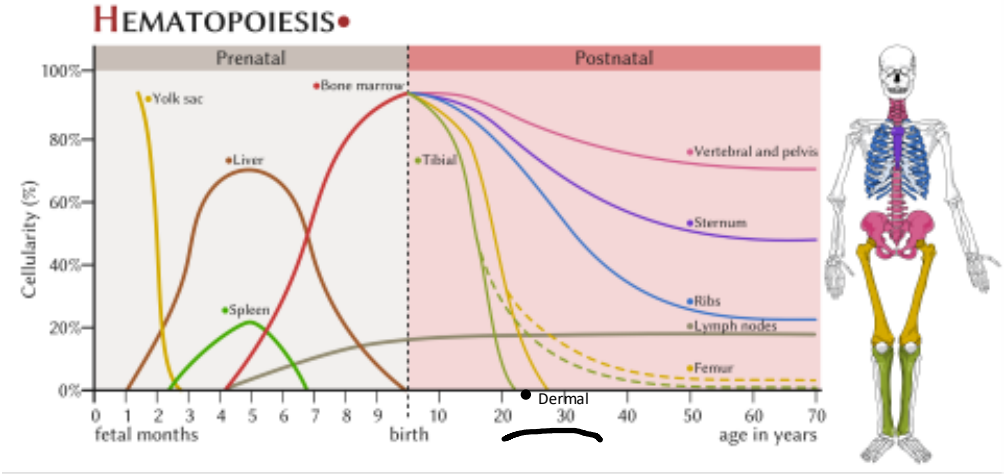
Blueberry Muffin Rash

- Widespread purpura and papules
- First described in 1960[1]
  - Rubella-infected neonates in American rubella epidemic
- Etiology: cutaneous extramedullary hematopoiesis



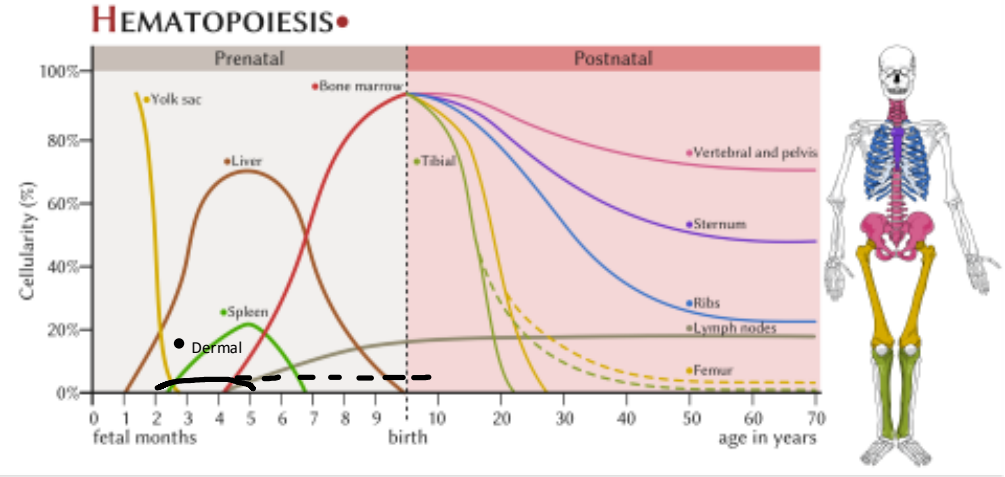
Blueberry Muffin Rash

- Widespread purpura and papules
- First described in 1960[1]
  - Rubella-infected neonates in American rubella epidemic
- Etiology: cutaneous extramedullary hematopoiesis



Blueberry Muffin Rash

- Widespread purpura and papules
- First described in 1960[1]
  - Rubella-infected neonates in American rubella epidemic
- Etiology: cutaneous extramedullary hematopoiesis



Laboratory Results

- Hb 9.1, T 102, **L 68, 34% blasts**
- Chemistry without any abnormalities
- Chest X-ray: normal, no mediastinal mass

Diagnosis, Flow Cytometry: Bilineage Leukemia

	Myeloid Clone	Lymphoid Clone
	cMPO +	cCD79a +
CD45	+/-	+
CD34	-	zwak
CD117	-	neg
SSC	++	+/-
CD79a	-	+
CD19	+/-	+
CD10	-	-
CD20	-	-
NG2	-	-
CD22	partly	+
CD24	-	+/-
cTDT	+/-	+
cMPO	+	-

Genetics: *KMT2A-AFF1* (*MLL-AF4*) rearrangement

Question: How Would You Start Treatment?

1. ALL induction
2. AML induction
3. Interfant induction
4. No treatment

Neonatal Leukemia

- <28 days post partum, often congenital, <1% of childhood leukemia
- AML > ALL
- Symptoms and signs: hepatomegaly, splenomegaly, cutaneous infiltration, CNS infiltration and hyperleukocytosis
- Often *KMT2A*-rearranged
- Prognosis
  - AML with Translocation t(8;16) associated with spontaneous remission
  - AML overall survival 25%
  - **ALL overall survival <20%**

Bilineage Leukemia: iBFM AMBI2018

Fig. 4. All ALAL cases: outcome of a historical control, Q2.

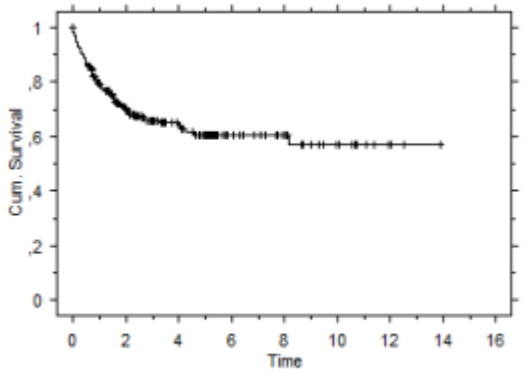
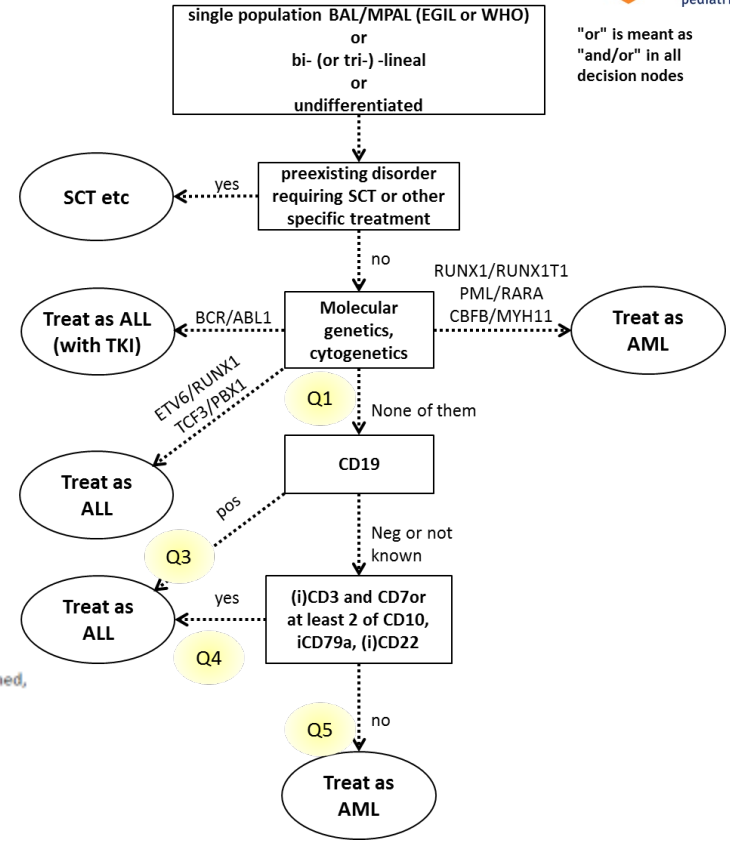


Fig. 4. EFS (iBFM AMBI2012 study) of ALALs without specific fusions or preexisting disorders. All types of treatment (ALL, AML, combined, other) included. Patients on iBFM AMBI2018 should have a non-inferior outcome



Bilineage Leukemia: iBFM AMBI2018

Fig. 4. All ALAL cases: outcome of a historical control, Q2.

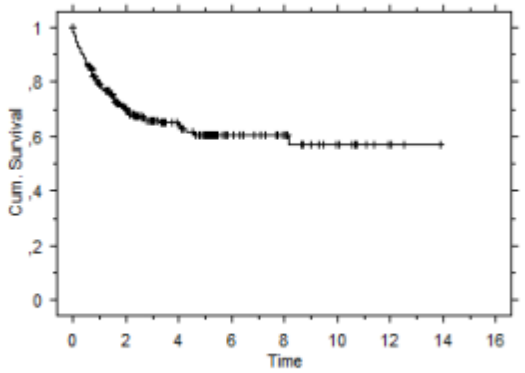
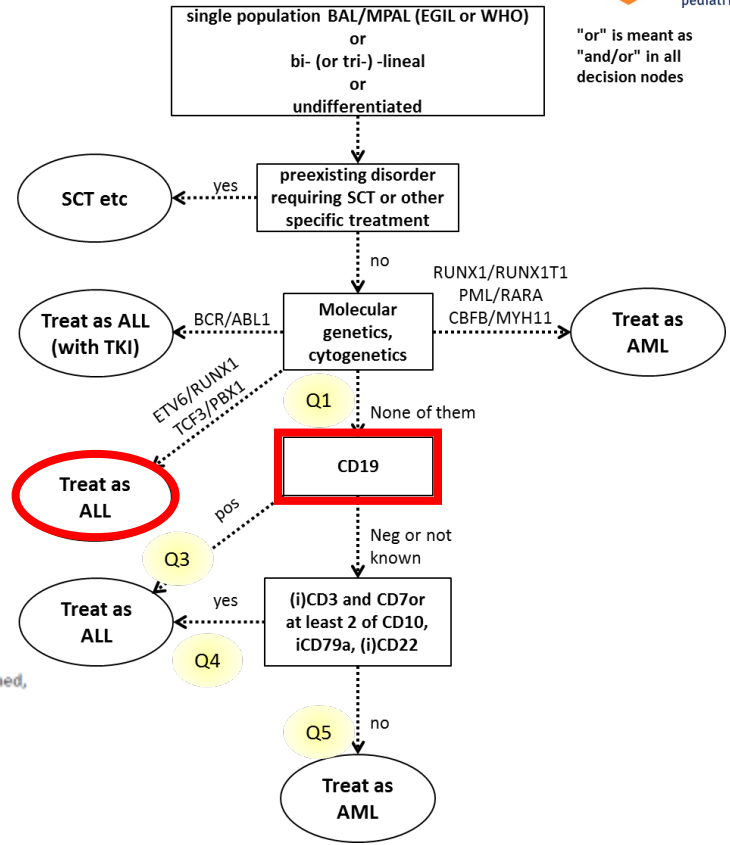
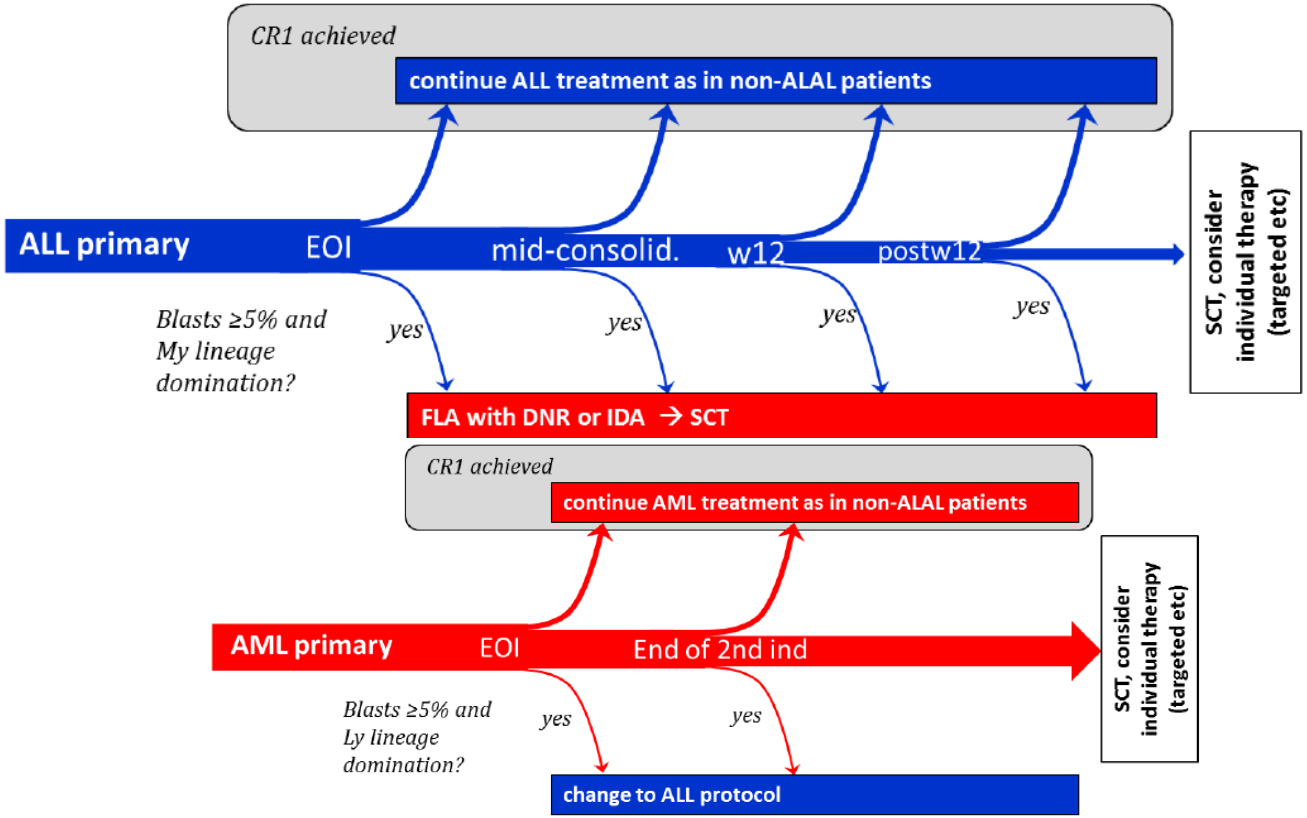


Fig. 4. EFS (iBFM AMBI2012 study) of ALALs without specific fusions or preexisting disorders. All types of treatment (ALL, AML, combined, other) included. Patients on iBFM AMBI2018 should have a non-inferior outcome



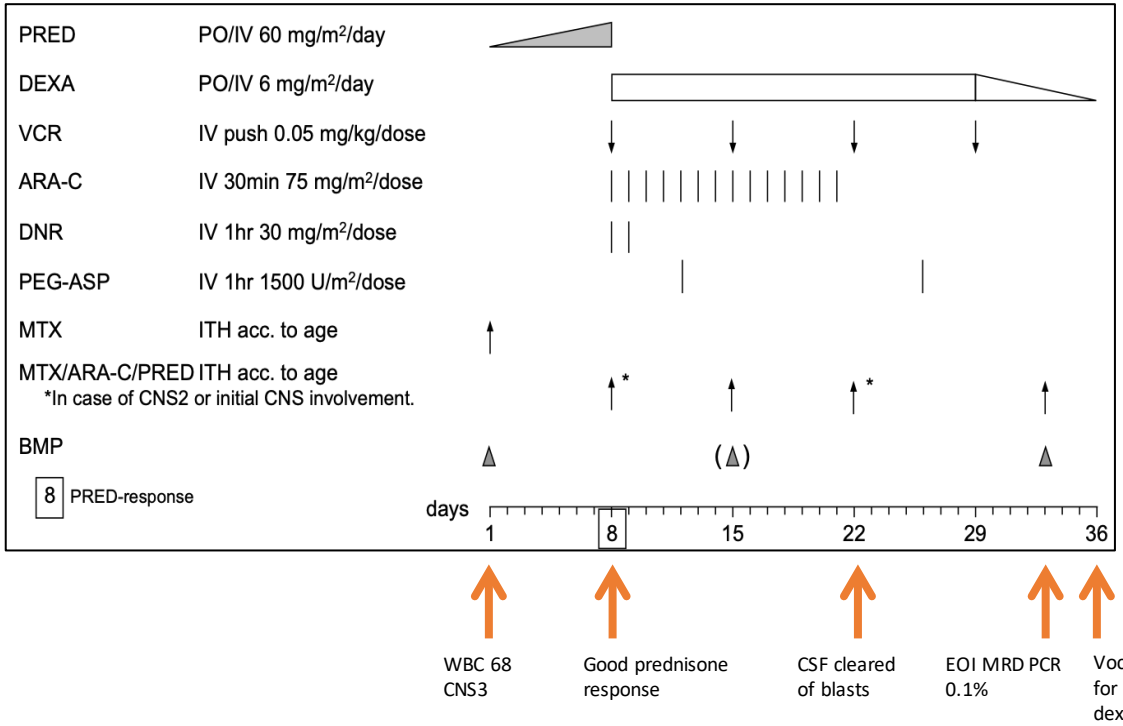
Bilineage Leukemia: iBFM AMBI2018

RECOMMENDED CHANGES OF TREATMENT



Treatment: Interfant Induction

LYMPHOID INDUCTION WITH ADDITION OF CYTARABINE

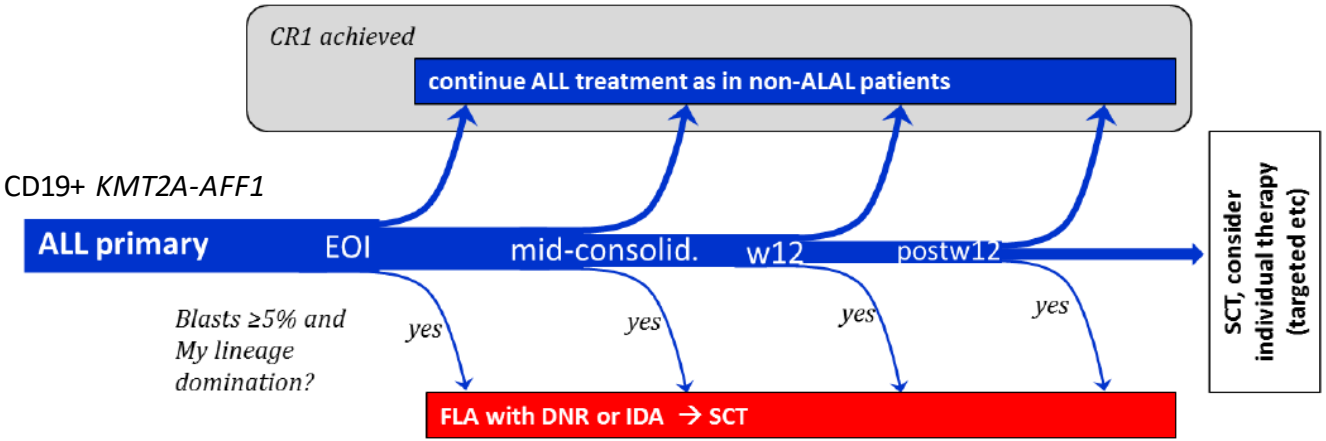


Risk group	Criteria
Medium risk (MR)*	**1.** age ≥ 6 months **OR** **2.** age < 6 months **AND** WBC< 300 x 10^9/L **AND** prednisone good response
High risk (HR)	**3.** age at diagnosis < 6 months AND **4.** WBC≥300 x 10^9/L **AND/OR** prednisone poor response

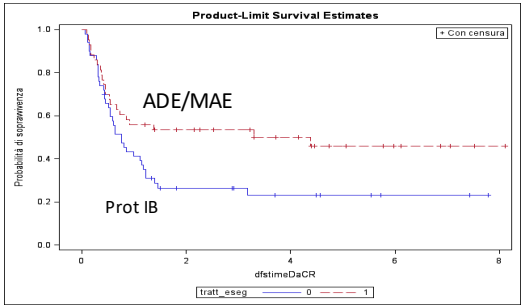
Bilineage Leukemia: iBFM AMBI2018

MRD EOI <5%:

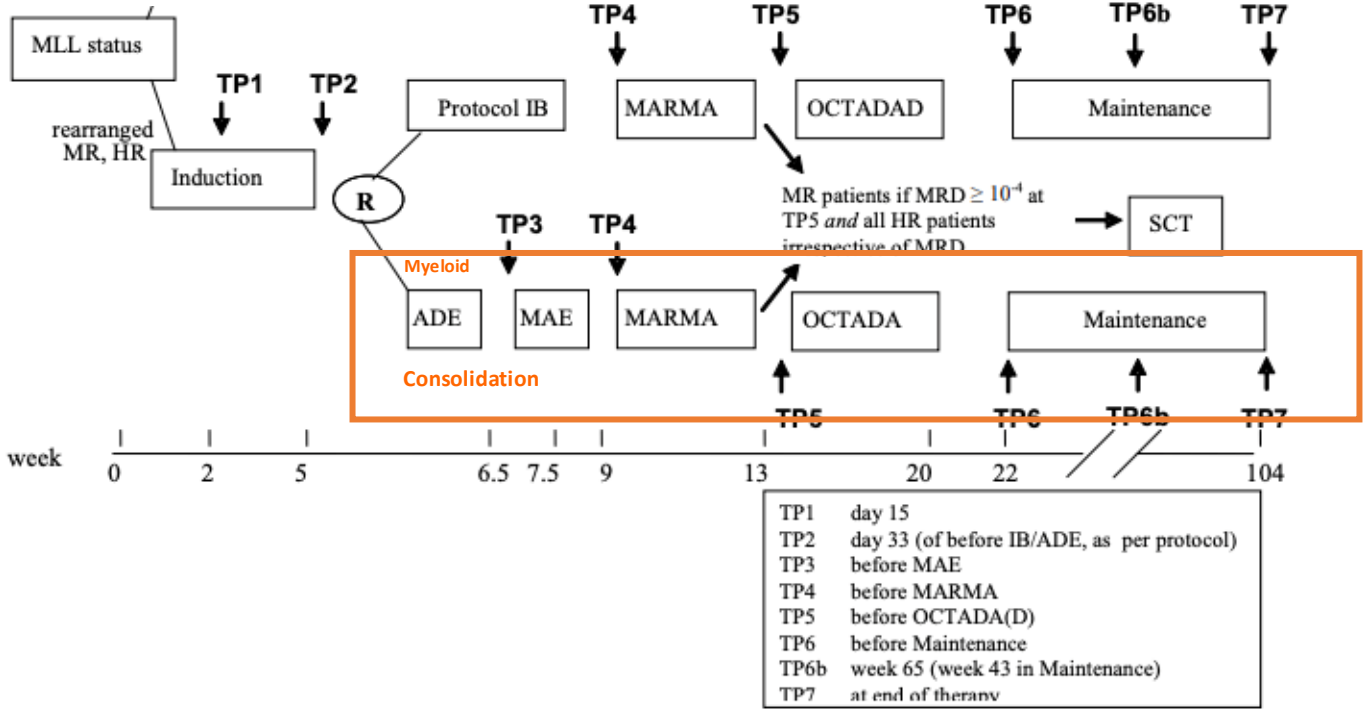
- MRD ≥0.05%: ADE/MAE



MRD EOI ≥0.05%

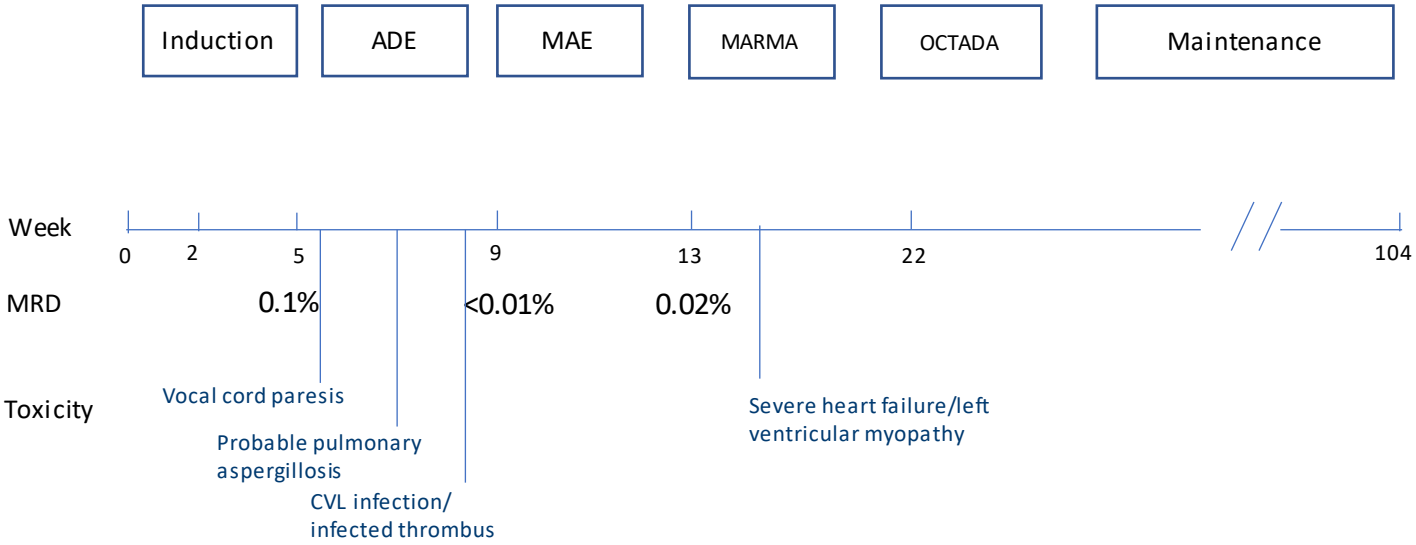


Interfant-06: With Myeloid Consolidation Blocks



Pieters R, et al. 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;2246-2256.

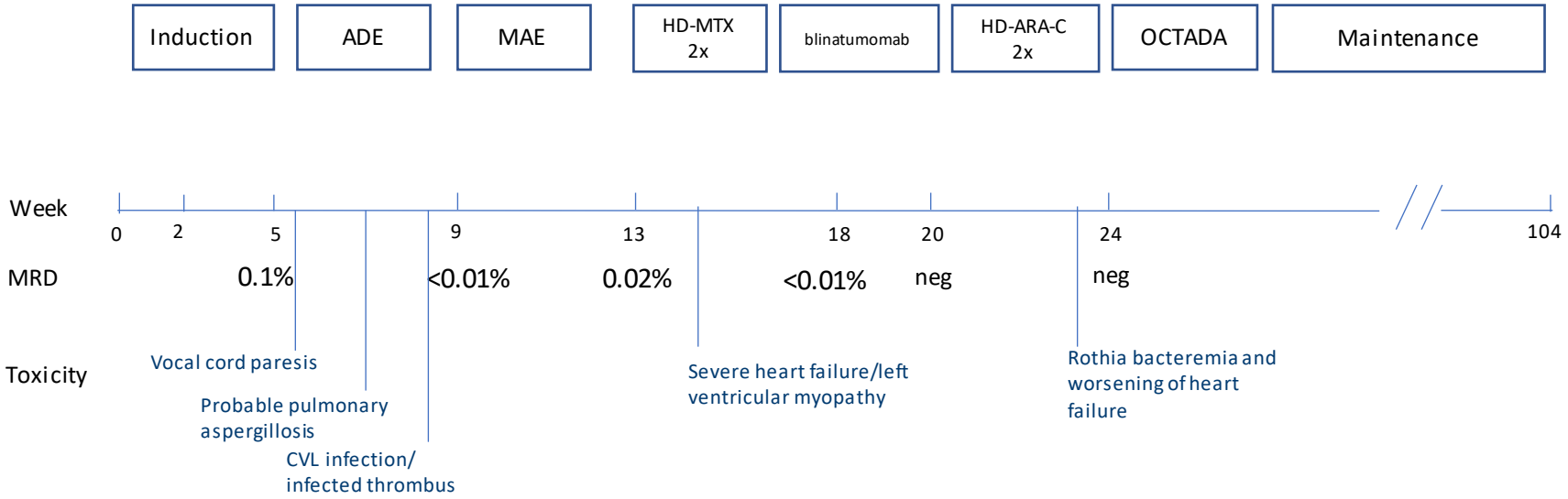
Treatment, Continued: More Toxicity Arises



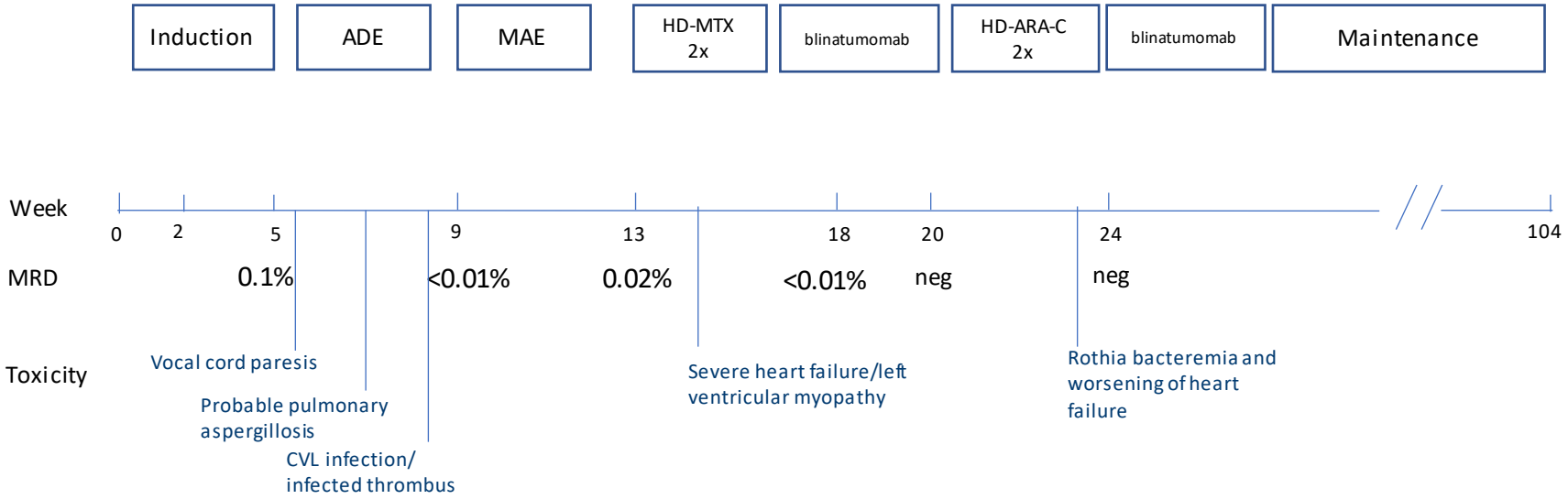
Question: How Would You Continue Treatment?

1. Maintenance treatment
2. MARMA – HD-MTX treatment
3. Blinatumomab
4. CAR T therapy

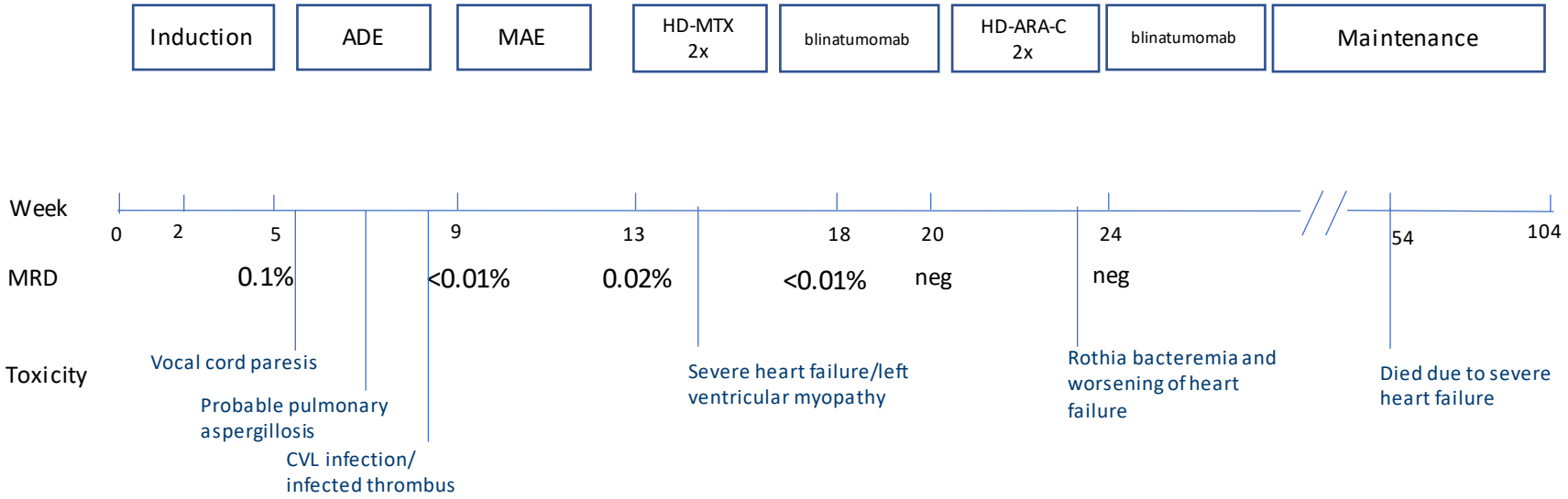
Treatment, Continued



Treatment, Continued



Treatment, Continued



Questions?

- Diagnose: congenitale acute bilineage leukemie, CNS3, t(4,11)/ KMT2A-AFF1 fusie
- Presentatie met leukemia cutis
- TPMT_ normaal genotype
- Datum van diagnose: 30-4-2020, start Interfant-06
- Datum Overlijden 14-5-2021: oorzaak ernsig hartfalen

- Behandeling: Interfant -06 Inductie, ADE/MAE, 1ste helft MARMA,
- blina 2de helft MARMA, blina (ipv OCTADA), maintenance
- Behandeling gecompliceerd door ernstig hartfalen

- Respons:
- dag 8: GPR (liquor nog blasten gezien)
- BMP dag 15 niet verricht (liquor uitslag niet betrouwbaar)
- Liquor dag 22 schoon
- BMP EOI CR dd 3-6-20 flow-MRD +/- 4% vrnl myeloid. MRD MLL PCR 0.06%. max 0.1%
- BMP na ADE, dd 8-7-20 MLL-target pos < 10-4. max pos 10-4
- BMP EOC na ADE/MAE dd 15-08: MLL target 0.02%, max 0.06%
- BMP dag 15 blina: dd25-9: pos NK
- BMP dag 29 blina: dd 14-10: pos NK (MLL neg)
- BMP na 2de helft MARMA, dd 13-11: neg

Toxiciteit:

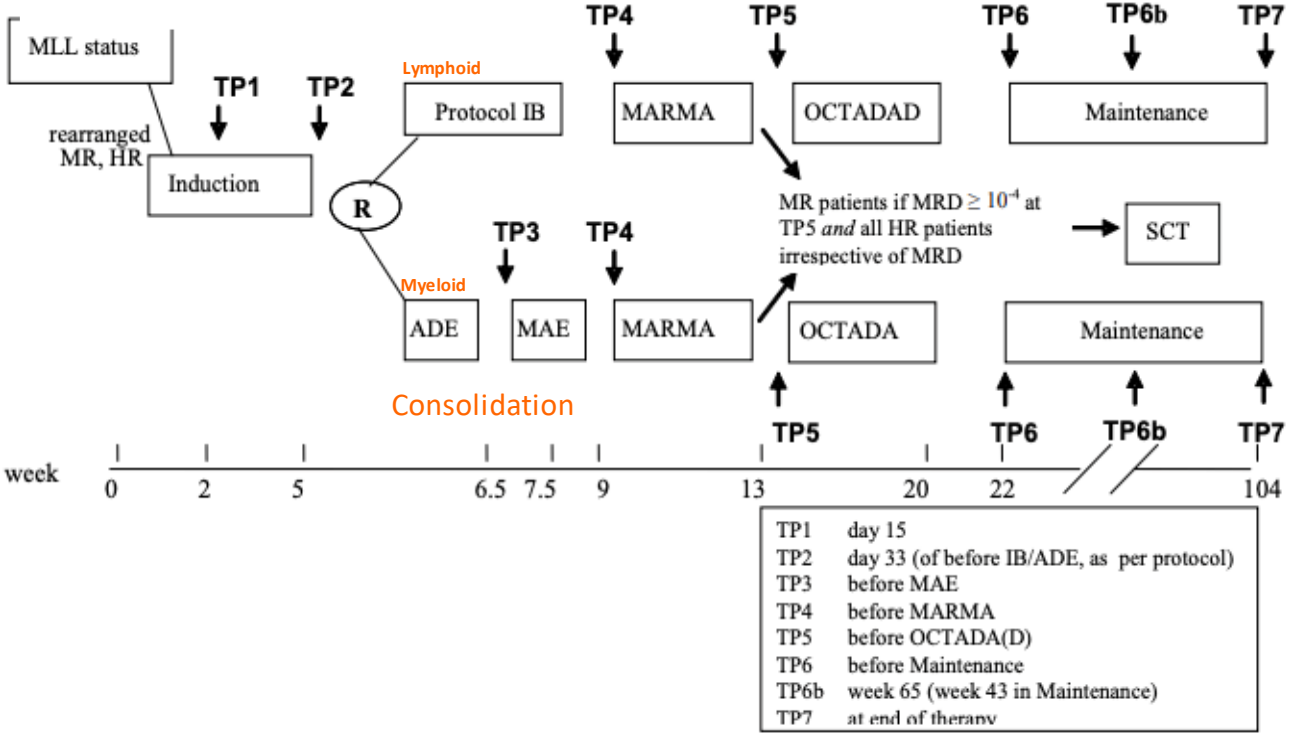
- hartfalen door cardiomyopathie met LVF, IC opname 30-8-2020. WD antracycline-toxiciteit (DD congenitaal)
- probable pulmonale aspergillus wv sinds 26-6 Ambisome en voriconazol; in aug-2020 switch isavuconazol ivm slechte spiegels voriconazol
- defecte CVL (Re VJI) wv lijnwissel dd 26-6 (V.jug.int links)
- Tunnelinfectie nieuwe lijn dd 3-7, (BK enterococ Faecalis, + CNS)
- geinfecteerde trombus (BK enterococ Faecalis, + CNS), wv dalteparine dd 6-7, en 6 wkn antibiotica. Stop dalterapine 1-11-2020
- reversibele stridor obv stembandparese

Aangepast antibioticabeleid:
- colonosisatie acinetobacter wv meropenem indicatie

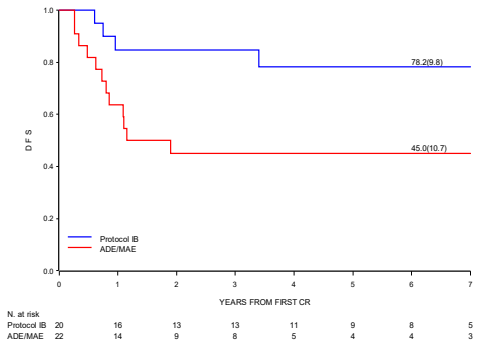
Bijzonderheden:
- echo cor; aanvankelijk afw triculspidaal klep en klein VSD, bij laatste echo dd 24-6 + 3-8 geen bijz. echter 30-8 cardiomyopathie met matig tot slechte LVF

na 1/2 MARMA: 2x HD-MTX afgerond. Gestaakt ivm hartfalen. Over op Blinatumoman dd 11-9;
herstart met 2de deel MARMA; hierna Rothia infectie en weer hartfalen, wv opnieuw blina ipv OCTADA

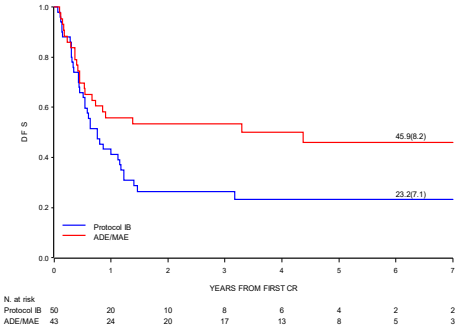
Interfant-06



Patients with negative MRD end of induction



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



Pieters R, et al. 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;2246-2256.

Global Leukemia Academy

BREAK

APTITUDE HEALTH

Global Leukemia Academy

Current Treatment Options for High-Risk ALL in Children

Christina Peters

APTITUDE HEALTH

Global Leukemia Academy 2022

R/R pediatric ALL: How to offer a chance of cure and reduce side effects and late complications?

Christina Peters, MD

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

Vienna, Austria

christina.peters@stanna.at

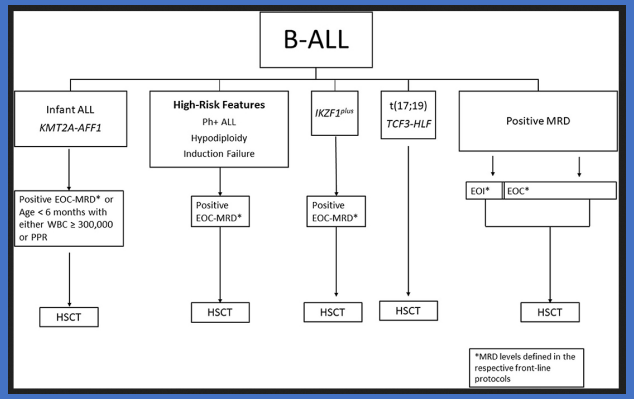
Company name	Disclosure
Amgen	Consultancy, honoraria and travel support
Novartis	Consultancy
Jazz	Speakers bureau
Pfizer	Consultancy
Medac	Consultancy
Neovii	Speakers bureau

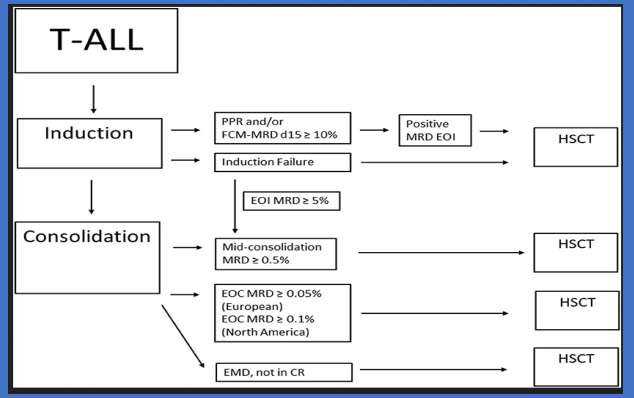
R/R Pediatric ALL: Strategies 2022

- Risk stratification: high/intermediate/low
- Treatment
  - Chemotherapy
  - Immunotherapy
    - Bispecific AB
    - AB-conjugates
    - CAR T cells
  - Hematopoietic cell transplantation
    - Donor type
    - Stem cell source
    - Conditioning regimen

Indication for Allogeneic HSCT

First Remission





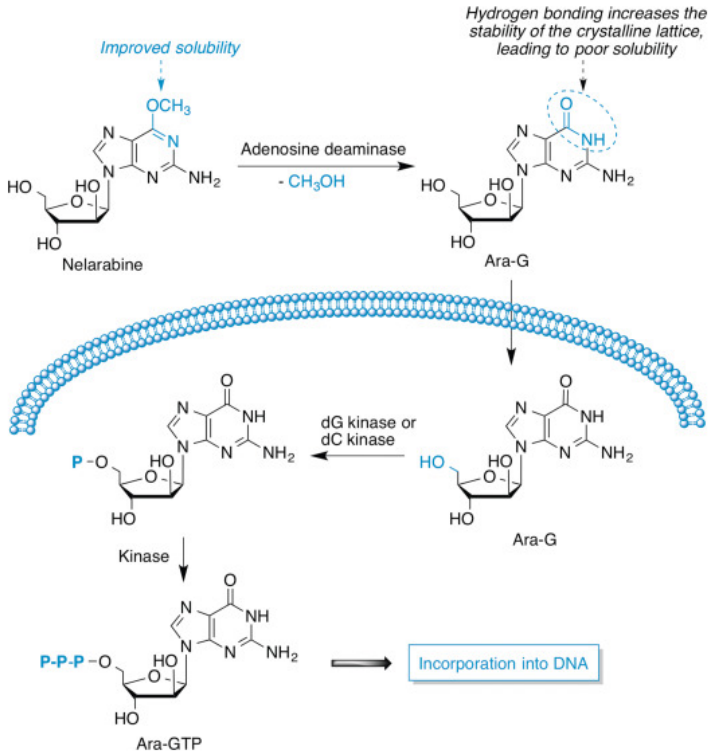
Second Remission: Risk Stratification

Children's oncology group (35)	**BFM group** (36)	**UK group** (37)	**IntReALL consortium**
Low Late B-ALL marrow, end-block 1 MRD <0.1% Late IEM, end-block 1 MRD <0.1%	Low (S1) Late IEM relapses	Standard Late IEM relapse	Standard (S1 and some S2) Early and late IEM relapses, of B-ALL or T-ALL Late B-ALL isolated marrow relapses Early/late B-ALL combined relapses
Intermediate Late B-ALL marrow, end-block 1 MRD ≥0.1% Late IEM, end-block 1 MRD ≥0.1%	Intermediate (S2) Early IEM relapses Late B-ALL isolated marrow relapses Early/late B-ALL combined relapses Very early IEM relapses	Intermediate Early IEM relapses Late B-ALL isolated marrow relapses Early/late B-ALL combined relapses	
High Early B-ALL marrow Early IEM T-ALL relapse, any site and timing	High (S3 and S4) Very early and early B-ALL marrow relapses Very early B-ALL combined relapses T-ALL marrow relapses (regardless of timing)	High Very early IEM relapse Very early and early B-ALL marrow relapses Very early B-ALL combined relapse T-ALL marrow or combined relapse, any timing	High (S3, S4 and some S2) All very early relapses, irrespective of site and phenotype Early B-ALL isolated marrow relapses T-ALL marrow relapses, combined or isolated (regardless of timing)

COG definitions: IEM relapse (<18 months from diagnosis), late IEM (≥18 months from diagnosis), early marrow relapse (<36 months from diagnosis), and late marrow relapse (≥36 months from diagnosis).
BFM and UK definitions: very early (<18 months from diagnosis), early (18 months from diagnosis but <6 months after end of treatment), and late (>6 months after end of treatment).
IEM, isolated extramedullary disease; B-ALL, B-cell-acute lymphoblastic leukemia; MRD, minimal residual disease; BFM Group, Berlin–Frankfurt–Munster Group; T-ALL, T-cell-acute lymphoblastic leukemia.

Truong J, et al. 2021.

Nelarabine

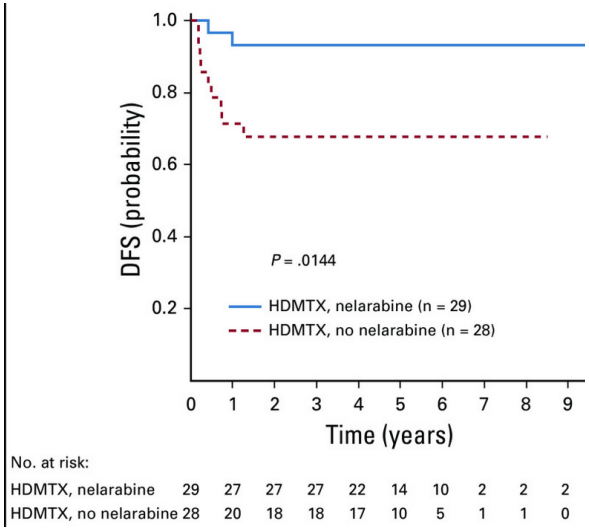


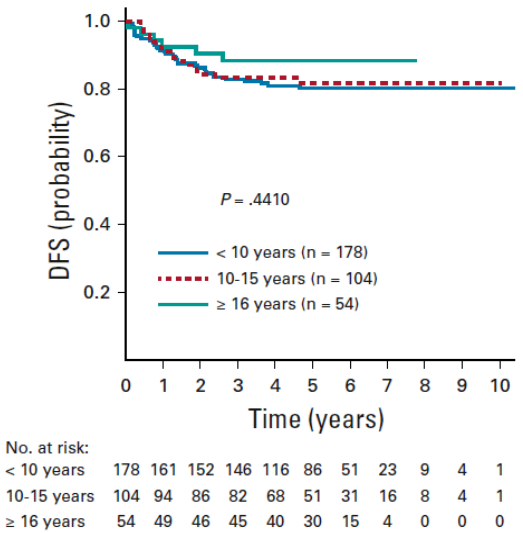
Nelarabine is the prodrug of 9-β-D-arabinofuranosylguanine (ara-G) which when phosphorylated intracellularly to ara-G triphosphate (ara-GTP), preferentially accumulates in cancerous T-cells. Ara-G is transported into the leukemic blast by 2 different transporters. It is then phosphorylated to ara-GTP. Upon incorporation of ara-GTP into DNA, apoptosis occurs as formation is terminated.

Roecker et al. *Clinic Med Insights*. 2010; Rondriguez et al. *Cancer Res*. 2002; Wang et al. *EJM Chem*. 2021

A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia, Children's Oncology Group AALL0434

Disease-free survival (DFS) for patients with CNS3 randomly assigned to high-dose methotrexate with leucovorin rescue (HDMTX) with or without nelarabine; 5-year DFS rates were 93.1% ± 6.5% for HDMTX with nelarabine and 67.9% ± 12.2% for HDMTX without nelarabine ($P = .014$).

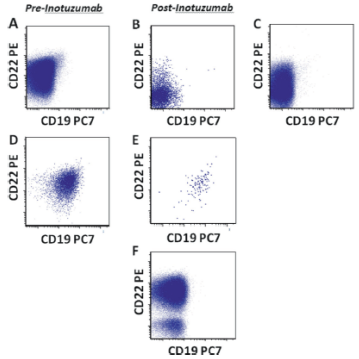




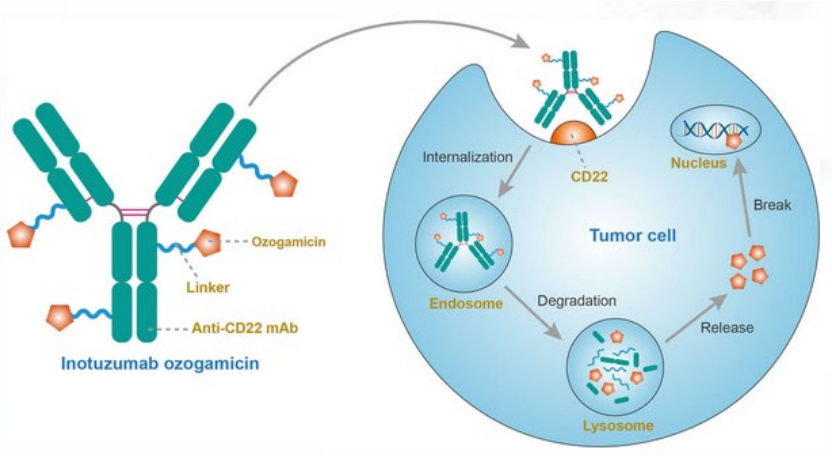
The addition of nelarabine to ABFM therapy improved DFS for children and young adults with newly diagnosed T-ALL without increased toxicity. Nelarabine decreased CNS relapses.
Nelarabine is safe and effective in the treatment of newly diagnosed T-ALL in children and young adults with excellent disease-free survival.

Dunsmore et al. *J Clin Oncol.* 2021;38:3282-3293.

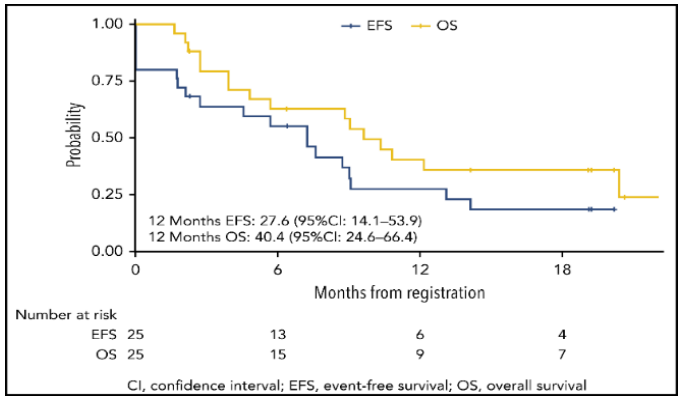
Inotuzumab-Ozogamicin



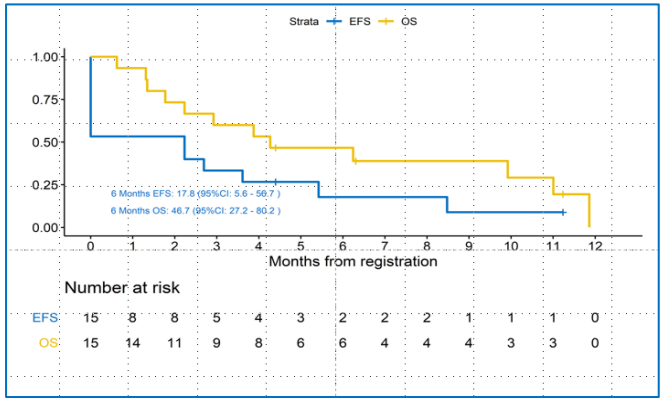
CD22 expression at relapse post-InO. CD22 expression in 2 patients evaluated pre- and post- InO and in 1 patient post-InO. CD22 is uniformly expressed on >99% B-lymphoblastic leukemia cells prior to InO (a, d); however, CD22 expression is diminished or absent (b, c, e) or absent in a subset of lymphoblasts (f) after InO



Bhojwani D, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Leukemia*. 2019

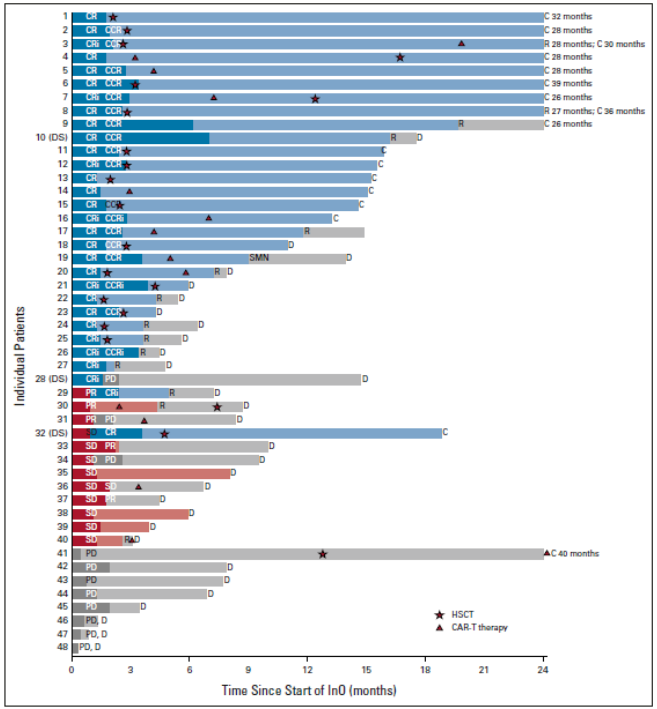


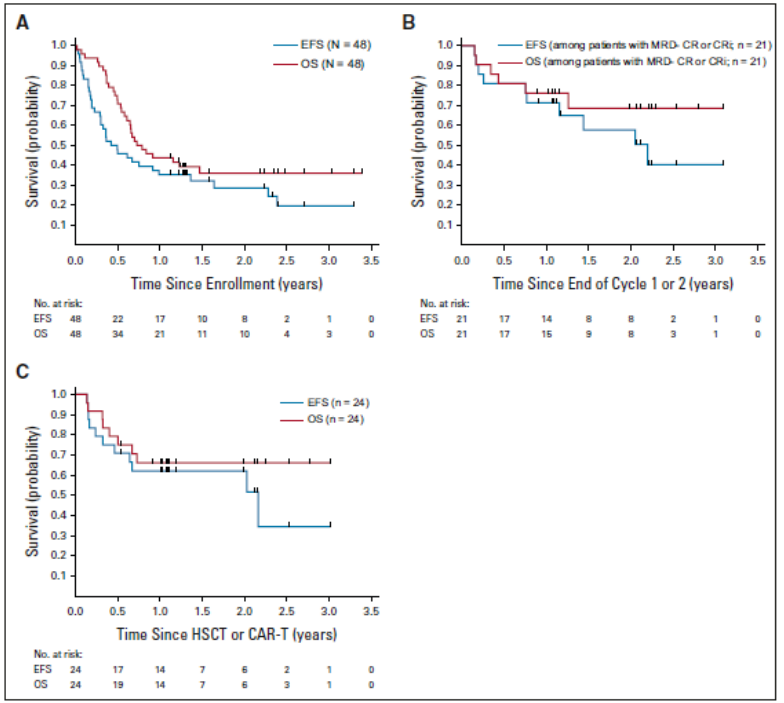
Brivio et al. A phase 1 study of inotuzumab ozogamicin in pediatric R/R ALL (ITCC-059 study). *Blood*. 2021



Brivio et al. Inotuzumab ozogamicin in infants and young children with r/refractory ALL: a case series. *Br J Haematol*. 2021

Phase II Trial of Inotuzumab Ozogamicin in Children and Adolescents With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia: Children's Oncology Group Protocol AALL1621

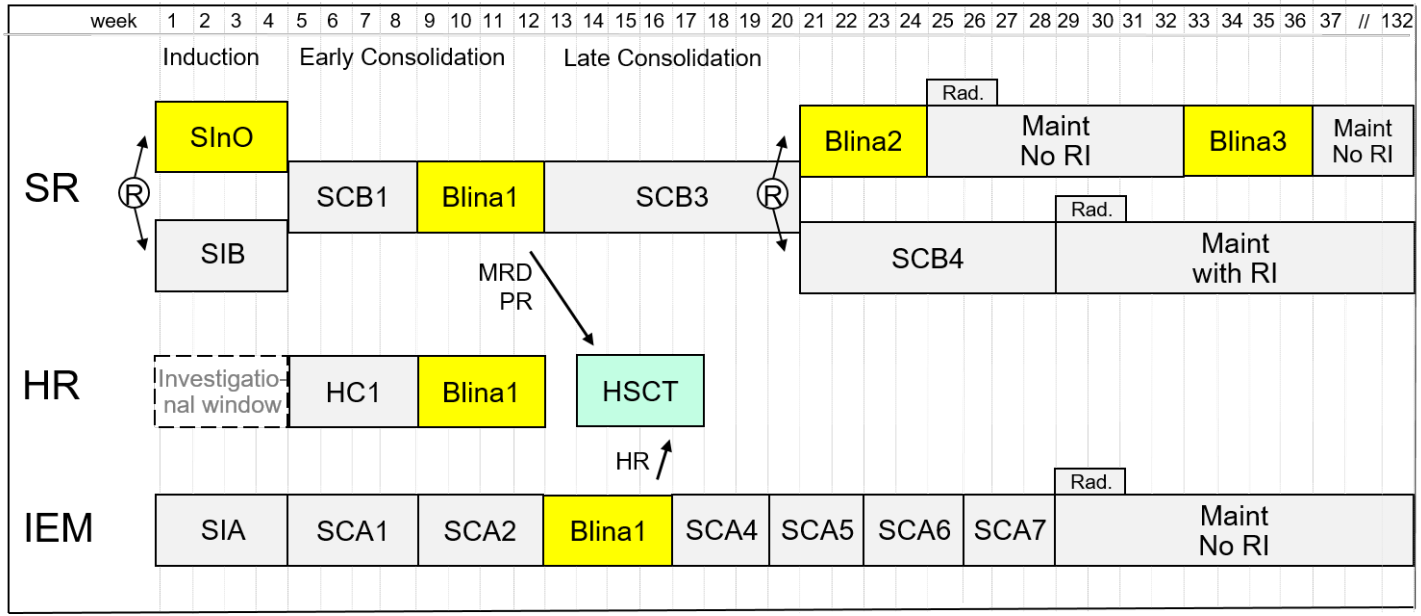




Caveat: prolonged cytopenia; VOD/SOS after HCT 28,6% grade 3

O'Brian et al. *J Clin Oncol.* 2022.

IntReALL BCP 2020



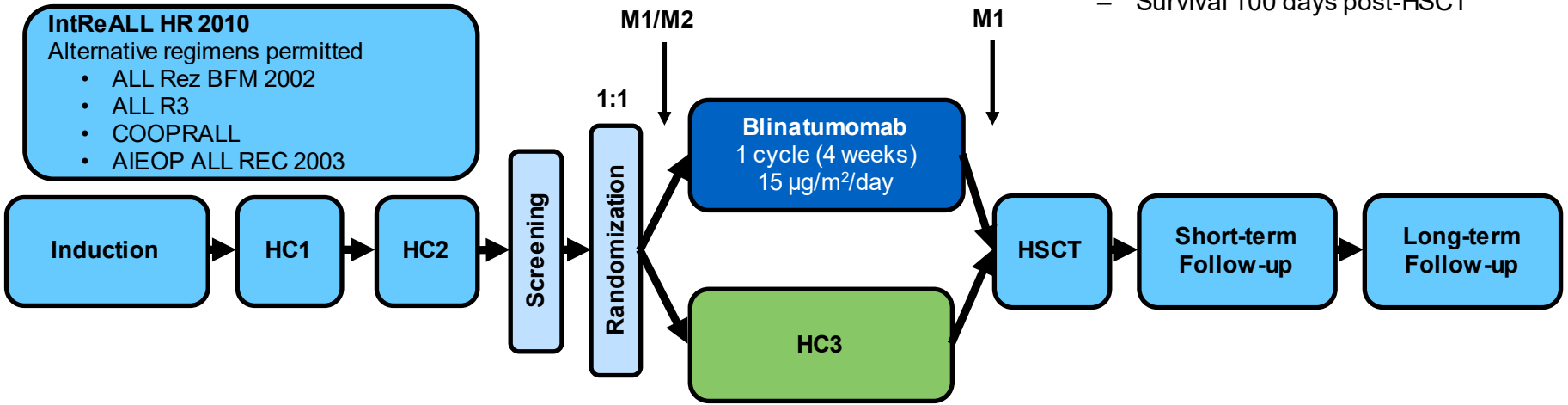
A. Attarbaschi, personal communication.

Amgen 20120215: Open-Label, Randomized, Phase III Trial – 47 Centers, 13 Countries

Key eligibility criteria
- Age >28 days <18 years
- HR first 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

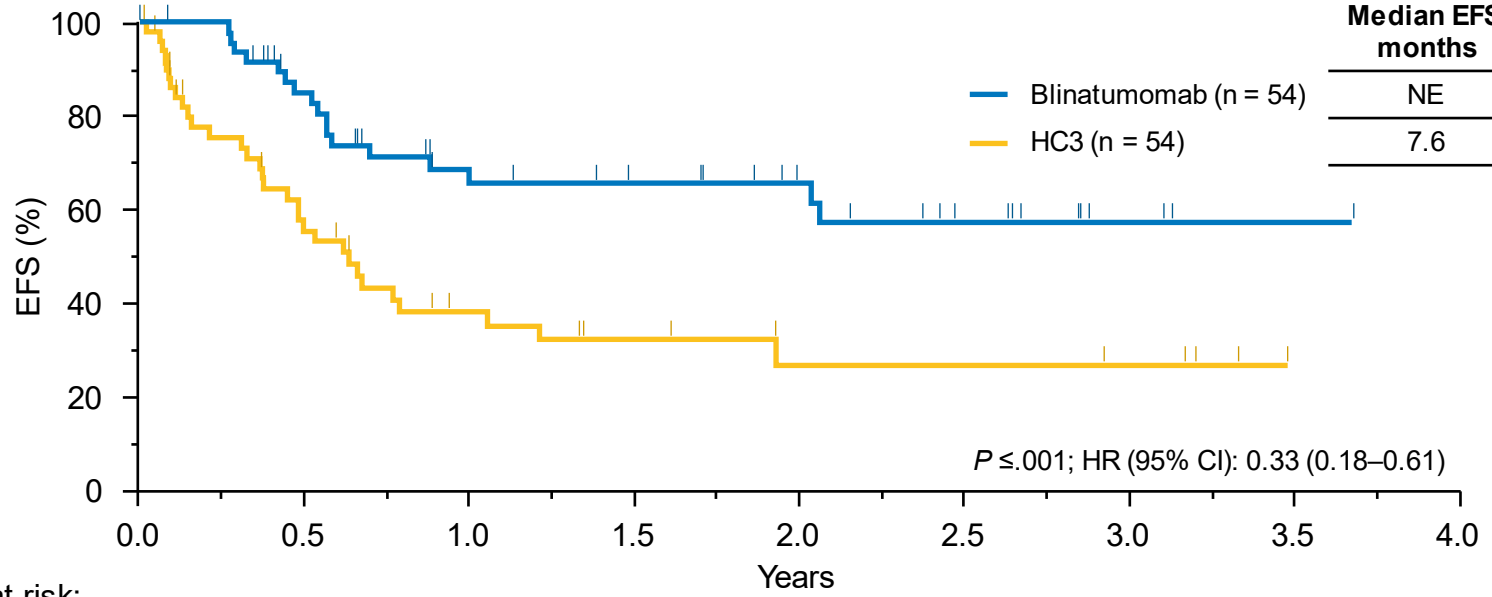
Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post-HSCT



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

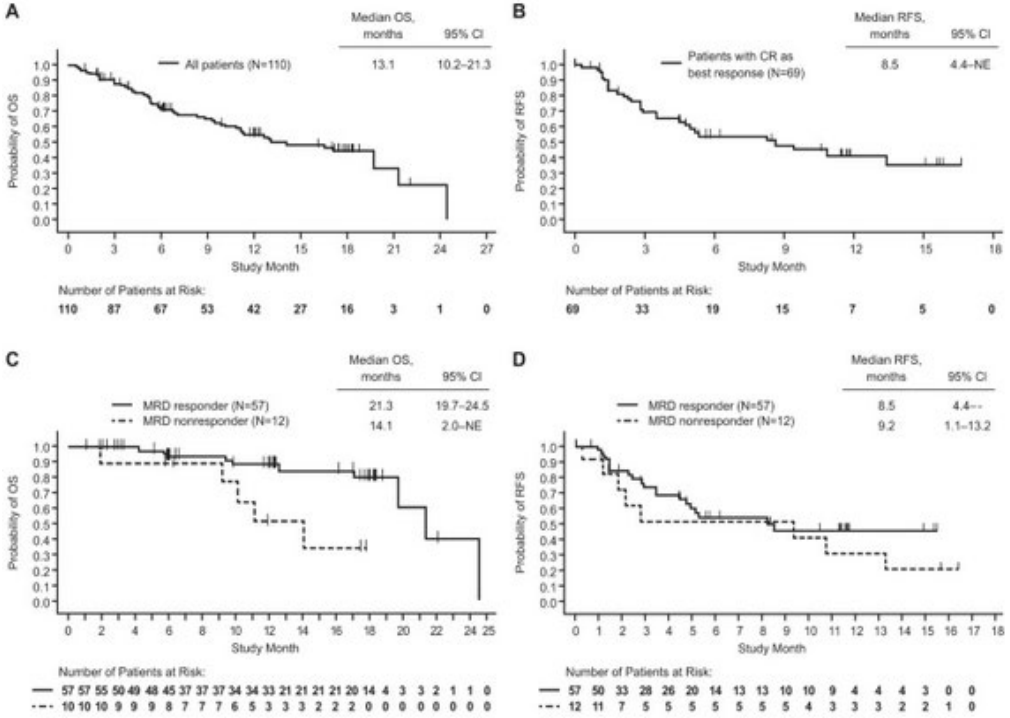
Patients at risk:

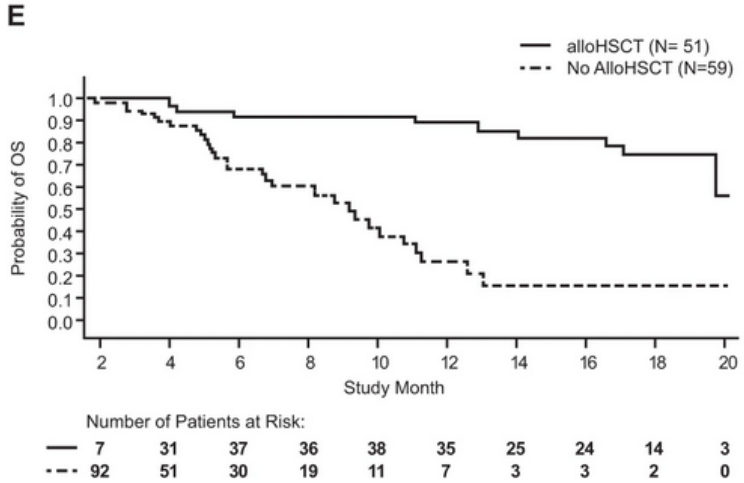
Blinatumomab	54	50	38	29	24	23	21	19	16	13	10	7	4	1	1	0
HC3	54	35	25	17	13	11	9	8	5	5	5	5	4	2	0	

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.

Infant ALL: Poorer Outcomes Compared With Older Children

- Biology: 80% *KMT2A*-rearrangement
- Treatment-related toxicity: 18.4% in prospective INTERFANT-trial
  - **Pieters R, et al. *Lancet*. 2007;370(9583):240-250.**
  - **Pieters R, et al. *J Clin Oncol.* 2019;37(25):2246-2256.**
- HSCT with TBI associated with several late effects
  - **Sanders JE, et al. *Blood.* 2005;105(9):3749-3756.**
- HSCT with chemo-conditioning is associated with higher relapse incidence
  - **Peters C, et al. *J Clin Oncol.* 2015;33(11):1265-1274.**
  - **Willasch AM, et al. *Bone Marrow Transplant*. 2020;55(8):1540-1551.**

Blinatumomab for Infants

- Clesham K, et al. *Blood*. 2020;135(17):1501-1504.
- Sutton R, et al. *Pediatr Blood Cancer.* 2021;68(5):e28922.
- Popov A, et al. 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.

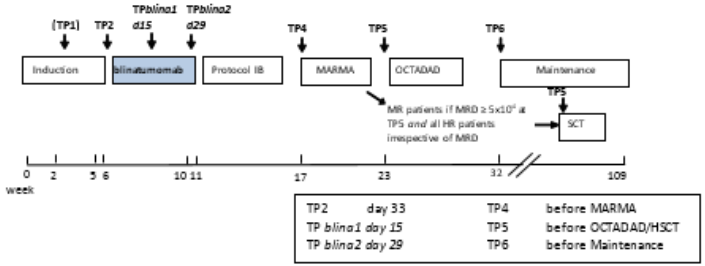


Table 1 Patient characteristics

	N=28
Age at diagnosis	
< 6 months	18 (64%)
≥ 6 months	10 (36%)
Gender	
male	11 (39%)
female	17 (61%)
Risk group	
Medium risk	19 (68%)
High risk	9 (32%)
End of induction	
M1	26 (93%)
M2	2 (7%)
MRD end of induction	
Low < 0.05%	17 (61%)
High ≥ 0.05%	11 (39%)

Table 2 MRD results

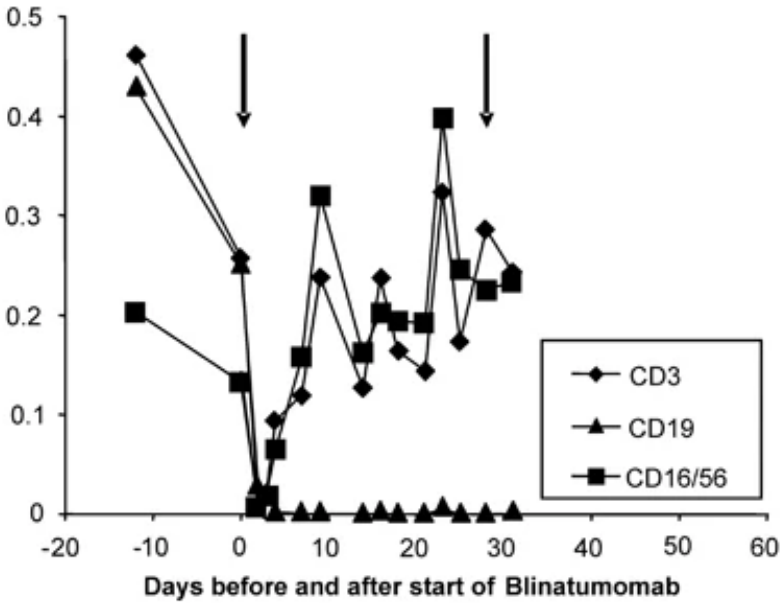
	Blina infant				IF06	MRD neg Blina infant vs IF06
MRD	number of patients	Neg	Pos <QR*	Pos	MRD neg	p-value
EOI	28	8 (29%)	5 (18%)	15 (54%)	19%	0.3169
Day 15 blina	28	15 (54%)	9 (32%)	4 (14%)	-	
Day 29 blina	28	15 (54%)	10 (36%)	3 (11%)	-	
TP4 before MARMA	26	15 (58%)	8 (30%)	3 (12%)	40%	0.1356
TP5 before OCTADAD/HSCT	23	19 (83%)	4 (17%)	0	63%	0.0997
TP6 before maintenance **	14	14 (100%)	0	0	NA	

*QR quantitative range, varied from 0.05 to 0.005%. NA not available
**MR patients only; IF06 Interfant06 as historical control

Van Der Sluis et al. *Blood.* 2021;138.

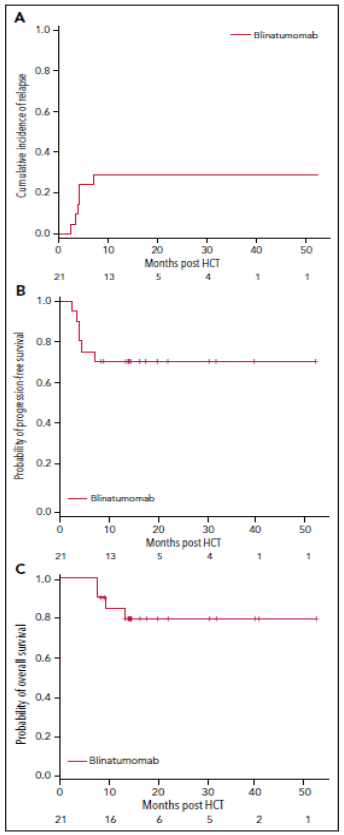
Blinatumomab After HSCT

- Handgretinger R, et al. *Leukemia.* 2011;25(1):181-184.
- Schlegel P, et al. *Haematologica.* 2014;99(7):1212-1219.
- Wu H, et al. *Am J Cancer Res.* 2021;11(6):3111-3122.
- Stein AS, et al. *Biol Blood Marrow Transplant.* 2019;25(8):1498-1504.
- Alcharakh M, et al. *Immunotherapy.* 2016;8(8):847-852.
- **Blinatumomab after T-cell receptor (TCR) alpha/beta-depleted HSCT (NCT04746209): Phase II**
- **Blinatumomab for MRD in pre-B-ALL patients following HSCT (NCT04044560): FORUM add on trial**



Handgretinger et al. *Leukemia.* 2011.

Blinatumomab After HSCT



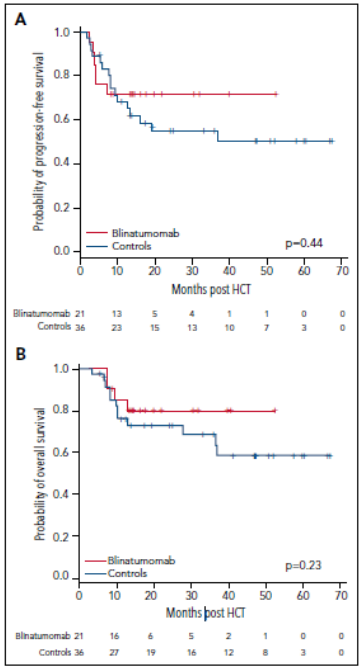
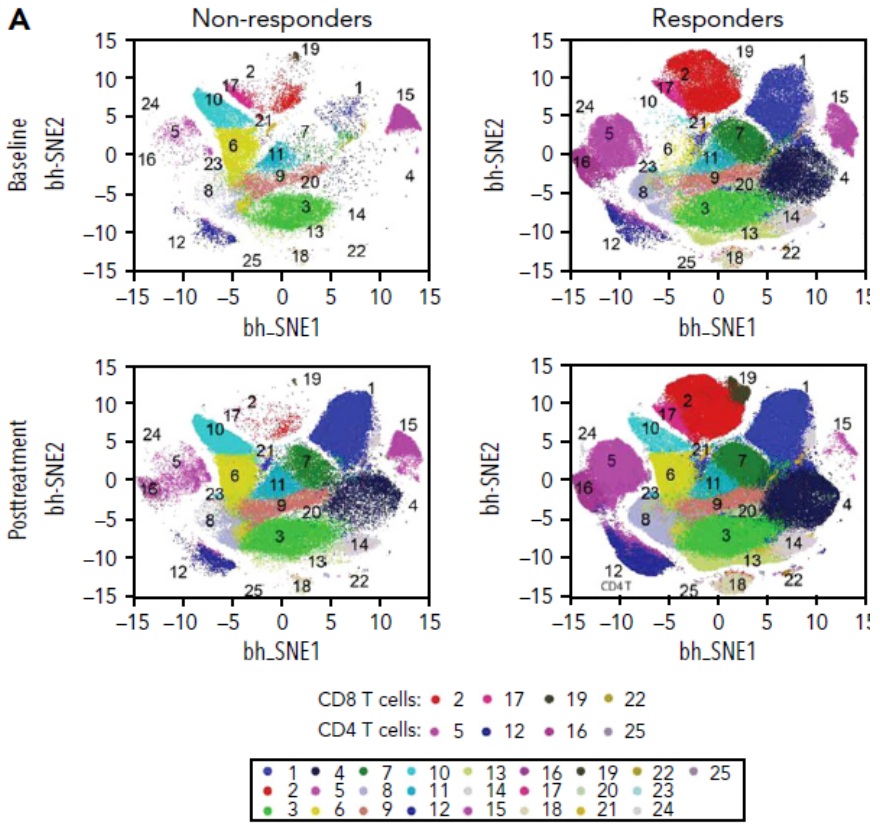


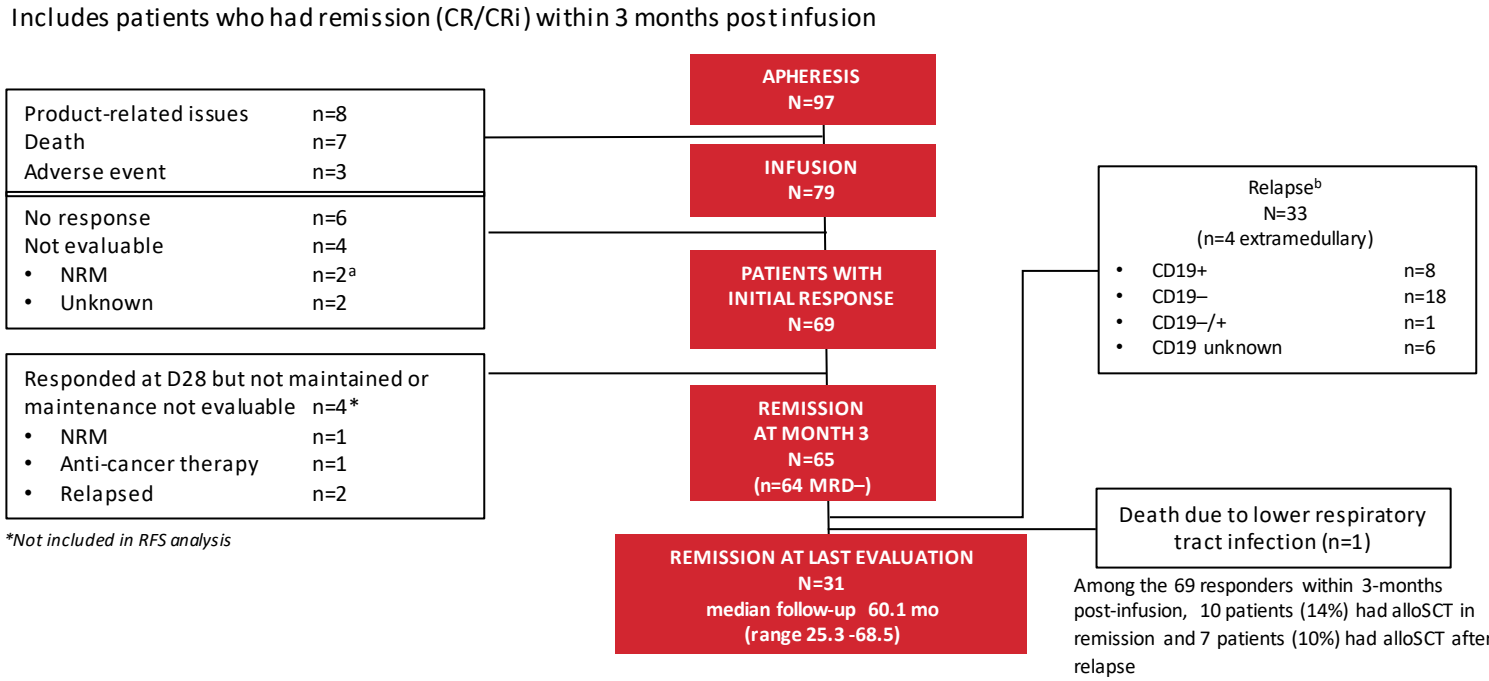
Figure 4. Comparison of PFS and OS between patients treated with blinatumomab maintenance and no posttransplant maintenance (matched-case cohort). At 1 year, the rates of PFS for the blinatumomab vs the control group were 71% vs 68%, P = .44 (A), and the rates for OS for the blinatumomab vs the control group were 85% vs 76%, P = .23 (B).



Subpopulations identified via viSNE analysis of 14 surface markers in all 56 samples. (A) viSNE map for nonresponders and responders color-coded according to PhenoGraph cluster annotation. viSNE maps were separated to baseline and posttreatment in both nonresponders and responders groups.

Gaballa et al. Blinatumomab maintenance after allogeneic hematopoietic cell transplantation for B-lineage acute lymphoblastic leukemia. *Blood.* 2022

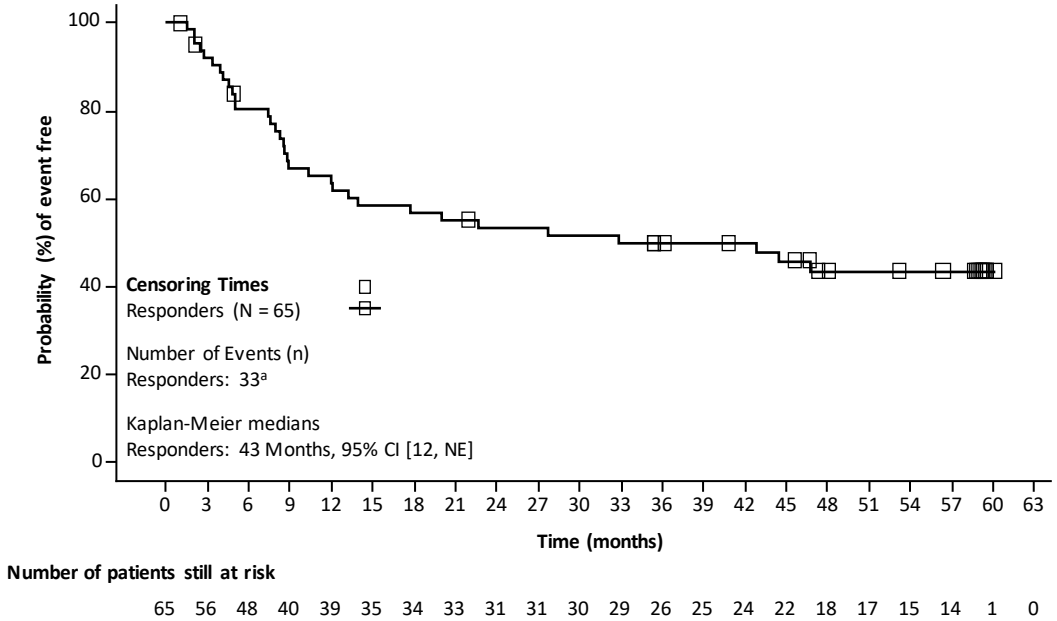
ELIANA Update: Patient Flow Chart



[a]Patient with Down syndrome died due to cerebral hemorrhage. [b]CD19 status at relapse was characterized based on MFC-MRD assay and NGS analysis. (Pulsipher et al. 2022, *Blood Cancer Discovery*).
alloSCT, allogeneic stem cell transplantation; CR, complete remission; CRi, CR with incomplete blood count recovery; D, day; MFC, multiparametric flow cytometry; MRD, minimal residual disease; mo, month; NGS, next-generation sequencing; NRM, non-relapse related mortality; RFS, relapse-free survival.

Rives et al. EHA 2022. Abstract 5112.

ELIANA Update: RFS for Patients With a CR/CRi Within 3 Months



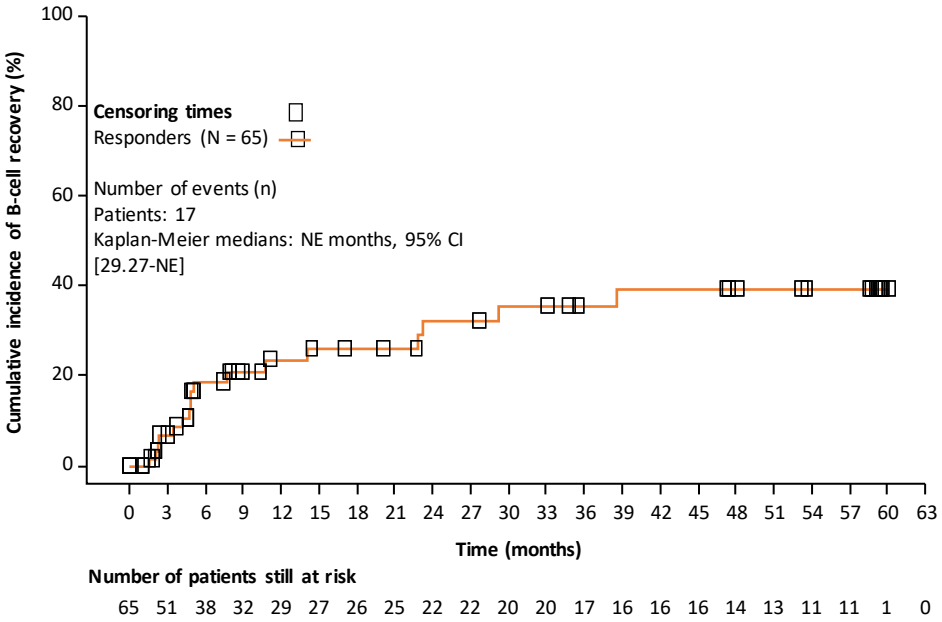
- No new long-term treatment-related safety events were observed in this longer-term >5-year follow-up
- Long-term remission rates up to 5.9-years of follow-up from ELIANA demonstrate that tisagenlecleucel may be a curative treatment option for heavily pretreated pediatric and young adult patients with R/R B-ALL

5-year RFS: 44% (95% CI, 31%-56%)

Note: RFS is without censoring for SCT and other cancer therapies
[a]One patient who died at Month 17 while in CR was censored as the event happened after at least 2 missing assessments.
CR, complete remission; CRi, CR with incomplete blood count recovery; NE, not estimable; RFS, relapse-free survival; SCT, stem cell transplant.

Rives et al. EHA 2022. Abstract 5112.

ELIANA Update: B-Cell Recovery



- The probability of B-cell aplasia at:
  - Month 6 was 83% (95% CI, 71%–91%)
  - Month 12 was 71% (95% CI, 57%–82%)
- Patients with B-cell recovery experienced a 2-year cumulative incidence of relapse of 40%
- Median time to B-cell recovery was 39 months in responders

Note: B-cell recovery is censored for HSCT.
(H)SCT, (hematopoietic) stem cell transplantation; NE, not estimable.

Rives et al. EHA 2022. Abstract 5112.

CAR T Cells for Infant BCP-ALL

	Participants
Whole cohort (n=38)	
Age at diagnosis, months	5·2 (2·6–7·6)
Sex	
Female	17 (45%)
Male	21 (55%)
White blood cell count at diagnosis, × 10^9 cells per L	375 (130–797)
Presenting with CNS involvement	18/32 (47%)
Treated according to Interfant-06 protocol	31 (82%)
KMT2A rearrangement	29 (76%)
Refractory to one or more previous treatment lines	19 (50%)
Previous HSCT	25 (66%)
Number of previous lines of therapy not including HSCT	2 (2–3)
Previous inotuzumab	7 (18%)
Previous blinatumomab	14 (37%)
Participants who received a tisagenlecleucel infusion (n=35)	
Median age at infusion, months	17·0 (14·9–24·6)
Bone marrow disease burden before lymphodepletion	
Median (IQR)	5% (0·2–31·0)
Measurable residual disease negative	7 (20%)
0–<1%	5 (14%)
1–<5%	5 (14%)
5–<10%	2 (6%)
10–<50%	9 (26%)
50–100%	7 (20%)
CNS disease before lymphodepletion	1 (3%)

Data are median (IQR), n (%), or n/N (%). Data on race or ethnicity were not collected. HSCT=haematopoietic stem-cell transplantation. *n=34.

Table 1: **Baseline characteristics**

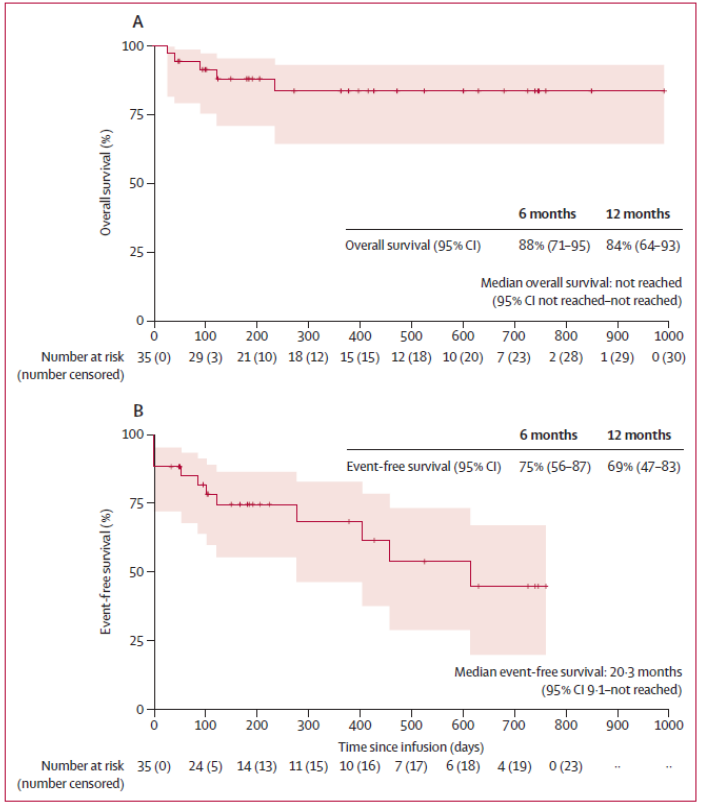


Figure 2: **Overall survival and event-free survival**

Ghorashian et al. Tisagenlecleucel therapy for relapsed or refractory B-cell acute lymphoblastic leukaemia in infants and children younger than 3 years of age at screening: an international, multicentre, retrospective cohort study. *Lancet Haematol.* 2022

CAR T Cells for Infant BCP-ALL

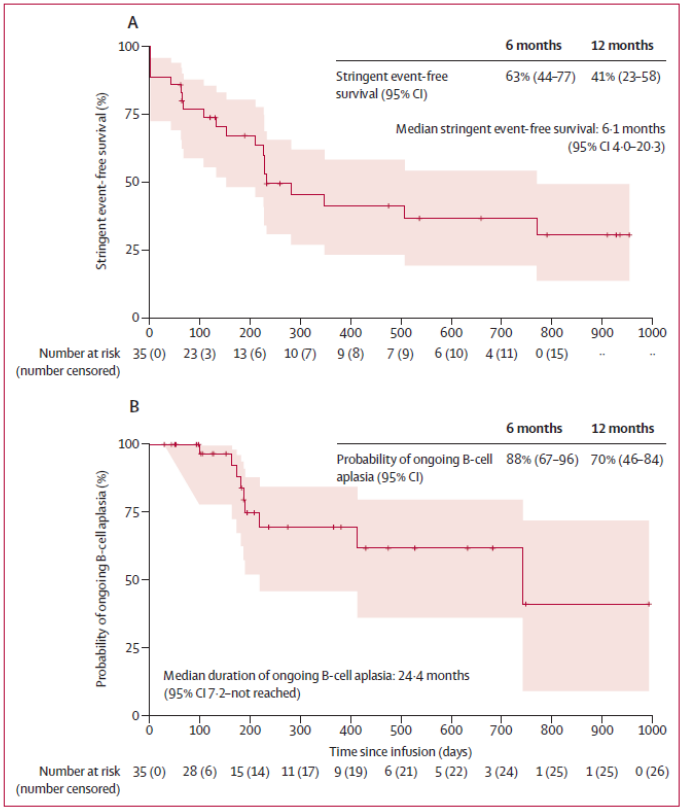


Figure 3: **Stringent event-free survival and probability of ongoing B-cell aplasia**
(A) Stringent event-free survival. (B) Ongoing B-cell aplasia. Shaded areas are 95% CIs.

	Patients who received a tisagenlecleucel infusion (n=35)	ELIANA cohort (n=75)
Cytokine release syndrome		
Any grade	21 (60%)	58 (77%)
Grade 1–2	16 (46%)	23 (31%)
Grade 3	3 (9%)	16 (21%)
Grade 4	2 (6%)	19 (25%)
Median duration, days	1·5 (0·0–4·0)	8·0 (NR–NR)
Tocilizumab administered	8 (23%)	28 (37%)
Managed in ICU	9 (26%)	35 (47%)
Median duration in ICU, days	2 (2–10)	7 (NR–NR)
Neurotoxicity or immune effector cell-associated neurotoxicity syndrome		
Any grade	9 (26%)	30 (40%)
Grade 1–2	9 (26%)	20 (27%)
Grade 3	0	10 (13%)
Grade 4	0	0
Cytopenia for ≥30 days		
Any grade	15/23 (65%)	28 (37%)
Grade 1–2	3/23 (13%)	4 (5%)
Grade 3	9/23 (39%)	12 (16%)
Grade 4	3/23 (13%)	12 (16%)
Hypogammaglobulinaemia	27/31 (87%)	NR
Infection		
Any grade	10/34 (29%)	32 (43%)
Grade 1–2	2/34 (6%)	14 (19%)
Grade 3	8/34 (24%)	16 (21%)
Grade 4	0/34	2 (3%)

Data are median (IQR), n (%), or n/N (%). ICU=intensive care unit. NR=not reported.

Table 2: **Toxicity of tisagenlecleucel therapy**

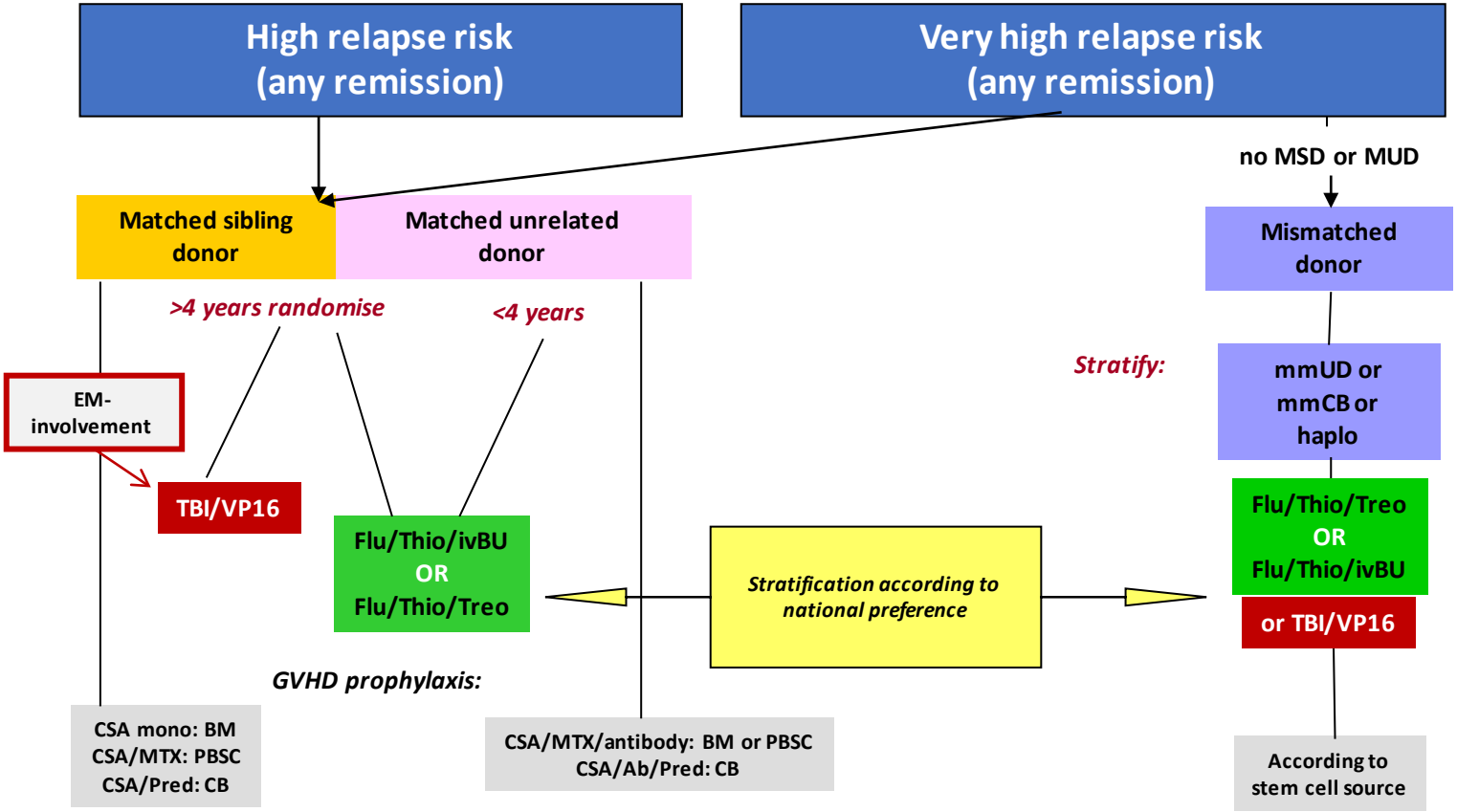
Ghorashian et al. Tisagenlecleucel therapy for relapsed or refractory B-cell acute lymphoblastic leukaemia in infants and children younger than 3 years of age at screening: an international, multicentre, retrospective cohort study. *Lancet Haematol.* 2022

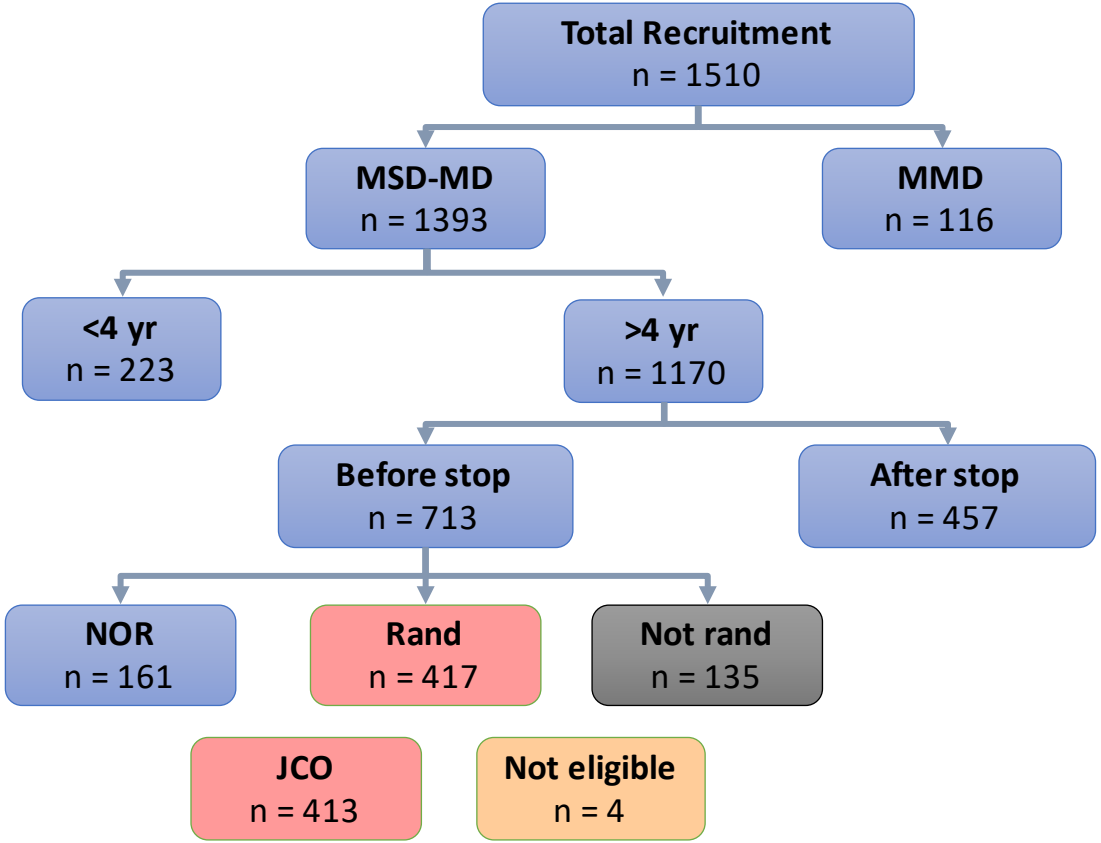
ALLO-SCT FOR CHILDREN AND ADOLESCENTS WITH ALL: ALL SCT ped FORUM

(FOR OMITTING RADIATION UNDER MAJORITY AGE)

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

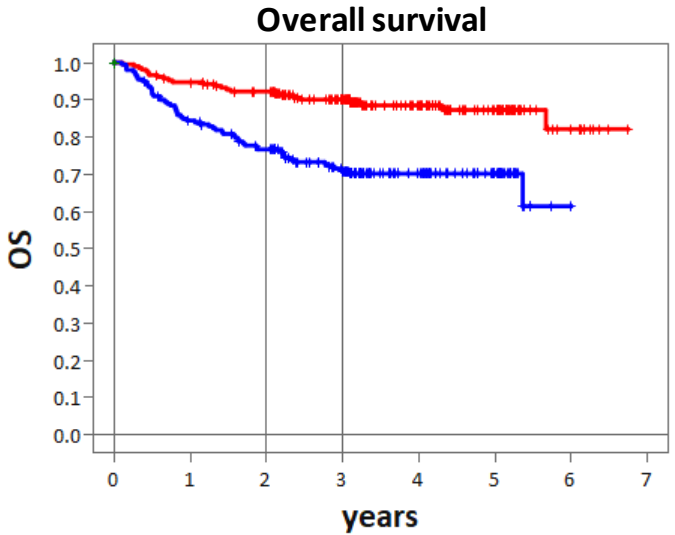
Study Design: ALL SCT ped FORUM 2012

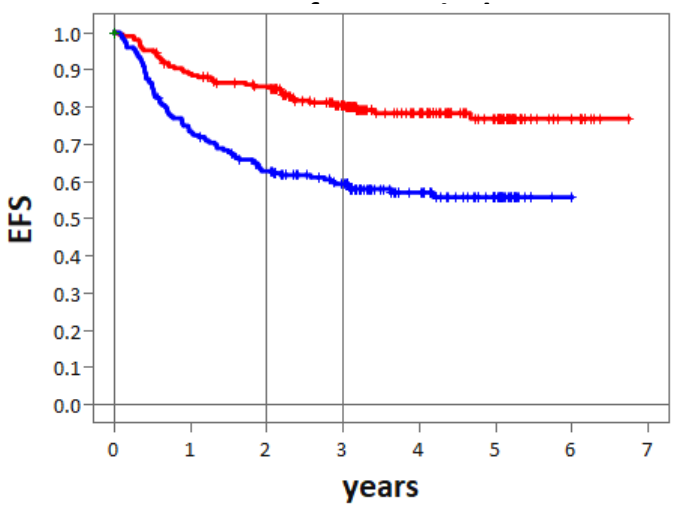




Peters et al. *J Clin Oncol.* 2021.

MSD/MD ≥4 Years, Randomised, Intention to Treat

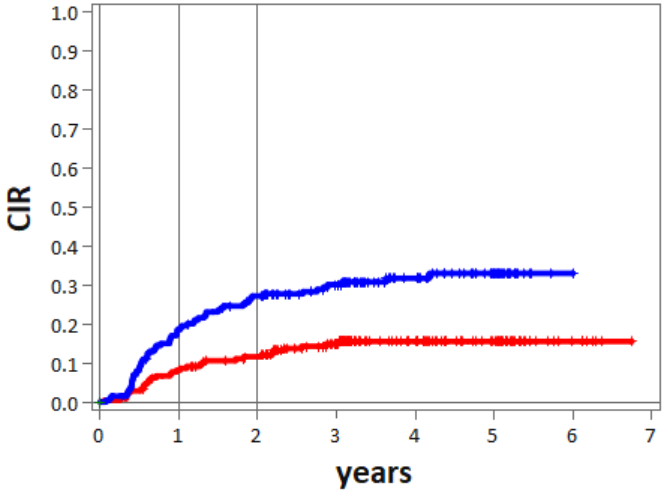


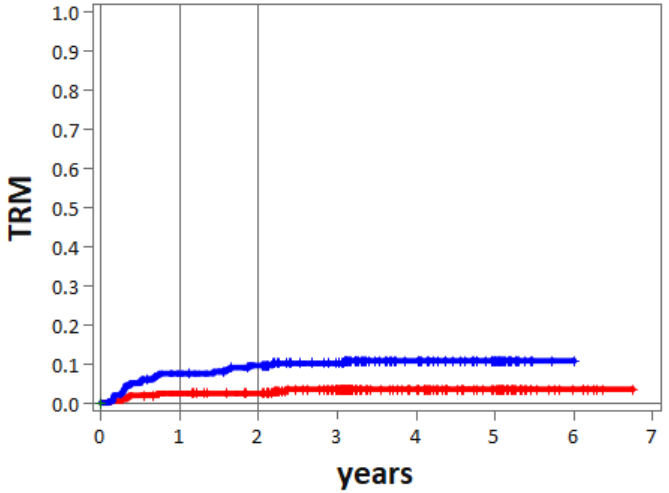


	Patients	Events (+)	2-yr OS	3-yr OS	*P* value	Events (+)	2-yrs EFS	3-yrs. EFS	*P* value
TBI/VP16	212	24 (+5)	0.92±0.02	0.90±0.02	<.001	43 (+12)	0.86±0.02	0.81±0.03	<.001
CHC	201	58 (+9)	0.77±0.03	0.71±0.03	.	84 (+12)	0.63±0.04	0.59±0.04	.

Med observation time: 3.7 years

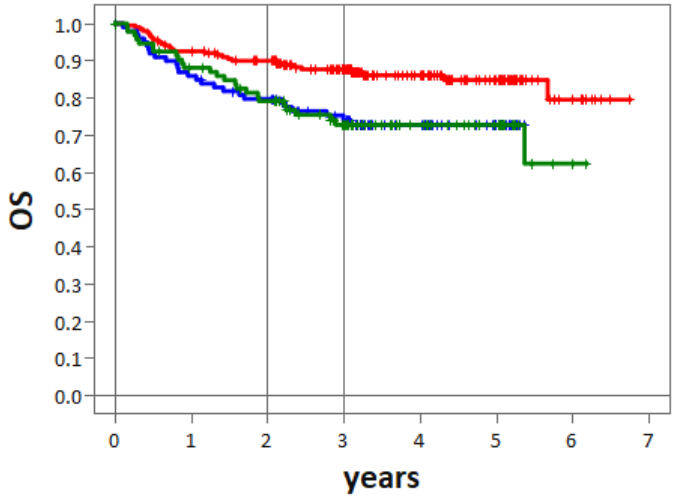
MSD/MD ≥4 Years, Randomised, Intention to Treat

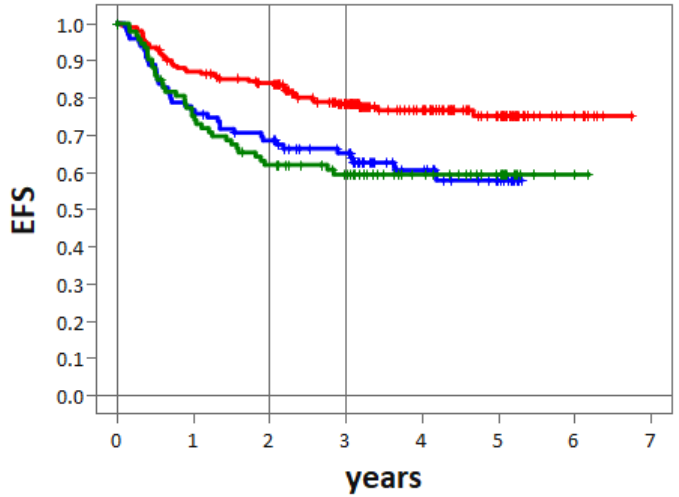




		Relapses		TRM		Sec. mal	EFS
Arm	Patients	Relapses	2-yr CIR	TRM	2-yr CI		2-yr EFS
TBI/VP16	212	31 (+7)	**0.12±0.02**	7	**0.02±0.01**	+5	**0.86±0.03**
CHC	201	63 (+8)	0.27±0.03	21 (+4)	0.10±0.02	+1	0.63±0.04
P value	.	.	<.001	.	.007	.	<.001

MSD/MD >4 Years, Randomised, as Treated

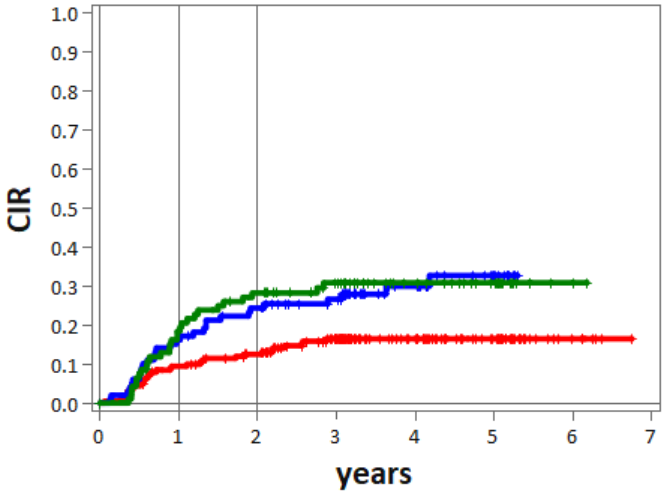


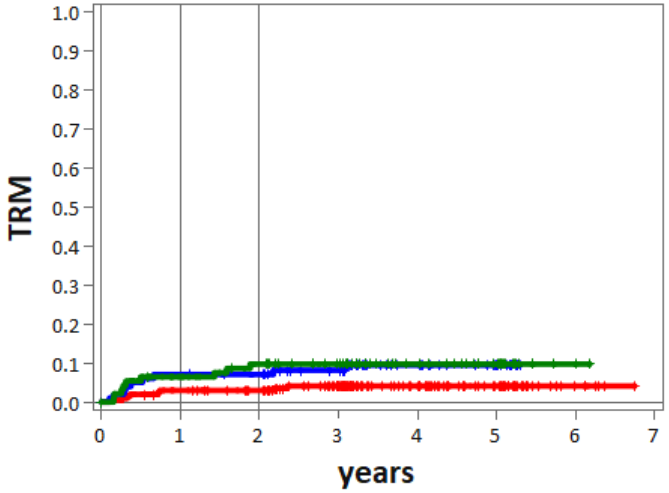


Given	Patients	Eval patients	Events	2-yr OS	3-yr OS	*P* value
TBI	202	202	28	0.90±0.02	0.88±0.02	.006
BU	100	100	26	0.80±0.04	0.74±0.04	.
TREO	93	93	25	0.79±0.04	0.73±0.05	.

Events	2-yr EFS	3-yr EFS	*P* value
45	0.84±0.03	0.78±0.03	.001
38	0.69±0.05	0.65±0.05	.
37	0.62±0.05	0.59±0.05	.

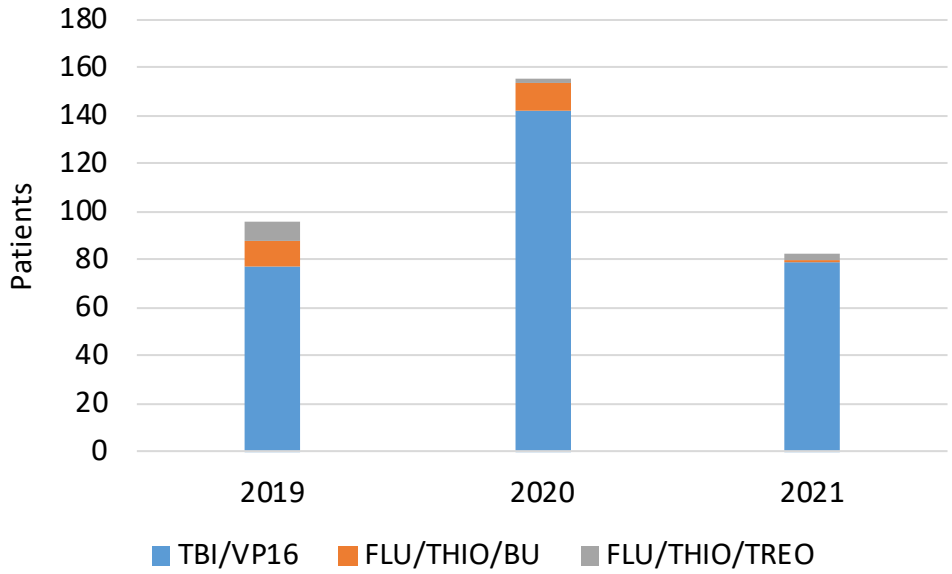
MSD/MD >4 Years, Randomised, as Treated



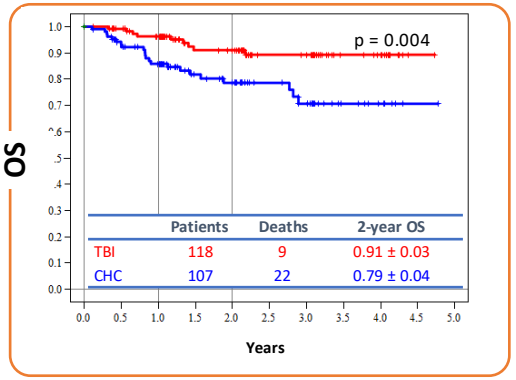


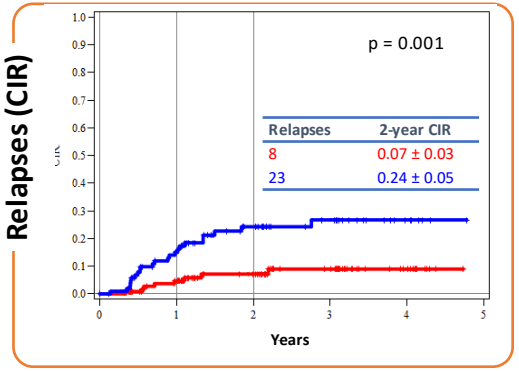
Given	Patients	n(CIR)	2-yr CIR	n(TRM)	2-yr TRM	n(Sec. mal)	2-yr EFS
TBI	202	32	0.12±0.02	8	0.03±0.01	5	0.84±0.03
BU	100	30	0.24±0.04	9	0.07±0.03	0	0.69±0.05
TREO	93	28	0.28±0.05	9	0.10±0.03	0	0.62±0.05
P value	.	.	.007	.	.111	.	.001

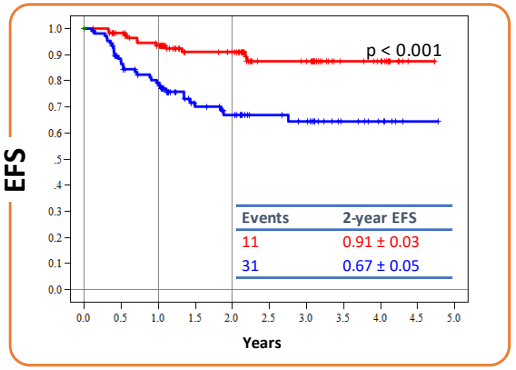
MSD/MD ≥4 Years, After Rando-Stop, n = 342 (transplanted before Oct 2021)

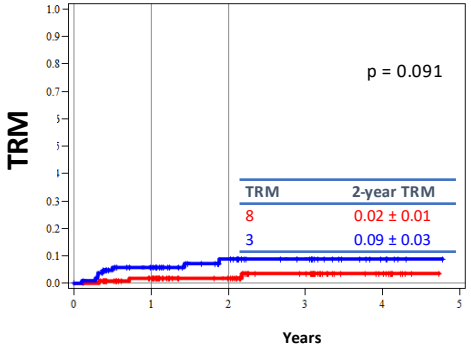


MSD/MD ≥4 Years, Randomised, CR1 Intention to Treat

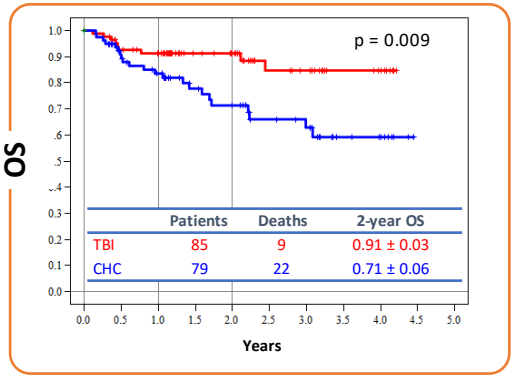


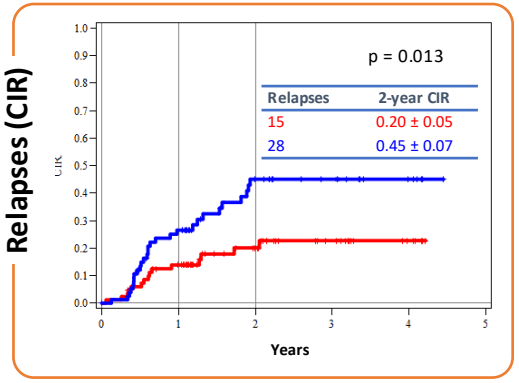


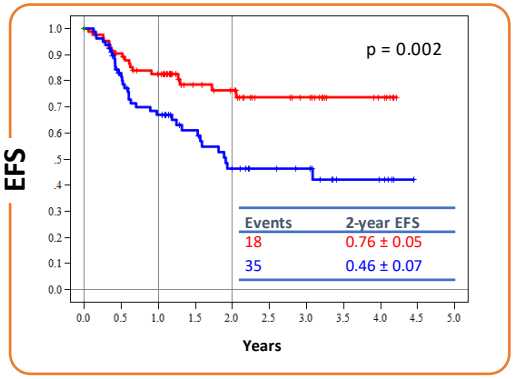


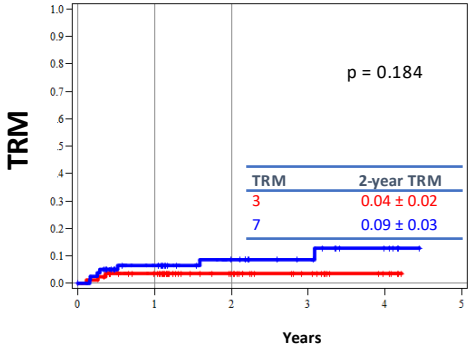


MSD/MD ≥4 Years, Randomised, CR1 Intention to Treat

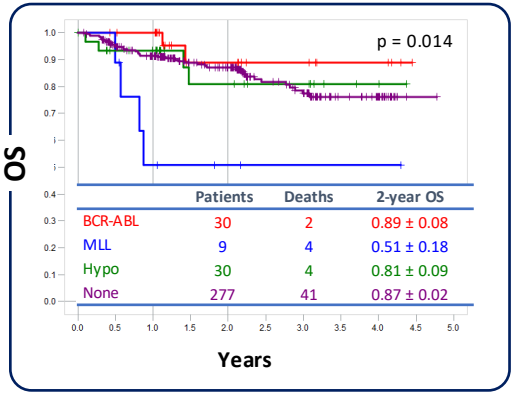


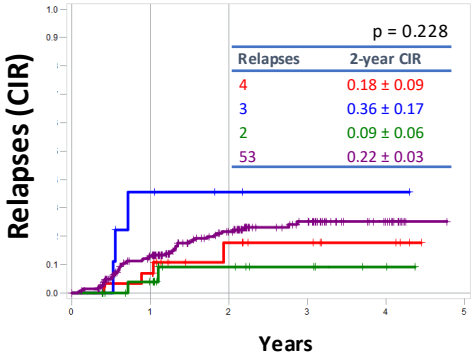


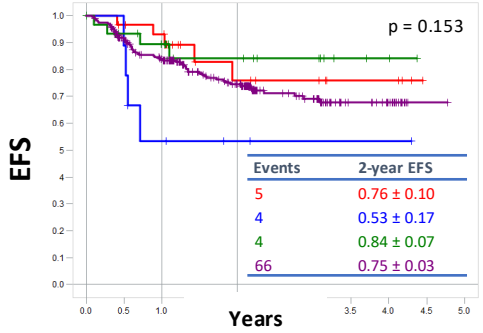


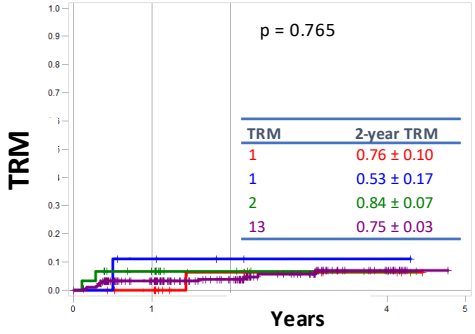


MSD/MD ≥4 Years, Randomised, Chromosomal Aberrations



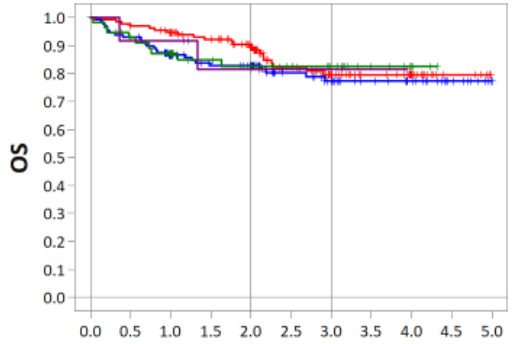






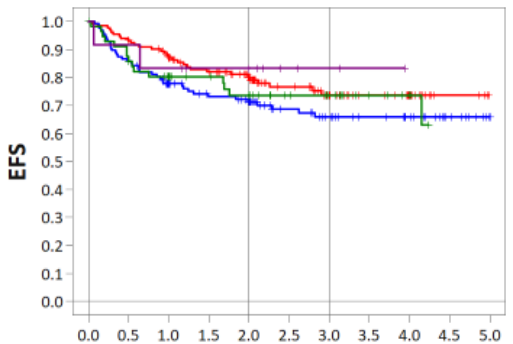
MSD/MD ≥4 Years, Randomised, MRD pre-SCT

OS



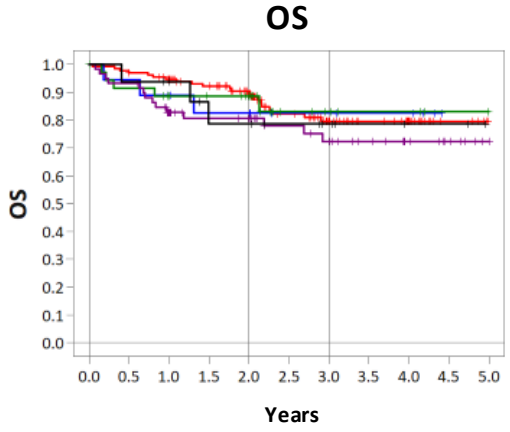
	Patients	Events	2-year OS	3-year OS	*P* value
MRD– (PCR)	132	21	0.89 ± 0.03	0.79 ± 0.04	.714
MRD+(PCR)	129	27	0.83 ± 0.03	0.77 ± 0.04	.
MRD–(FCM)	56	9	0.83 ± 0.05	0.83 ± 0.05	.
MRD+(FCM)	12	2	0.81 ± 0.12	0.81 ± 0.12	.

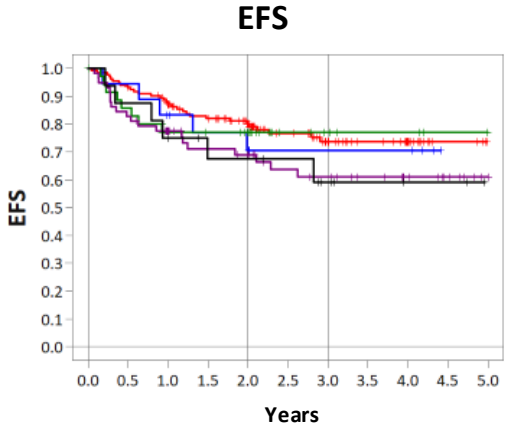
EFS



Events	2-year EFS	3-year EFS	*P* value
30	0.80 ± 0.04	0.74 ± 0.04	.395
39	0.71 ± 0.04	0.66 ± 0.05	.
15	0.74 ± 0.06	0.74 ± 0.06	.
2	0.83 ± 0.11	0.83 ± 0.11	.

MSD/MD ≥4 Years, Randomised, MRD pre-SCT

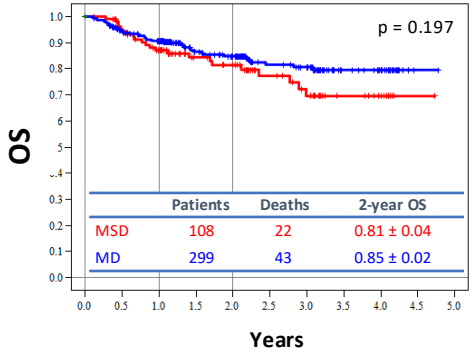


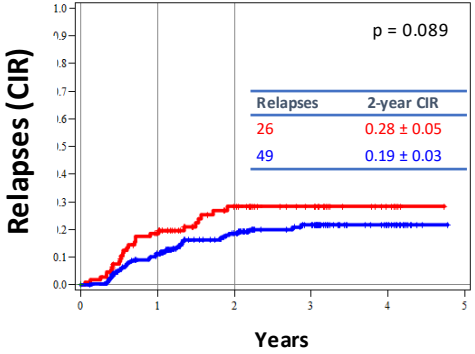


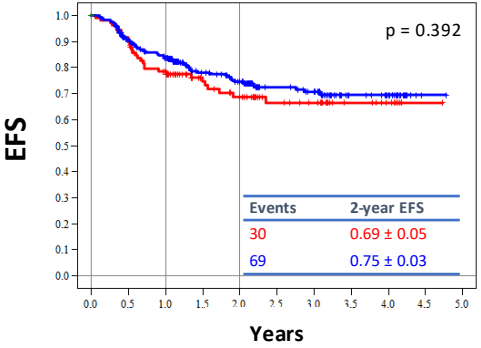
pcr_g	Patients	Eval. patients	Events	2-year OS	3-year OS	*P* value
Neg	132	132	21	0.89 ± 0.03	0.79 ± 0.04	.634
10^{-6}	19	18	3	0.83 ± 0.09	0.83 ± 0.09	-
10^{-5}	35	35	6	0.89 ± 0.05	0.83 ± 0.07	-
10^{-4}	59	59	14	0.81 ± 0.05	0.72 ± 0.07	-
$>10^{-4}$	16	16	4	0.79 ± 0.11	0.79 ± 0.11	-

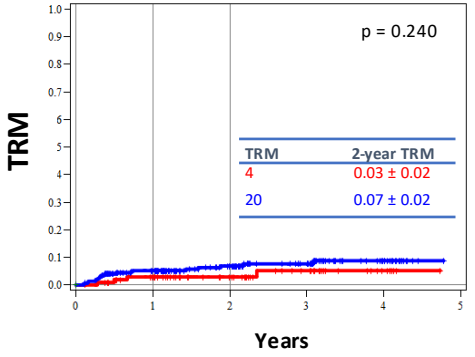
Events	2-year EFS	3-year EFS	*P* value
30	0.80 ± 0.04	0.74 ± 0.04	.375
5	0.71 ± 0.11	0.71 ± 0.11	-
8	0.77 ± 0.07	0.77 ± 0.07	-
20	0.69 ± 0.06	0.61 ± 0.07	-
6	0.68 ± 0.12	0.59 ± 0.13	-

MSD/MD ≥4 Years, Randomised, Donor Type



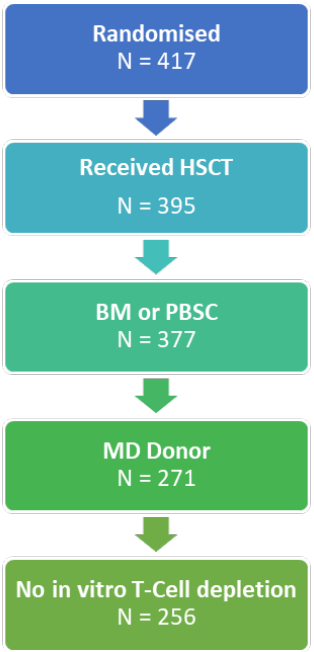






Research Question and Study Cohort

Impact of stem cell source PBSC vs BM from MUD on clinically relevant outcomes in randomized FORUM cohort?



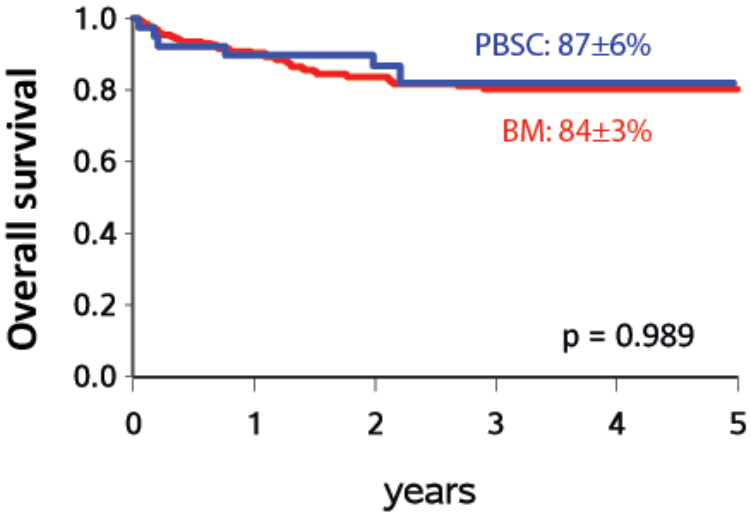
Median observation time
3.1 years

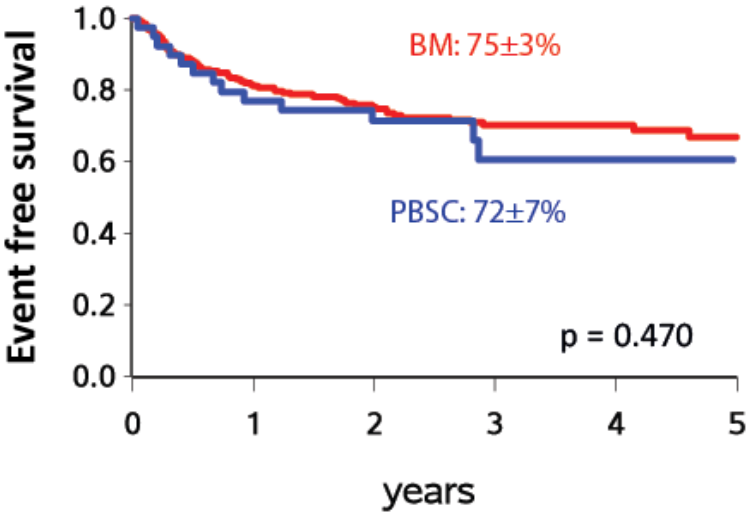
GVHD-prophylaxis:

CSA/ATG/MTX short

Roland Meissel personal communication.

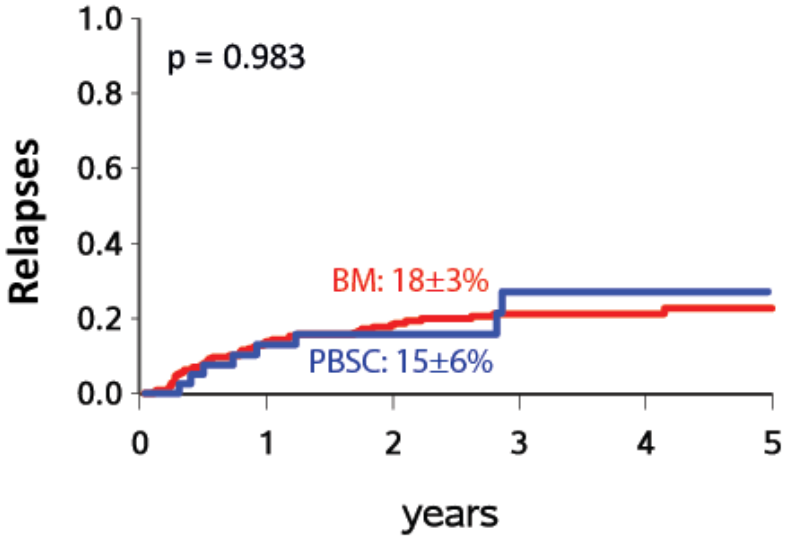
Outcome 1: Equivalent OS and EFS

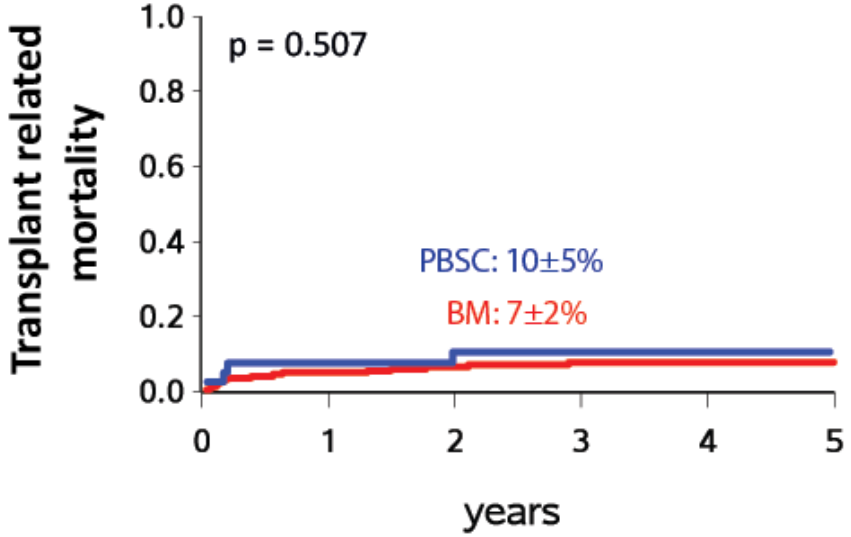




Roland Meissel personal communication.

Outcome 1: Equivalent CIR and TRM

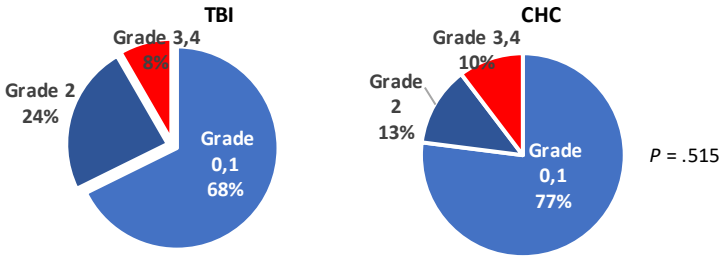




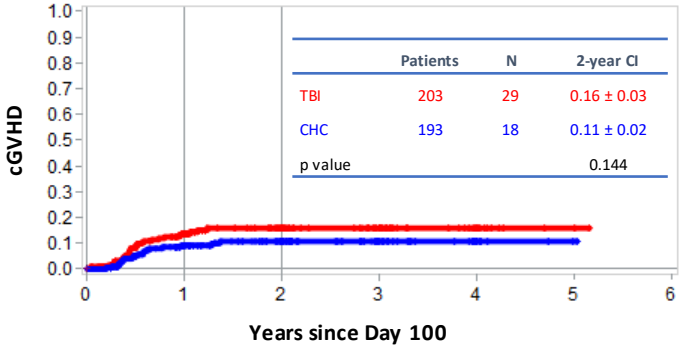
Roland Meissel personal communication.

MSD/MD ≥4 Years, Randomised, Acute and Chronic GVHD; GVHD Relapse-Free Survival

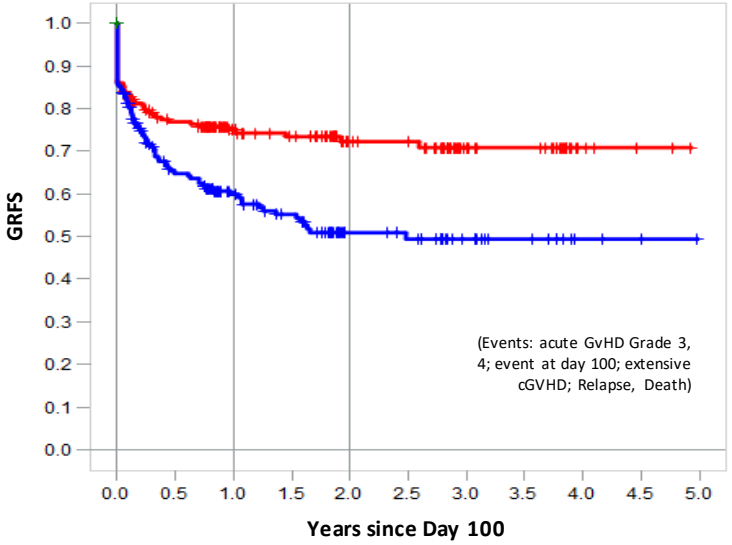
Acute GVHD



Chronic GVHD



GVHD-RFS

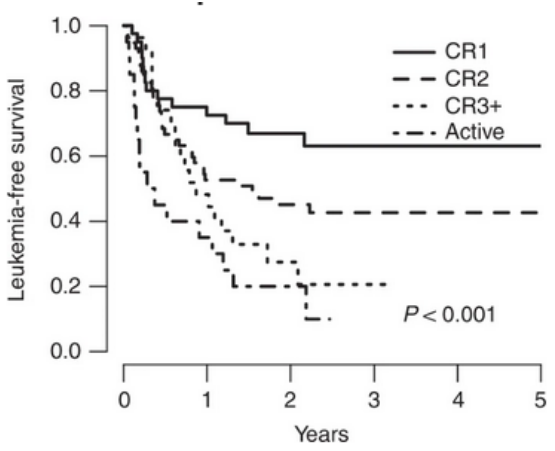


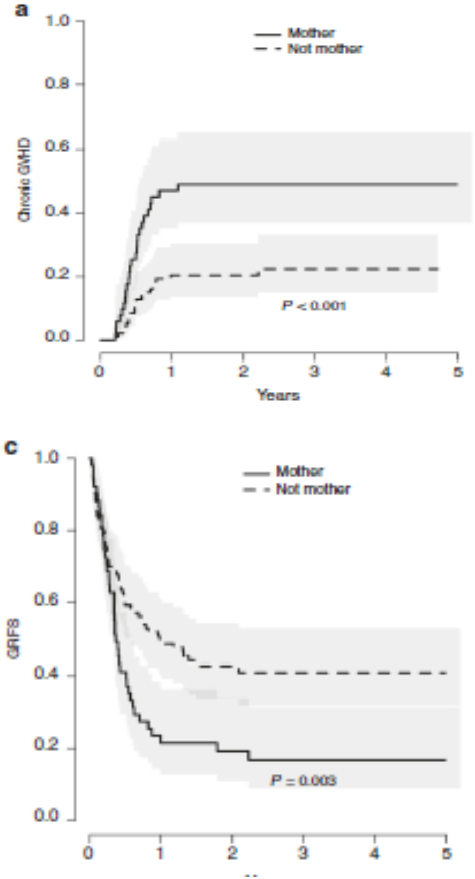
Arm	Patients	Eval. patients	Events	1-year GRFS	2-year GRFS	*P* value
TBI	212	208	54	0.75 ± 0.03	0.72 ± 0.03	.000
Chemo	201	198	87	0.60 ± 0.04	0.51 ± 0.04	

Multivariate Analysis

	OS (52 deaths/ 333 evaluable patients)		EFS (77 events/ 333 evaluable patients)		Relapses (59 events/333 evaluable patients)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Arm						
CHC vs TBI	3.1 (1.7–5.7)	.000	2.8 (1.7–4.6)	<.0001	2.5 (1.4–4.4)	.0001
Donor						
MSD vs MD	0.8 (0.4–1.4)	.385	0.8 (0.5–1.4)	.507	0.7 (0.4–1.1)	.122
Remission status (vs CR1)						
CR2	1.5 (0.8–2.7)	.208	1.7 (1.0–2.7)	.037	1.7 (1.0–3.1)	.057
CR3	0.7 (0.1–2.9)	.579	0.6 (0.2–2.2)	.483	0.3 (0.04–2.5)	.268
MRD						
Positive vs negative	1.4 (0.8–2.4)	.290	1.4 (0.9–2.3)	.119	1.4 (0.8–2.4)	.260
Age						
>10 years vs <10 years	1.8 (1–3.1)	.048	1.5 (1–2.4)	.080	1.5 (1–2.4)	.080
Immunophenotype (vs BCP)						
T-ALL	1.1 (0.5–2.3)	.897	0.8 (0.4–1.6)	.492	0.9 (0.4–1.9)	.708
Other	1.1 (0.1–8)	.958	0.6 (0.1–4.4)	.616	NA	–

HLA-Haploidentical Family Donors: The New Promise for Childhood ALL?





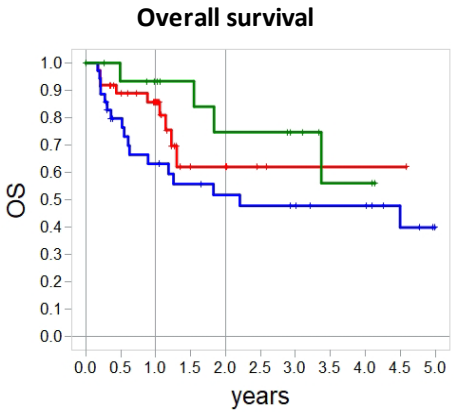
T-cell-depleted hHSCT	T-cell-replete hHSCT
1. For a recipient with donor-specific anti-HLA antibodies, a donor without the corresponding HLA antigen is preferred (MFI <1,000)	1. For a recipient with donor-specific anti-HLA antibodies, a donor without the corresponding HLA antigen is preferred (MFI <1,000)
2. NK-cell alloreactive donor if available	2. Younger donor over older donor
3. Younger donor over older donor	3. A male donor for a male recipient
4. A male donor for a male recipient	4. Sibling or offspring donor over parent donor
5. First-degree relative over second-degree HLA-half-matched donor	5. Between parent donors, father is preferred over mother donor
6. Between parent donors, mother is preferred over father	6. An ABO-matched donor is preferred to a minor ABO-mismatched donor, and a minor ABO-mismatched donor is preferred to major ABO-mismatched donor.
7. ABO-matched donor	7. First-degree relative over second-degree HLA-half-matched donor (Beijing protocol)
8. CMV-seropositive donor for CMV-seropositive recipient	8. Donor with KIR ligand match (Beijing protocol)
	9. Donor with NIMA mismatch over NIPA mismatch (Beijing protocol)

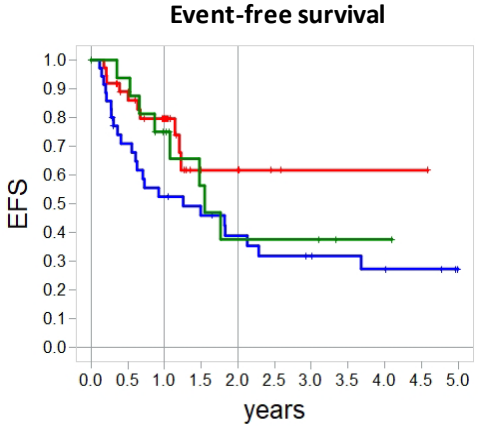
Table modified from Ciurea et al. (73). MFI, mean fluorescence intensity; NK, natural killer; NIMA, non-inherited maternal antigens; NIPA, non-inherited paternal antigens.

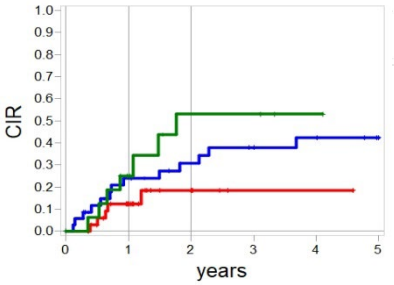
Rocha et al. *BMT.* 2021.

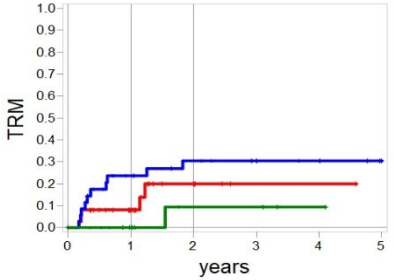
Ab Rahman et al. *Front Pediatr.* 2021.

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









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	

Peters, personal communication.

Danke !

Peter Bader

Franco Locatelli

Study Committee

National Coordinators

Participating centres

MARVIN data base

Ulli Pötschger

Helga Annadotier

Paulina Kurzmann

Jenny Glogowa

Data Safety Monitoring Board

Data managers

Tijana Frank

Question 1

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 T-ALL in second remission
4. Patients who received inotuzumab ozogamicin pre-transplant

Question 2

Which pediatric patients are at high risk for post-transplant relapse?

1. Children with *BCRABL*+ rearrangement
2. Patients with high MRD-load at day +60 post-transplant
3. Patients transplanted from an unrelated donor
4. Patients with T-ALL

Question 3

Patients who experience a very early B-precursor ALL post allogeneic HSCT should NOT receive following treatment option:

1. Immediate second allogeneic HCT with reduced conditioning regimen without remission induction
2. Blinatumomab
3. CAR T cells
4. Conventional chemotherapy + blina + CAR Ts + allo-HSCT

Global Leukemia Academy

Case 2: Relapse/ Refractory ALL

Hannah von Mersi & Anna Cvrtak

APTITUDE HEALTH

Making the Impossible Possible

Part 1 – Relapse/Refractory Setting ALL

Global Leukemia Academy – Case Report

Hannah von Mersi and Anna Cvrtak

St. Anna Children´s Hospital

Vienna, Austria

Pat. F. R. Initial Presentation 12/2017

- Female, 13 years
- Clinical presentation: lumbosacral and pelvic pain, pains in right lower extremity, recurrent fever, fatigue, nausea, and feebleness
- Patient history: trigeminal neuralgia (7/17), Lyme disease (ca. 2012)
- Laboratory results: WBC 3.41 G/L; ANC 0.89 G/L; L 1.84 G/L; Hb 9.3 g/dL; Plt 17,000 G/L; LDH 789U/L

Hannah von Mersi, Anna Cvrtak

Diagnosis and Initial Treatment

- BCP-ALL (B-III with B-II subclone)
- Genetics: 46XX; del9p13; del21q22; suspected *IGH-DUX4* gene fusion
- CNS Status 2

- Treatment
  - According to AIEOP BFM 2009, HR-Group

Hannah von Mersi, Anna Cvrtak

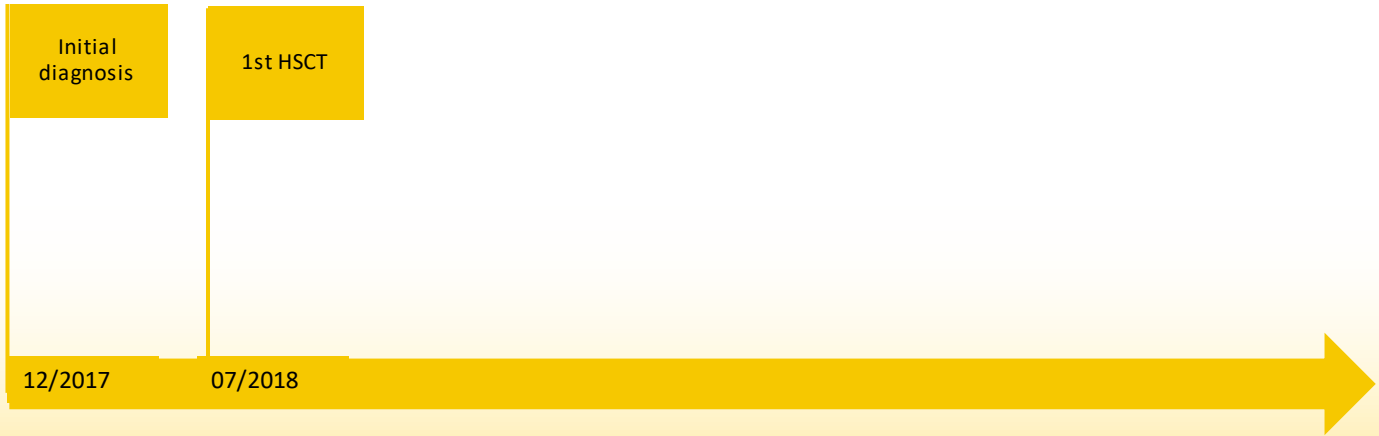
Response and Treatment Adaptation

- Response
  - Day 8: Good prednisolone response
  - Day 15: Flow MRD 4.4% blasts
  - Day 33: Flow MRD negative

- PCR MRD
  - Day 33 (TP1): 3×10^{-2}
  - Day 78 (TP2): 7×10^{-3} → Indication for HSCT
  - Before HR-2: 1×10^{-2}
  - Before HR-3: 4×10^{-3}

- Blinatumomab
  - PCR MRD after 14 days BLINA: 2×10^{-4}

Hannah von Mersi, Anna Cvrtak



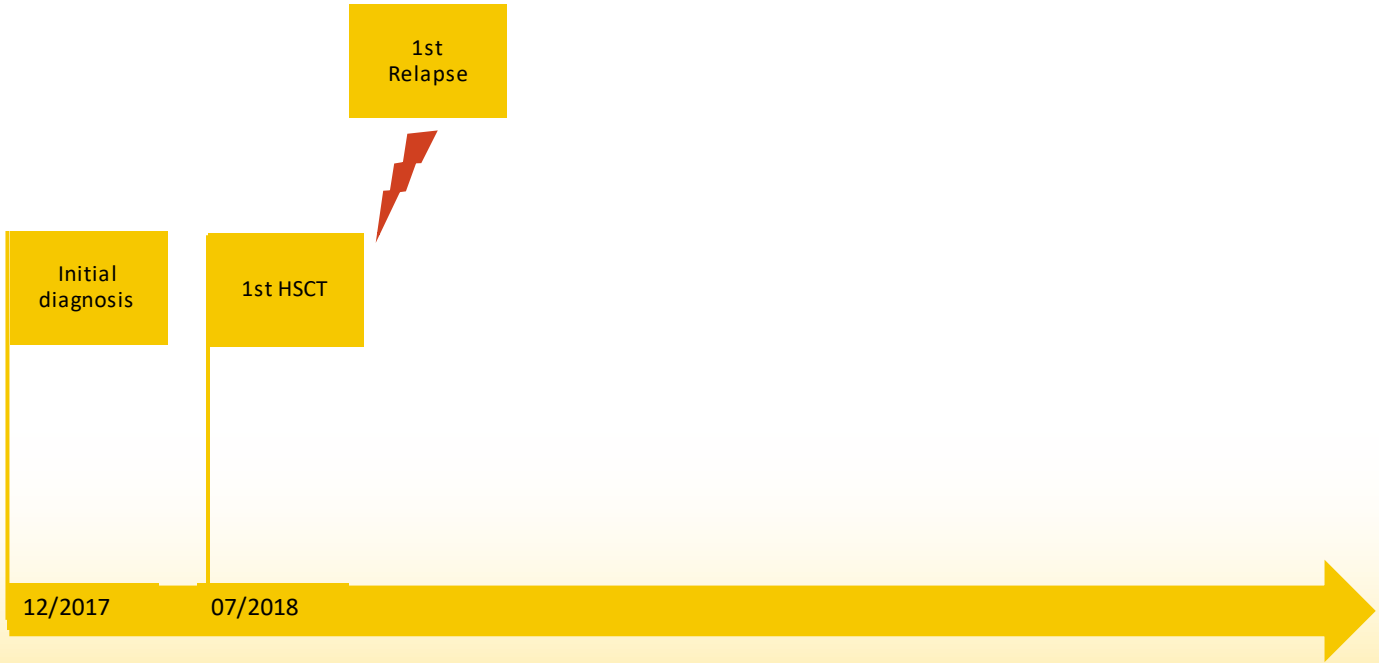
Hannah von Mersi, Anna Cvrtak

First HSCT

- 9/10 HLA MUD
- 2.4 × 10^6/kg CD34+ cells (BM)
- Conditioning: TBI 12 Gy + VP16

- Response
  - Day +28 after first HSCT: full donor chimerism

Hannah von Mersi, Anna Cvrtak



Hannah von Mersi, Anna Cvrtak

First Relapse: Therapy

- 21 months after first HSCT
- Late isolated BM relapse
- Blast cell population: CD19+ and CD19– subclone

- Treatment
  - Dexamethasone pre-phase and Protocol Ib variant
  - CAR T cells (tisagenlecleucel [KYMRIAH®])

- Response
  - CD19+ subclone negative
  - CD19– subclone persistent (flow MRD 0.19% blasts, PCR-MRD 2×10^3 blasts)

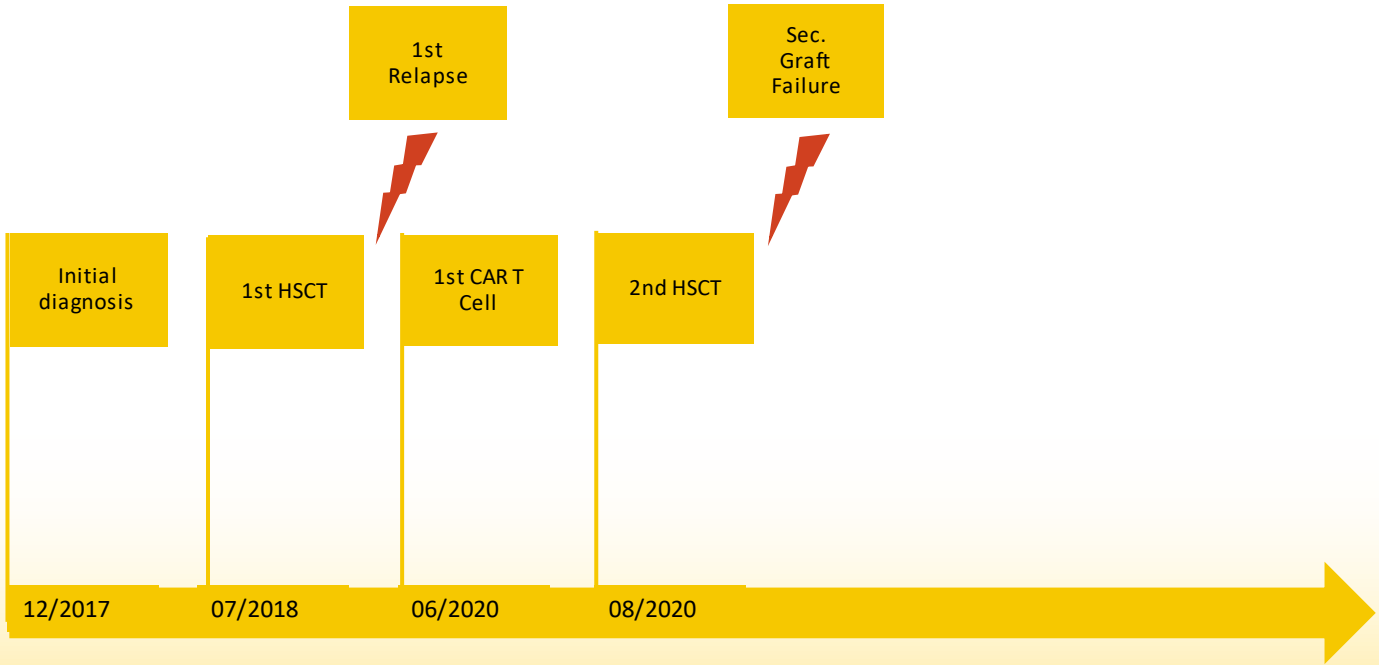
Hannah von Mersi, Anna Cvrtak

First Relapse: HSCT After CAR T Cells

- Treatment following CAR T cells
  - Second HSCT (haploidentical mother) with reduced-toxicity conditioning with FLU/TREO/THIO
  - 3.0×10^6/kg CD 34+; 38×10^6 CD3+

- Response
  - Day +28 after second HSCT
    - CD19+ negative, CD19– PCR-MRD 10^{-4}
    - BM full donor chimerism
  - Day +90 after second HSCT
    - CD19+ negative, CD19– negative

Hannah von Mersi, Anna Cvrtak

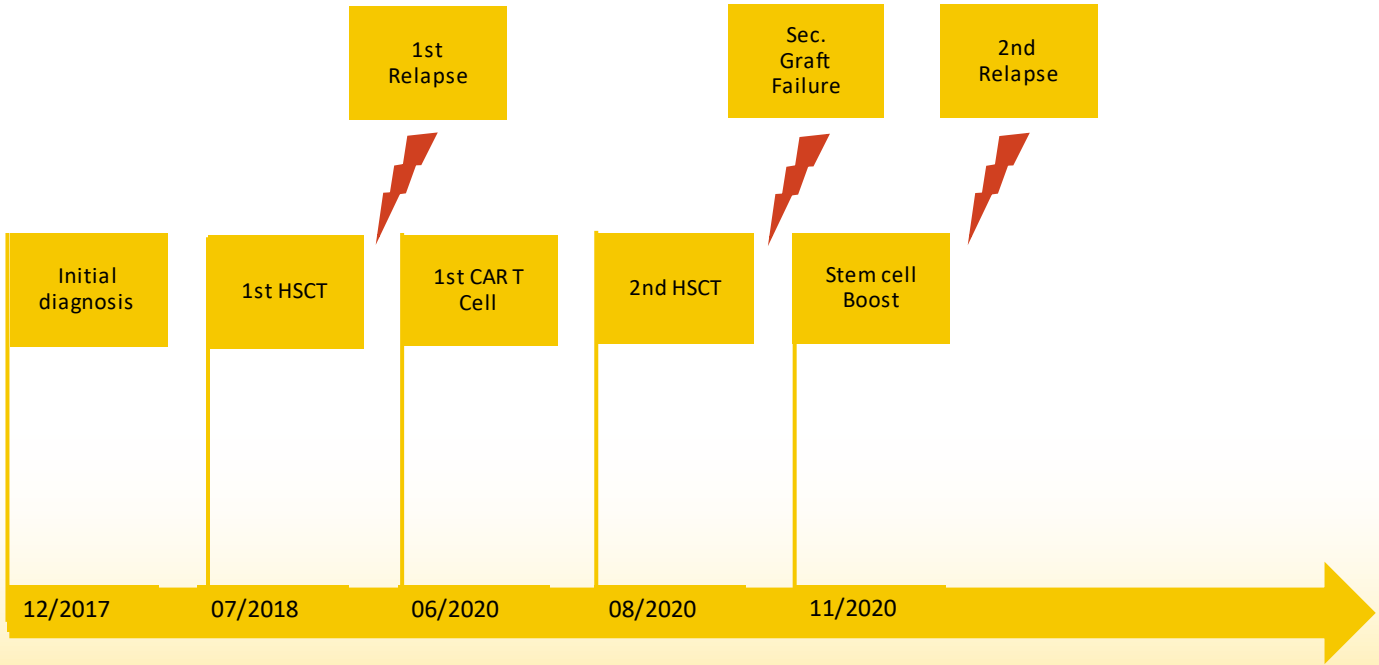


Hannah von Mersi, Anna Cvrtak

Secondary Graft Failure

- Day +107 after second HSCT
- Treatment
  - Stem cell boost of haploidentical mother with alpha-/beta-depleted PBSC
  - 3.8 × 106/kg CD34+ cells
- Response
  - Good immunologic recovery
  - Complete donor chimerism

Hannah von Mersi, Anna Cvrtak



Hannah von Mersi, Anna Cvrtak

Second Relapse

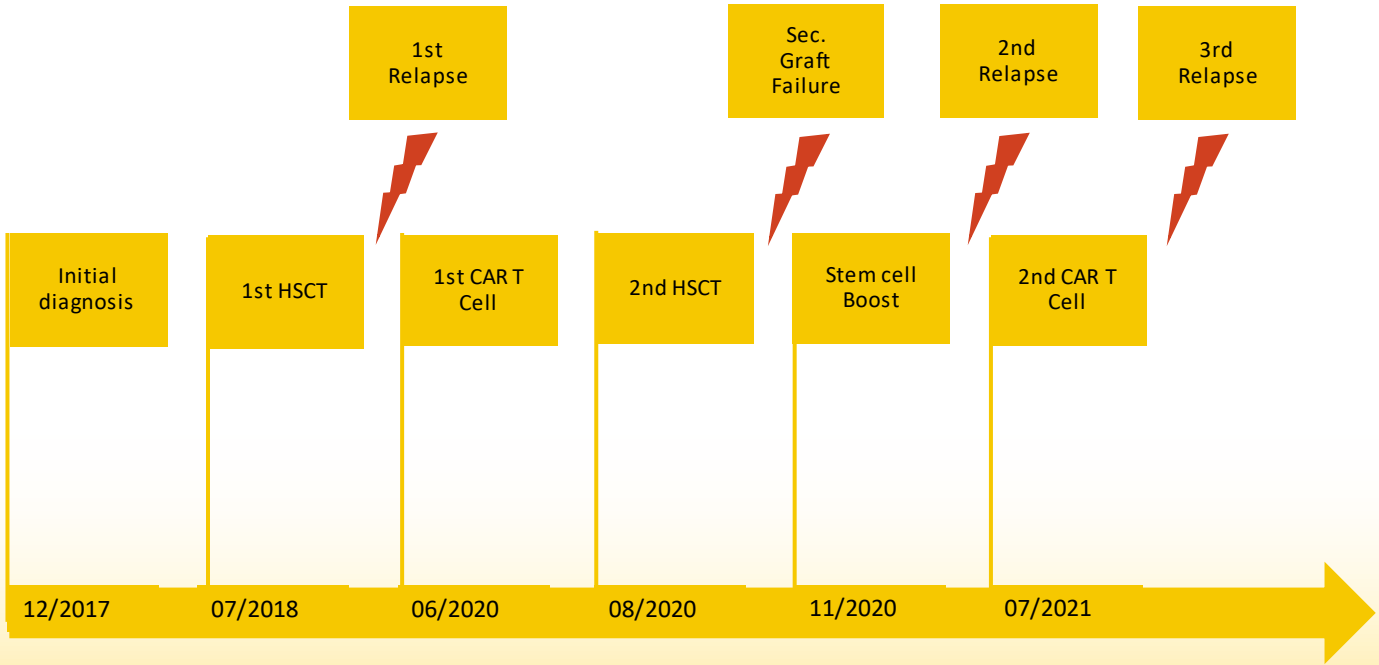
- 10 months after second HSCT
- Early isolated BM relapse
- Blast cell population: CD19+, CD22+, CD24+, CD10+, CD34+, CD20–, CD58–, CD11a–

- Treatment
  - Dexamethasone pre-phase, Protocol Ib variant
  - Second CAR T-cell reinfusion (tisagenlecleucel [KYMRIAH] – new product)

- Response
  - Day +28 and +104 after CAR T-cell reinfusion; CR, flow MRD negative

Hannah von Mersi, Anna Cvrtak

Complications After Initial Treatment



Hannah von Mersi, Anna Cvrtak

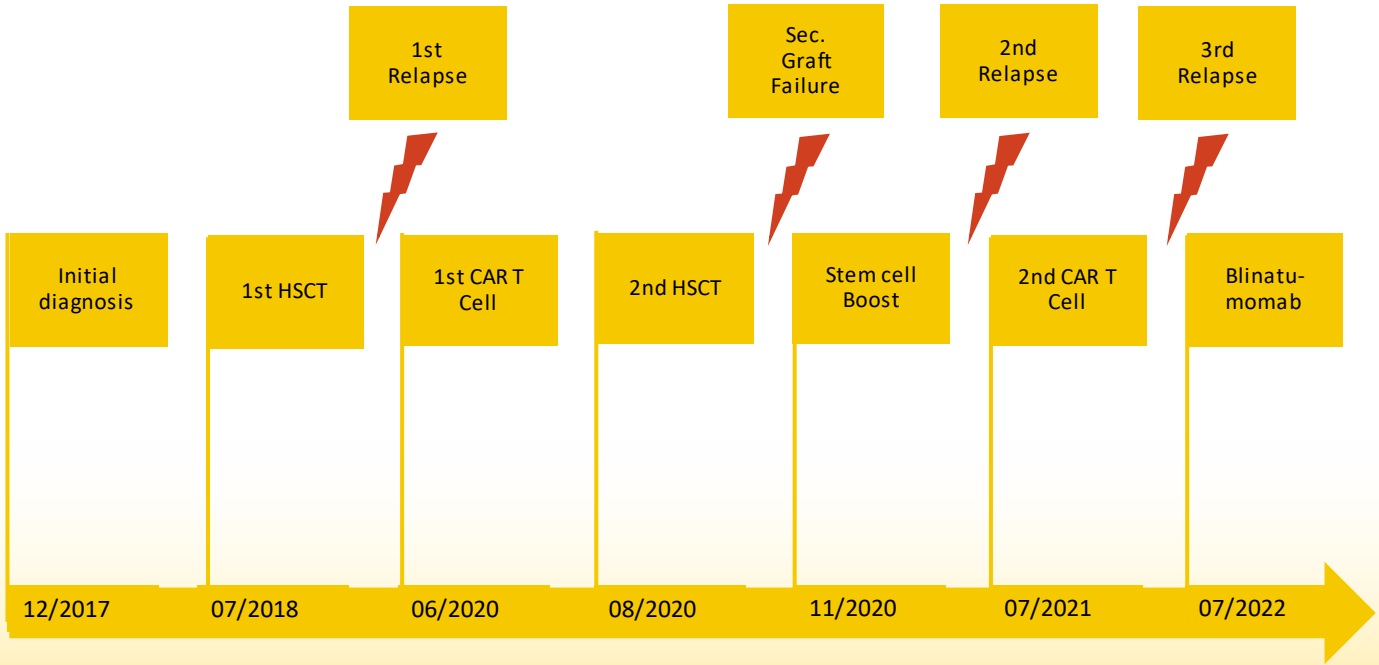
Third Relapse

- 11 months after second HSCT
- Early isolated extramedullary relapse (lymphatic tissue in appendix vermiformis, multiple vertebral bone infiltration)
- Initially BM morphologically negative, flow MRD 0.07% blasts

- Treatment
  - 15 days of blinatumomab (initially 5 mg/m^2 for 4 days, then 15 mg/m^2)

- Response
  - CR, flow MRD negative

Hannah von Mersi, Anna Cvrtak


1st Relapse
Sec. Graft Failure
2nd Relapse
3rd Relapse
Initial diagnosis
1st HSCT
1st CAR T Cell
2nd HSCT
Stem cell Boost
2nd CAR T Cell
Blinatu-momab
12/2017
07/2018
06/2020
08/2020
11/2020
07/2021
07/2022

St. Anna Children´s Hospital

Andishe Attarbaschi
Heidrun Boztug
Michael Dworzak
Gernot Engstler
Anna Füreder
Wolfgang Holter
Anita Lawitschka
Roswitha Lüftinger
Christina Peters
Herbert Pichler
Fiona Poyer
Natalia Zubarovskaya

Thank you!

Global Leukemia Academy

Case 2 continued: Management of Infections & Toxicities

Anna Cvrtak & Hannah von Mersi

APTITUDE HEALTH

Making the Impossible Possible

Part 2 – Management of Infections and Toxicities

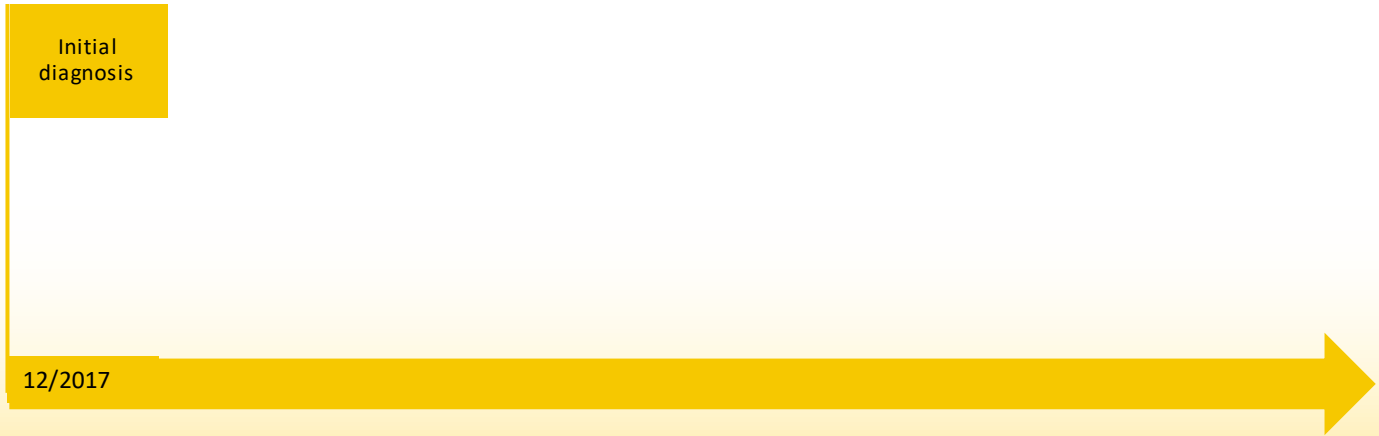
Global Leukemia Academy – Case Report

Anna Cvrtak and Hannah von Mersi

St. Anna Children´s Hospital

Vienna, Austria

Complications After Initial Treatment



Hannah von Mersi, Anna Cvrtak

Complications After Initial Treatment

Acute pancreatitis

- Asparaginase associated (first dose in Protocol Ia)
- Maximal values: amylase 983 U/L; lipase 1557 U/L
- Initial conservative treatment
- Pain exacerbation despite continuous infusion of morphine and hemodynamic instability

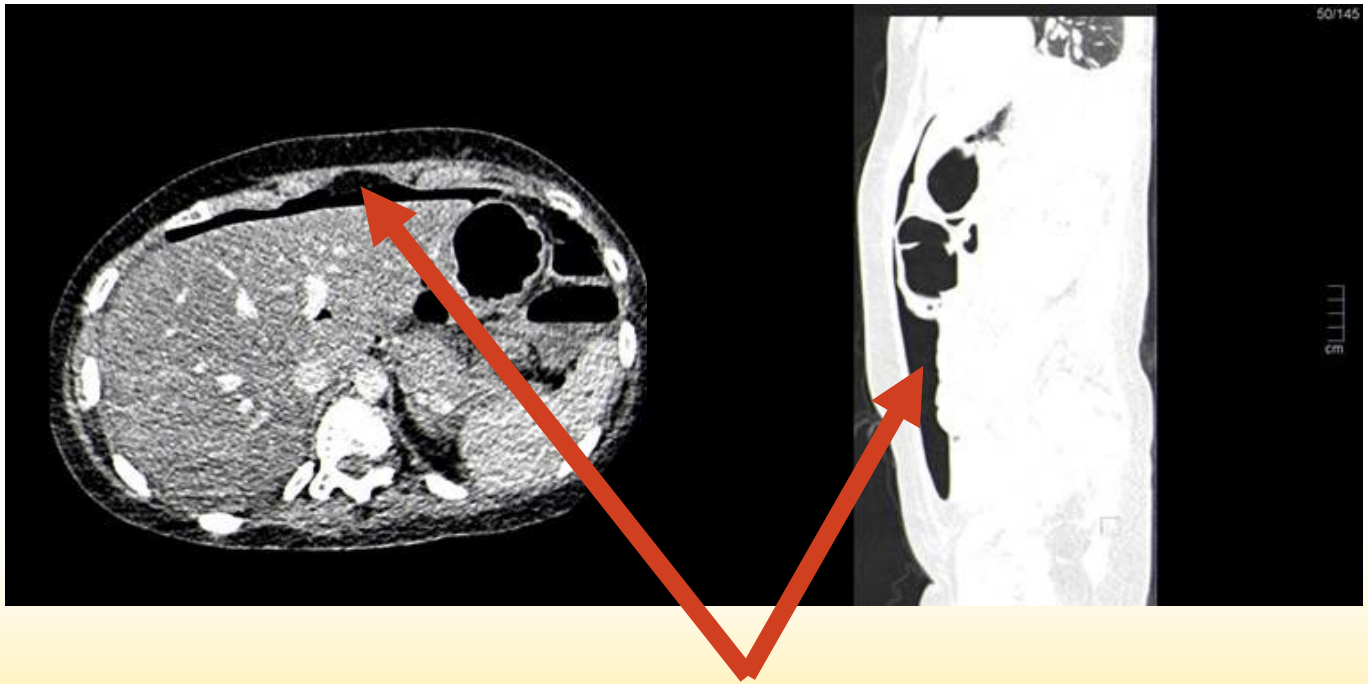
Hannah von Mersi, Anna Cvrtak

Which Differential Diagnosis Has to Be Considered at This Timepoint?

1. Sepsis
2. Gastrointestinal perforation
3. Necrotizing pancreatitis
4. Ileus
5. All listed answers have to be considered

Hannah von Mersi, Anna Cvrtak

Complications After Initial Treatment



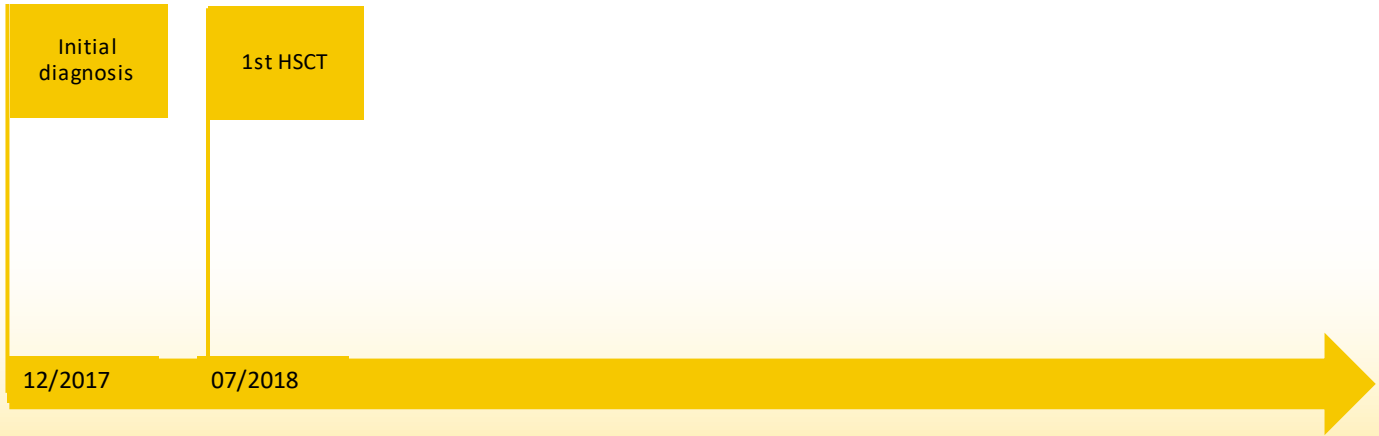
Hannah von Mersi, Anna Cvrtak

Complications After Initial Treatment

- Suspected acute pancreatitis with gastric perforation
- Explorative laparoscopy: ulcus perforans
- Surgical treatment, antibiotics

Hannah von Mersi, Anna Cvrtak

Complications After First HSCT



Complications After First HSCT

Acute GvHD (skin IV°)

- Start day +18 after HSCT, initially III°
- Histologic confirmation by biopsy
- Start of systemic steroid treatment (2 mg/kg/d) on day +21; good response
- Flare-up of GvHD after gradual reduction of steroid dose on day +34
- Increase of steroid dose and initiation of ECP

Hannah von Mersi, Anna Cvrtak

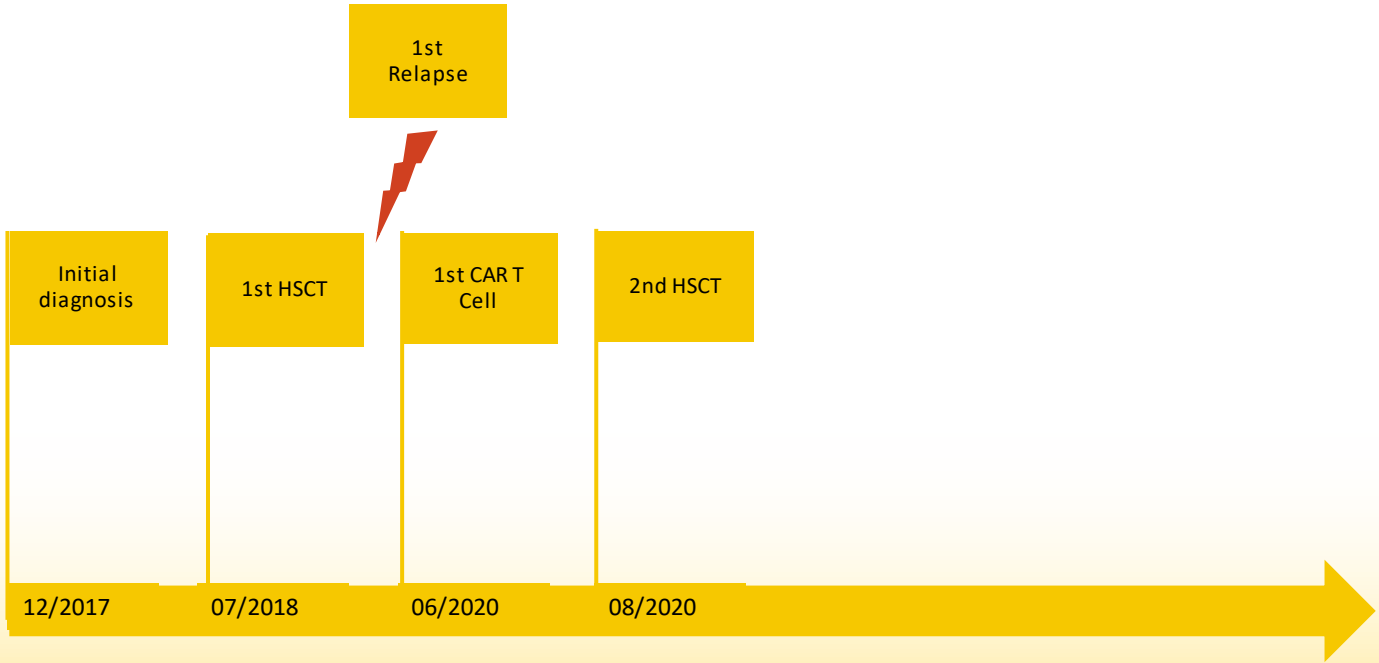
Complications After First HSCT

BK polyomavirus – associated hemorrhagic cystitis

- Associated with immunosuppression due to acute GvHD (steroid, calcineurin inhibitor)
- Initially increase of BK in urine followed by BK viremia (maximal value 10^8 co./mL)
- Treatment: cidofovir, fluid substitution
- Development of chronic kidney failure due to treatment toxicity in combination with leukemia treatment

Hannah von Mersi, Anna Cvrtak

Complications After Second CAR T-Cell Therapy



Hannah von Mersi, Anna Cvrtak

Complications After Second CAR T-Cell Therapy

Clinical presentation

- Blurred vision
- Cephalea
- Progression of left orbital swelling

Which differential diagnosis has to be considered at this timepoint?

(OPEN DISCUSSION)

Hannah von Mersi, Anna Cvrtak

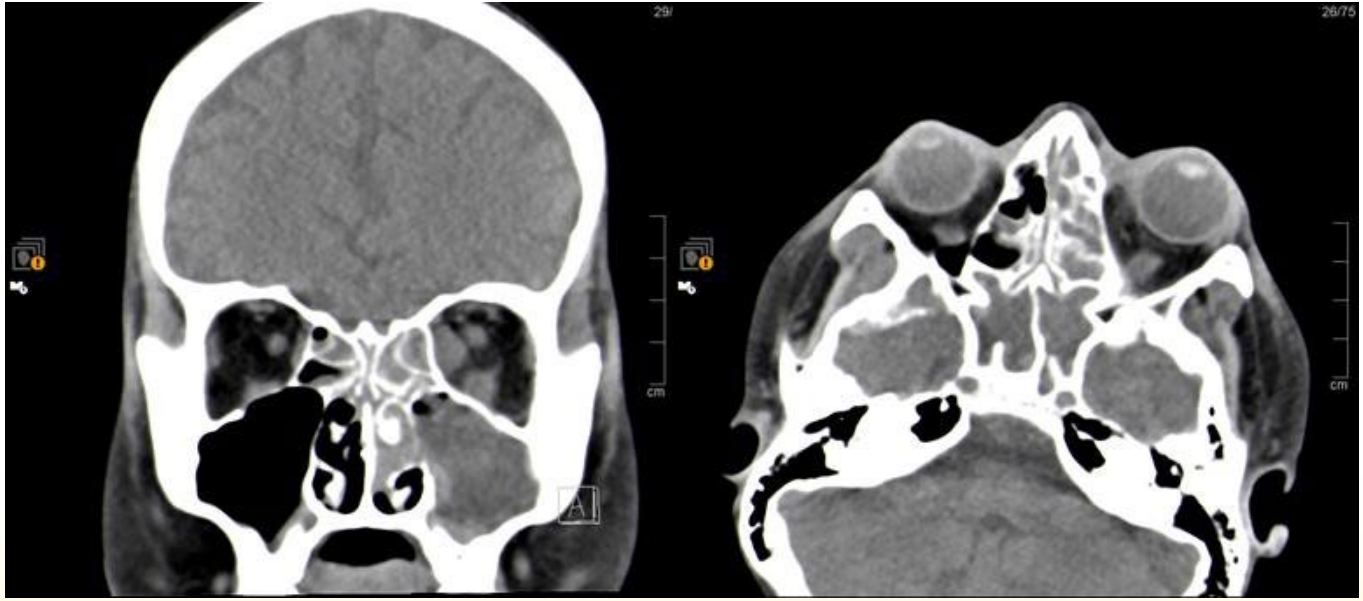
Which Differential Diagnosis Has to Be Considered at This Timepoint?

Possible differential diagnosis

- Sepsis
- Sinus venous thrombosis
- Relapse
- Infection (bacterial/fungal)
- Drug toxicity
- Bleeding

Hannah von Mersi, Anna Cvrtak

Complications After Second CAR T-Cell Therapy



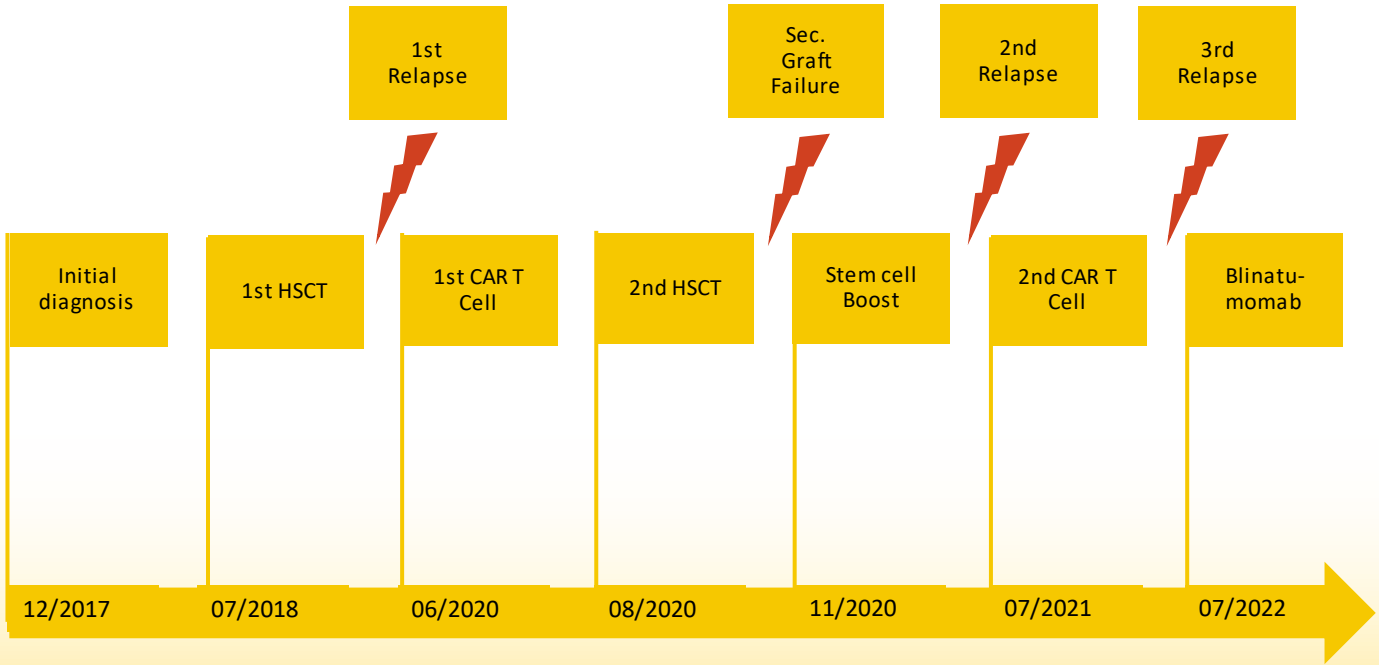
Hannah von Mersi, Anna Cvrtak

Complications After Second CAR T-Cell Therapy

Invasive fungal infection of left paranasal sinus involving left orbit and left optic nerve

- Endoscopic inspection and surgical treatment
- Detection of *Aspergillus fumigatus* in all samples
- Treatment with caspofungin and isavuconazole, granulocyte transfusions, stem cell boost
- Improvement of symptoms; culture and PCR negative

Hannah von Mersi, Anna Cvrtak



Hannah von Mersi, Anna Cvrtak

Current state

- Chronic kidney disease, no indication of dialysis at the moment
- Loss of vision in left eye
- Continuous antifungal treatment with isavuconazole
- Cachexia
- Overall good quality of life

St. Anna Children´s Hospital

Andishe Attarbaschi
Heidrun Boztug
Michael Dworzak
Gernot Engstler
Anna Füreder
Wolfgang Holter
Anita Lawitschka
Roswitha Lüftinger
Christina Peters
Herbert Pichler
Fiona Poyer
Natalia Zubarovskaya

Thank you!

Global Leukemia Academy

Session Close

Franco Locatelli

APTITUDE HEALTH

Question 1

Which of the following subsets of first-relapse ALL patients can be considered as very high risk?

1. All patients with B-ALL relapsing within 18 months from diagnosis
2. All patients with hypodiploidy
3. All patients with t(17;19) or t(1;19)
4. Each of the 3 previous subsets

Question 2

Which assertion is correct for children with B-ALL?

1. Inotuzumab is approved by EMA for induction treatment of relapsed B-ALL in childhood
2. Inotuzumab recommended dosage is 3 mg/m^2
3. Blinatumomab is approved for consolidation treatment before HSCT in children with high-risk first relapse B-ALL
4. None of the patients experiencing relapse later than 6 months after treatment discontinuation should be transplanted

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!

Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

APTITUDE HEALTH