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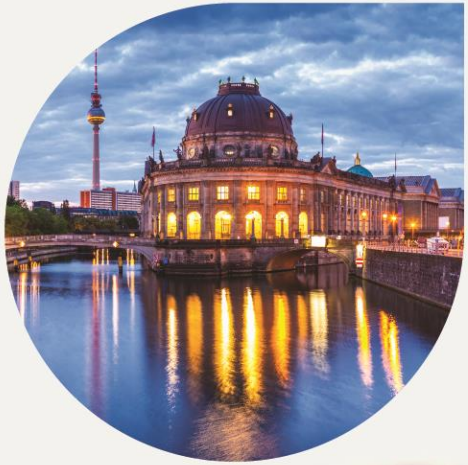

Global Leukemia Academy

Pediatric ALL Patients Breakout

Emerging and Practical Concepts and Controversies in Leukemias

23–24 October 2020

APTITUDE HEALTH

Global Leukemia Academy

Virtual breakout: Pediatric ALL patients – session open

Franco Locatelli

Global Leukemia Academy

APTITUDE HEALTH

Meet the Faculty

Franco Locatelli
Head of Department of Paediatric Haematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Rome. and Full Professor of Pediatrics at the Sapienza University of Rome, Italy

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

Patrick Brown, MD
Associate Professor of Oncology and Pediatrics, Director of the Pediatric Leukemia Program
Johns Hopkins University
Baltimore, MD, USA

Virtual breakout – pediatric ALL patients (Day 2)

Time CET	Title	Speaker
18.00 – 18.15	**Session open** • Educational ARS questions for the audience	Franco Locatelli
18.15 – 18.45	**First-line treatment of pediatric ALL** • Presentation (15 min) • Q&A (15 min)	Rob Pieters
18.45 – 19.15	**Current treatment options for relapsed ALL in children, including HSCT and COVID-19 considerations** • Presentation (15 min) • Q&A (15 min)	Franco Locatelli
19.15 – 19.45	**Bispecific T-cell engagers for pediatric ALL** • Presentation (15 min) • Q&A (15 min)	Patrick Brown
19.45 – 20.15	**Case-based panel discussion** • **Management of long- and short-term toxicities and treatment selection in pediatric patients** – Overview of long-term toxicities (10 min) – Patient case presentation (10 min) – Discussion (10 min)	Rob Pieters Patrick Brown *Faculty panel:* R. Pieters, F. Locatelli, P. Brown
20.15 – 20.30	**Session close** • Educational ARS questions for the audience	Franco Locatelli

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Educational ARS questions

Franco Locatelli

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Question 1

Which assertion is correct for children with ALL?

a) All patients with *MLL*-rearranged ALL should be transplanted

b) All patients with *BCR-ABL*–positive ALL should be transplanted

c) No patient with *BCR-ABL*–positive ALL should be transplanted

d) AlloSCT is part of treatment for children with early relapsed ALL

Question 2

Which assertion is correct for children with ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment

b) Blinatumomab and inotuzumab cannot be administered sequentially

c) Therapeutic drug monitoring of asparaginase improves outcome

d) Dexamethasone and vincristine are standard components of maintenance therapy

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First-line treatment of pediatric ALL

Rob Pieters

APTITUDE HEALTH

First-line treatment of pediatric ALL

Rob Pieters
Chief Medical Officer

Question 1

Which assertion is correct for first-line treatment of pediatric ALL?

a) A minority of patients with Ph+ ALL benefit from receiving allogenic SCT when receiving a tyrosine kinase inhibitor such as imatinib

b) The dose intensity of asparaginase has no impact on outcome

c) 6-mercaptopurine dose-intensity is of minor importance in maintenance therapy

d) Prednisone is a more effective drug than dexamethasone

Question 2

Which assertion is correct?

a) All children with a BCR-ABL–like ALL should be treated with a tyrosine kinase inhibitor such as imatinib or dasatinib

b) Cranial irradiation is indicated in B-lineage ALL and T-lineage ALL with a WBC >50 × 10^9/L at diagnosis

c) Copy number alterations (CNA) do not predict outcome

d) End of induction MRD and/or end of consolidation MRD is the most powerful prognostic factor

ALL: chemotherapy elements

- Induction: - steroid, VCR, L-Asp, (DNR), intrathecal
- Consolidation: - cyclophosphamide, araC, 6-MP, intrathecal
  - HD-MTX, 6-MP, intrathecal
- Reinduction/intensification: - steroid, VCR, L-Asp, (DNR), intrathecal
- Maintenance: - 6-MP/MTX (+ VCR/steroid pulses)

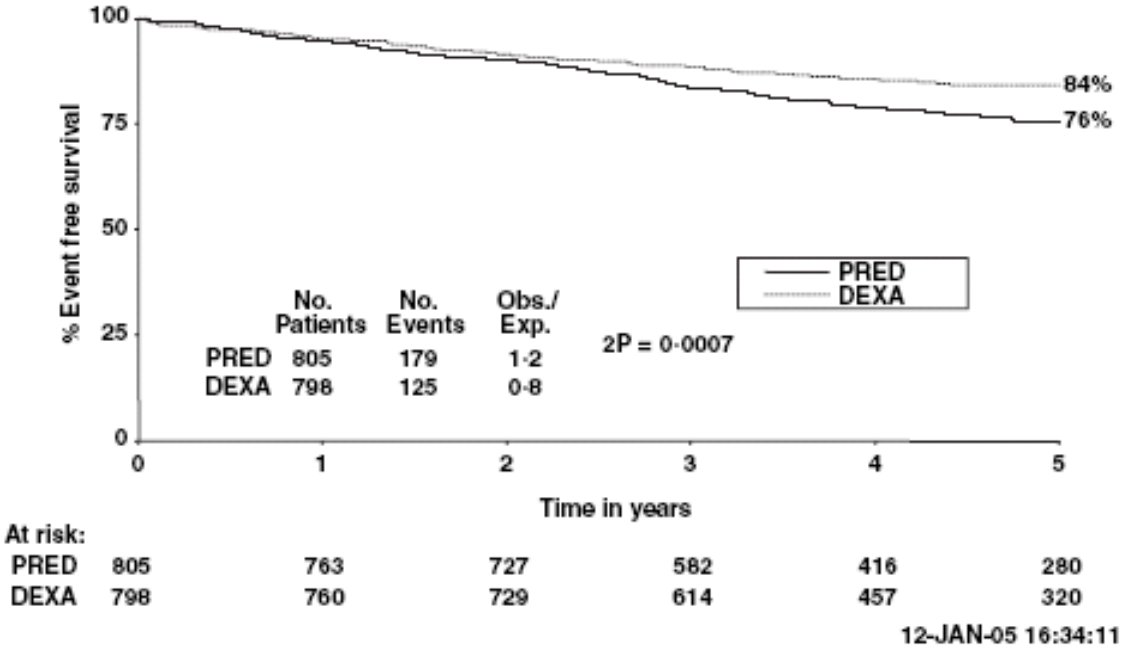
- (cranio[spinal] radiotherapy)
- (allogenic hematopoietic stem cell transplantation [HSCT])

ALL

- Therapy elements
  - Choice of steroid
  - Dose intensity asparaginase
  - Which intensification
  - Which maintenance
  - Which central nervous system treatment
  - Who should get SCT
  - Adolescents

- New developments: targeting therapy

EFS by randomized use of dexamethasone vs prednisone



Event-free survival by randomized steroid. Obs./Exp., observed/expected ratio.

Intensification of asparaginase

	EFS with less intensive Asp	EFS with more intensive Asp	difference	reference
Erwinase vs Coli Asp EORTC-CLG 58881	60%	73%	significant	Duval 2002
Erwinase vs Coli Asp DFCI 95-01	78%	89%	significant	Moghrabi 2007
20 extra wks of Asp IBFM/IDH ALL91	79%	88%	significant	Pession 2005
20 extra wks of Asp in IRG AIEOP ALL91	72%	76%	not sign	Rizzari 2001
20 wks of Asp in T-ALL POG 8704	55%	68%	significant	Amylon 1999
20 wks of Asp in T-NHL POG 8704	64%	78%	significant	Amylon 1999
Shorter or longer than 25 wks of Asp DFCI 91-01	73%	90%	significant	Silverman 2001

Pieters R, et al. *Cancer.* 2011;117(2):238-249.

ALL

- Therapy elements
  - Choice of steroid
  - Dose intensity asparaginase
  - Which intensification
  - Which maintenance
  - Which central nervous system treatment
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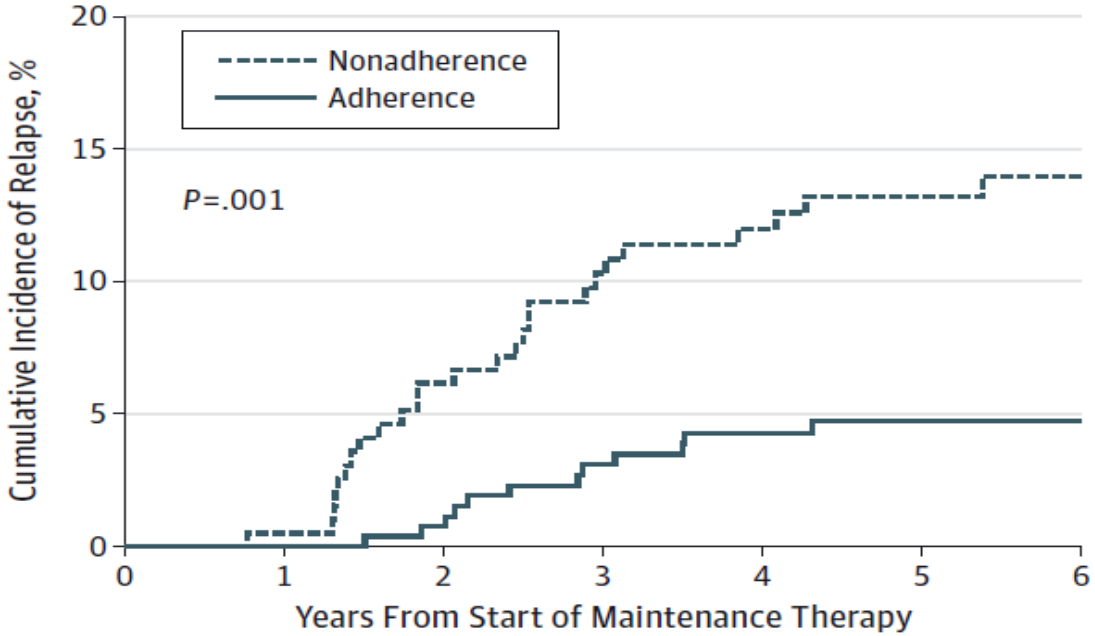
  - Adolescents

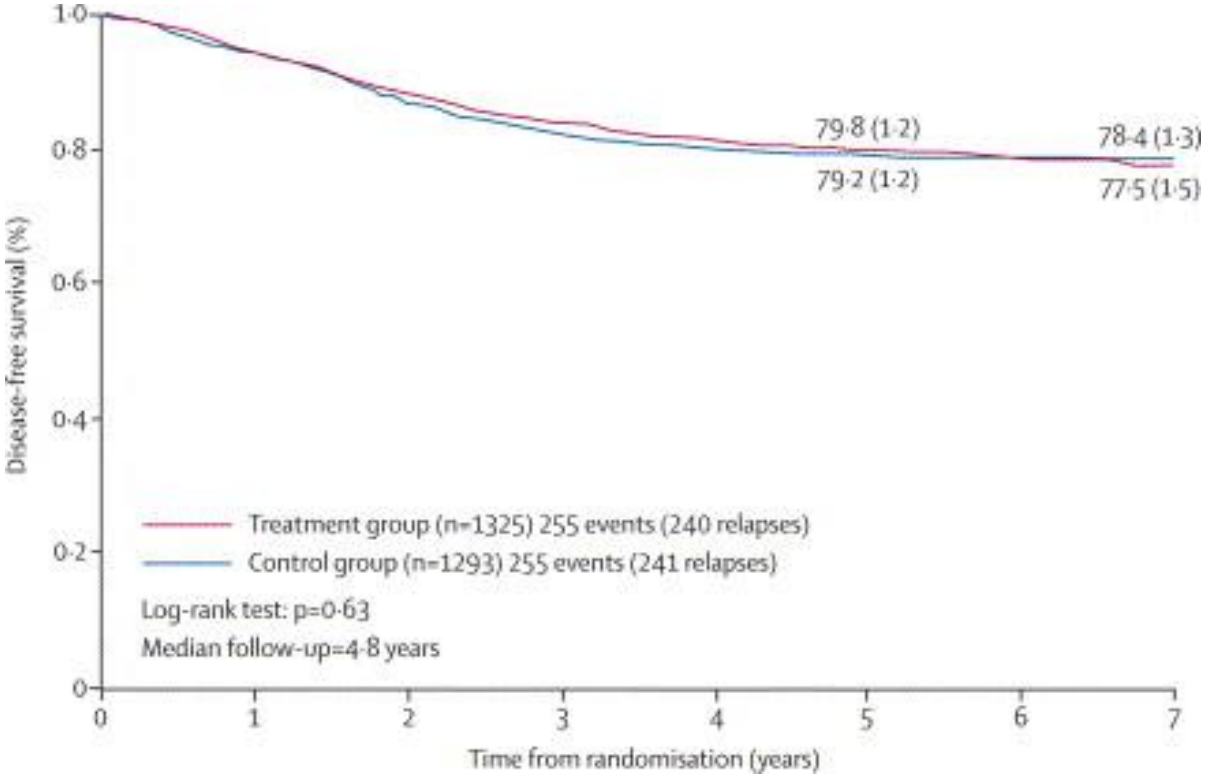
- New developments: targeting therapy

Low adherence to oral 6MP significantly increases relapse risk



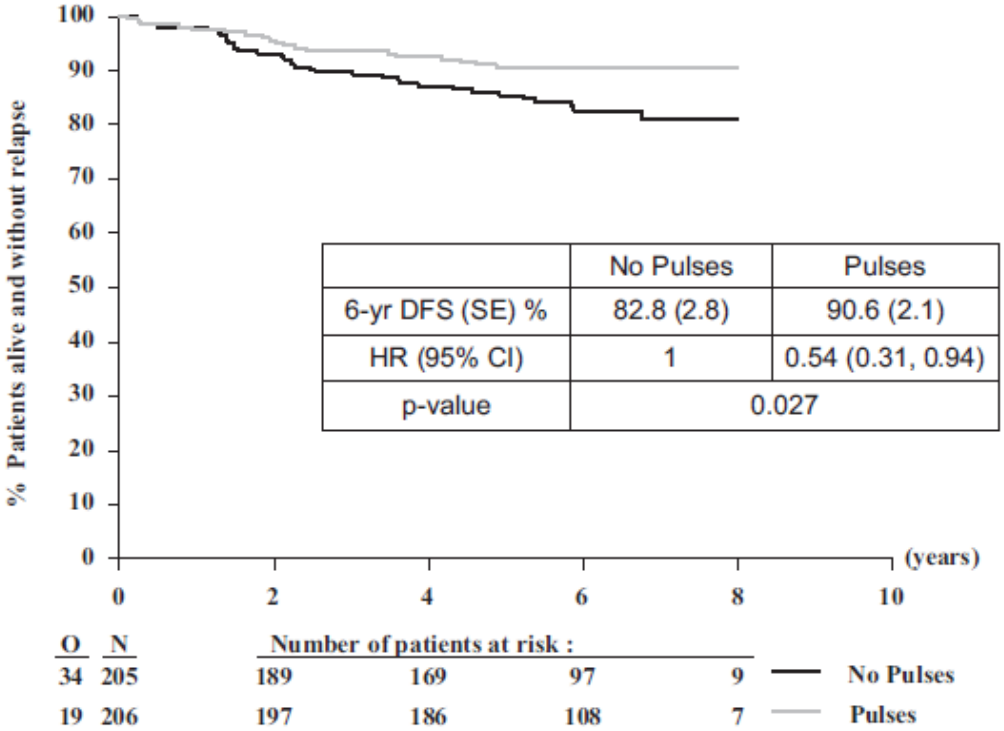
Bhatia S, et al. *JAMA Oncol*. 2015;1(3):287–295.

Dexa/VCR pulses during maintenance in average-risk ALL patients (BFM)



Conter V, et al. *Lancet.* 2007;369(9556):123-131.

Dexa/VCR pulses during maintenance in average-risk ALL patients (EORTC)



	No Pulses	Pulses
6-yr DFS (SE) %	82.8 (2.8)	90.6 (2.1)
HR (95% CI)	1	0.54 (0.31, 0.94)
p-value	0.027	

ALL

- Therapy elements
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- New developments: targeting therapy

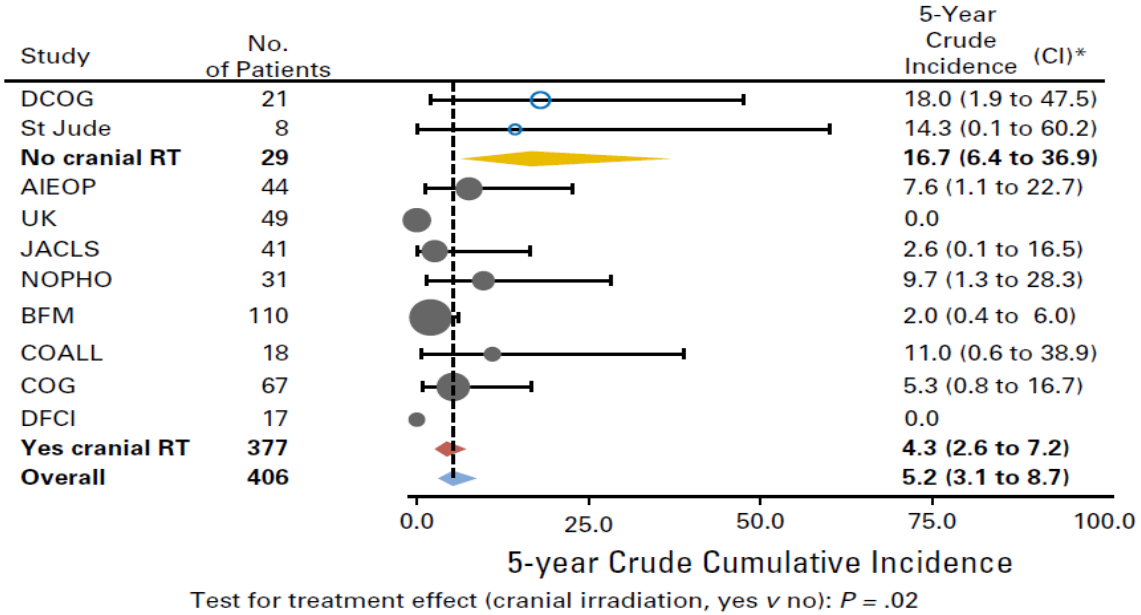
5-year outcomes to pre-emptive cranial radiotherapy (CRT) for ALL subgroups other than CNS3

Outcome	B Cell, WBC > 100 × 10^9/L			T Cell, WBC > 100 × 10^9/L		
	CRT			CRT		
	Yes	No	*P*	Yes	No	*P*
5-year cumulative incidence, %						
Death (100% minus survival)	21.6	17.5	.49	27.2	19.0	.15
Any event (100% minus EFS)	37.0	27.4	.08	34.3	24.4	.08
BM relapse	17.4	15.6	.67	7.6	8.4	.88
Isolated CNS relapse	1.6	3.3	.32	5.4	6.6	.69
Any CNS relapse	3.8	6.0	.35	11.0	10.0	.77
No. of studies	3	6		7	3	
No. of patients	141	594		596	248	

Vora A, et al. *J Clin Oncol.* 2016;34(9):919-926.

5-year outcomes to pre-emptive CRT 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

ALL

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  - Choice of steroid
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  - Which central nervous system treatment
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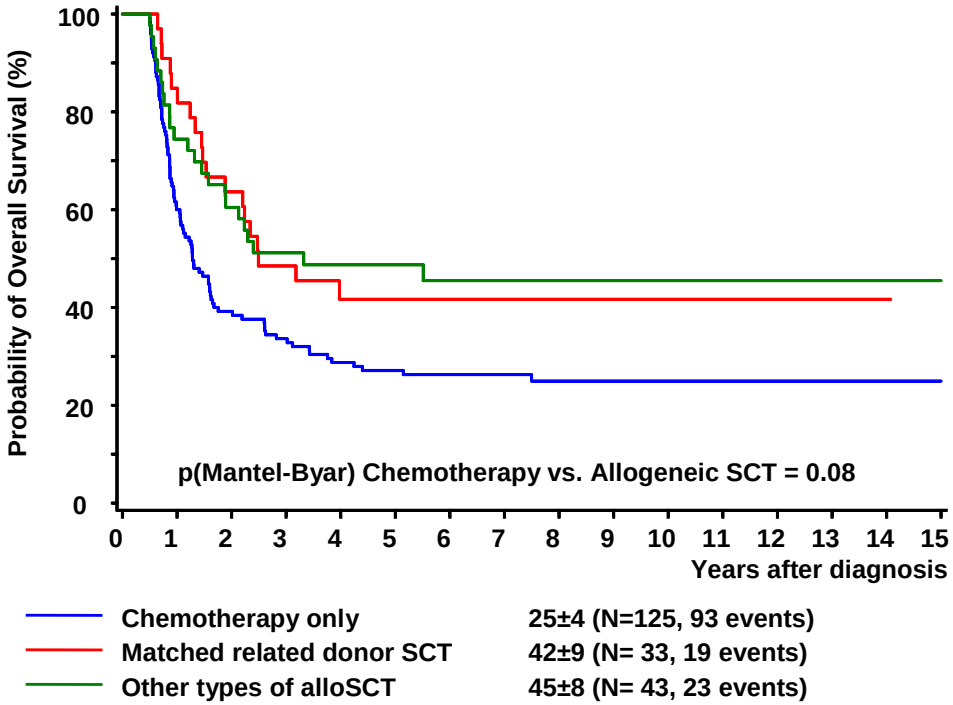
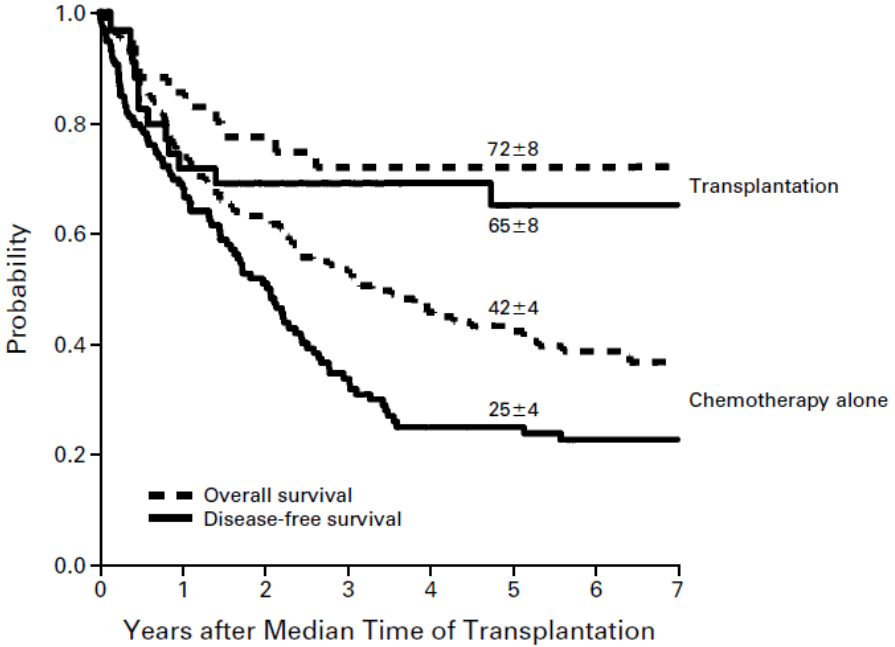
- New developments: targeting therapy

No CR after induction AND T-ALL: better survival with alloSCT



Children with t(9;22) ALL: historical benefit of allogenic transplantation



PATIENTS AT RISK

Chemotherapy alone	198	84	57	36	24	22	18	14
Transplantation from matched related donor	18	28	25	26	23	17	9	6

Arico M, et al. *N Engl J Med.* 2000;342(14):998-1006.

Increased use of imatinib in BCR-ABL–positive ALL: no indication for SCT?

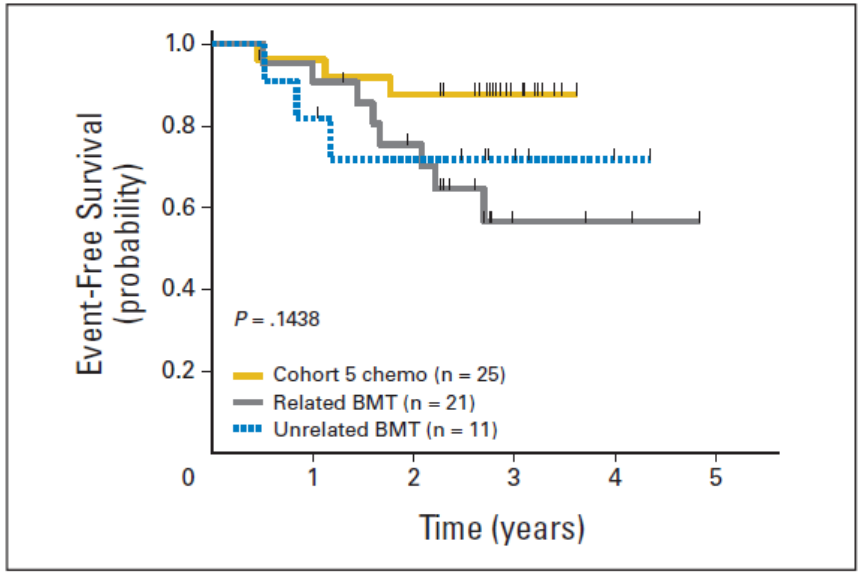
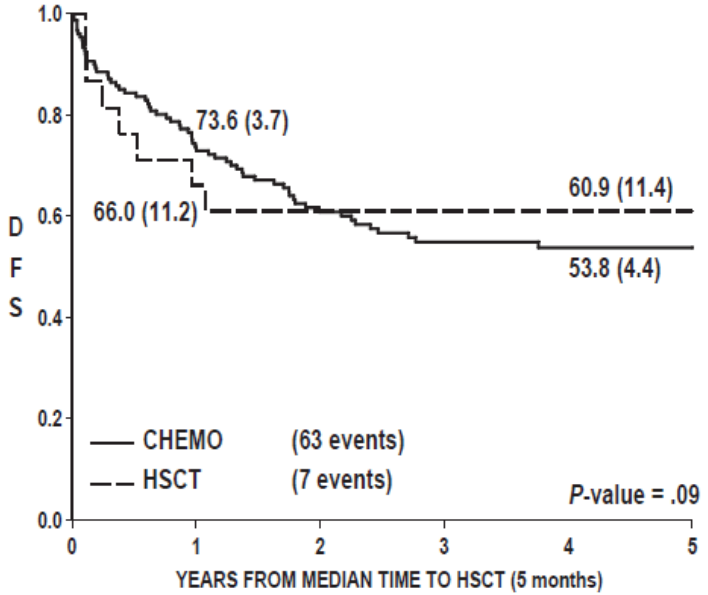
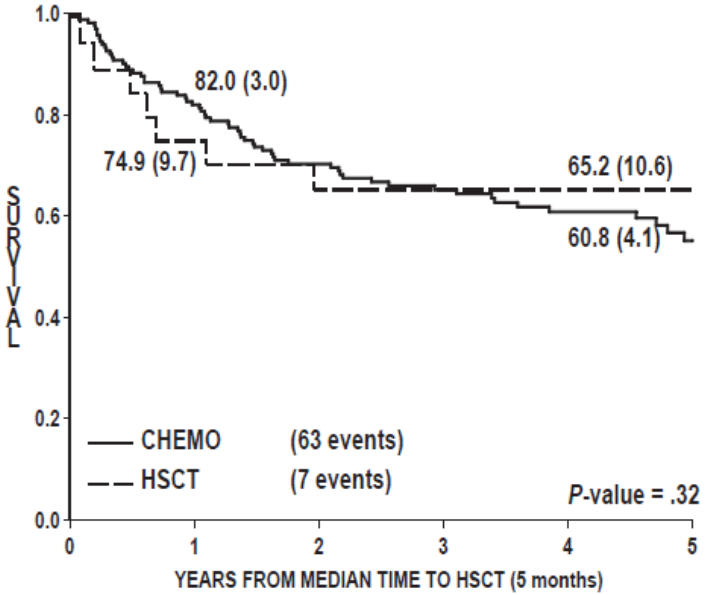


Fig 4. Comparison of event-free survival (EFS) for Cohort 5 chemotherapy only versus related-donor bone marrow transplantation (BMT) versus unrelated-donor BMT. Cohort 5 patients were compared with human leukocyte antigen (HLA) –identical sibling BMT (8 of 39 in cohorts 1-4; 13 of 44 in cohort 5) and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

AlloSCT in infant *MLL*-rearranged ALL – IF-99 medium-risk patients adjusted by waiting time to SCT



At risk						
CHEMO	153	102	75	59	42	26
HSCT	9	14	10	9	7	3

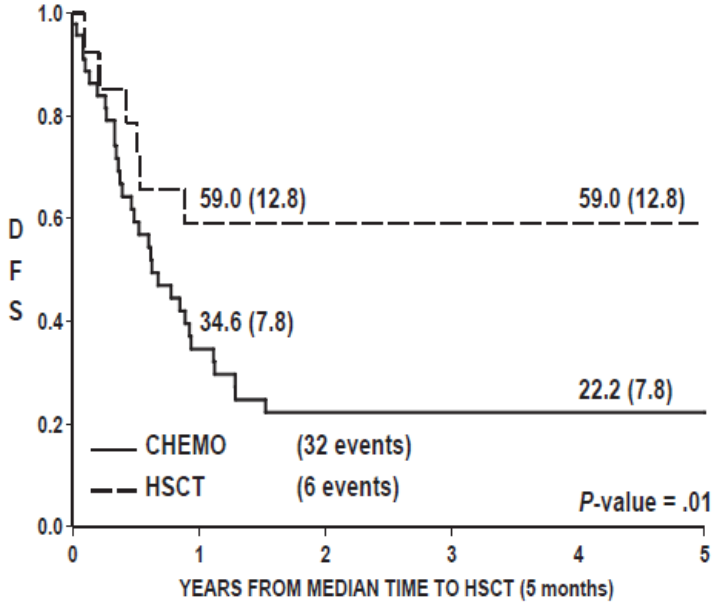


At risk						
CHEMO	170	129	103	81	59	34
HSCT	11	17	12	11	9	4

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.

Mann G, et al. *Blood*. 2010;116(15):2644-2650.

AlloSCT in infant *MLL*-rearranged ALL – IF-99 high-risk patients adjusted by waiting time to SCT



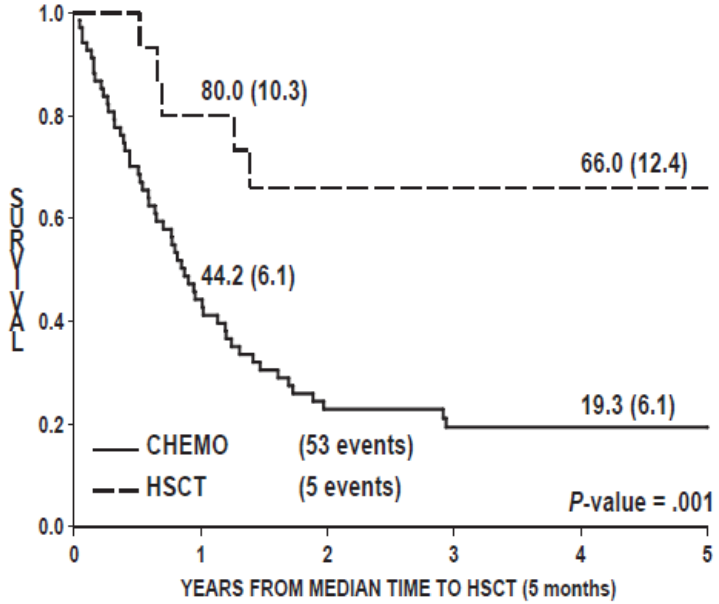


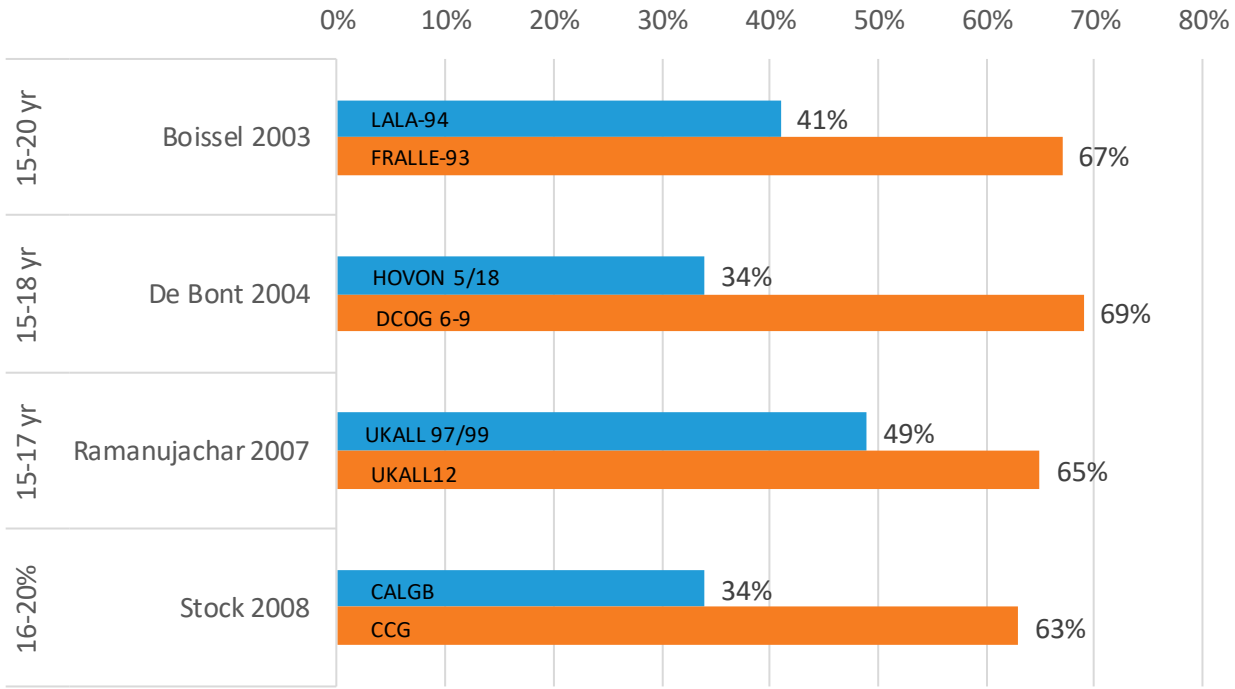
Figure 3. DFS and OS of 97 high-risk patients with *MLL*$^+$ infant ALL by treatment performed, adjusted by waiting time to HSCT. *P* value is from Cox Model. CHEMO indicates chemotherapy only; and HSCT, hematopoietic stem cell transplantation.

ALL

- Therapy elements
  - Choice of steroid
  - Dose intensity asparaginase
  - Which intensification
  - Which maintenance
  - Which central nervous system treatment
  - Who should get SCT
  - Adolescents

- New developments: targeting therapy

5-yr EFS in AYA patients treated on pediatric and adult protocols

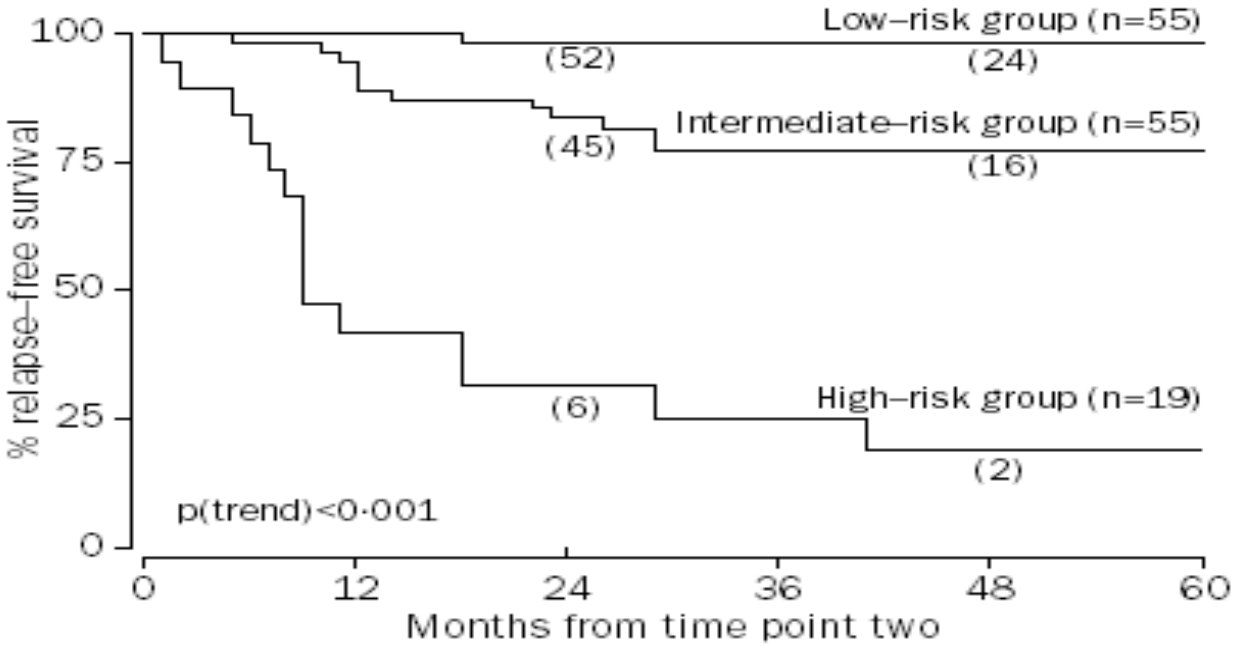


Boissel N, et al. *J Clin Oncol*. 2003;21(5):774-780; De Bont JM, et al. *Leukemia*. 2004;18(12):2032-2035; Ramanujachar R, et al. *Pediatr Blood Cancer*. 2007;48(3):254-261; Stock W, et al. *Blood*. 2008;112(5):1646-1654.

Targeting therapy in ALL

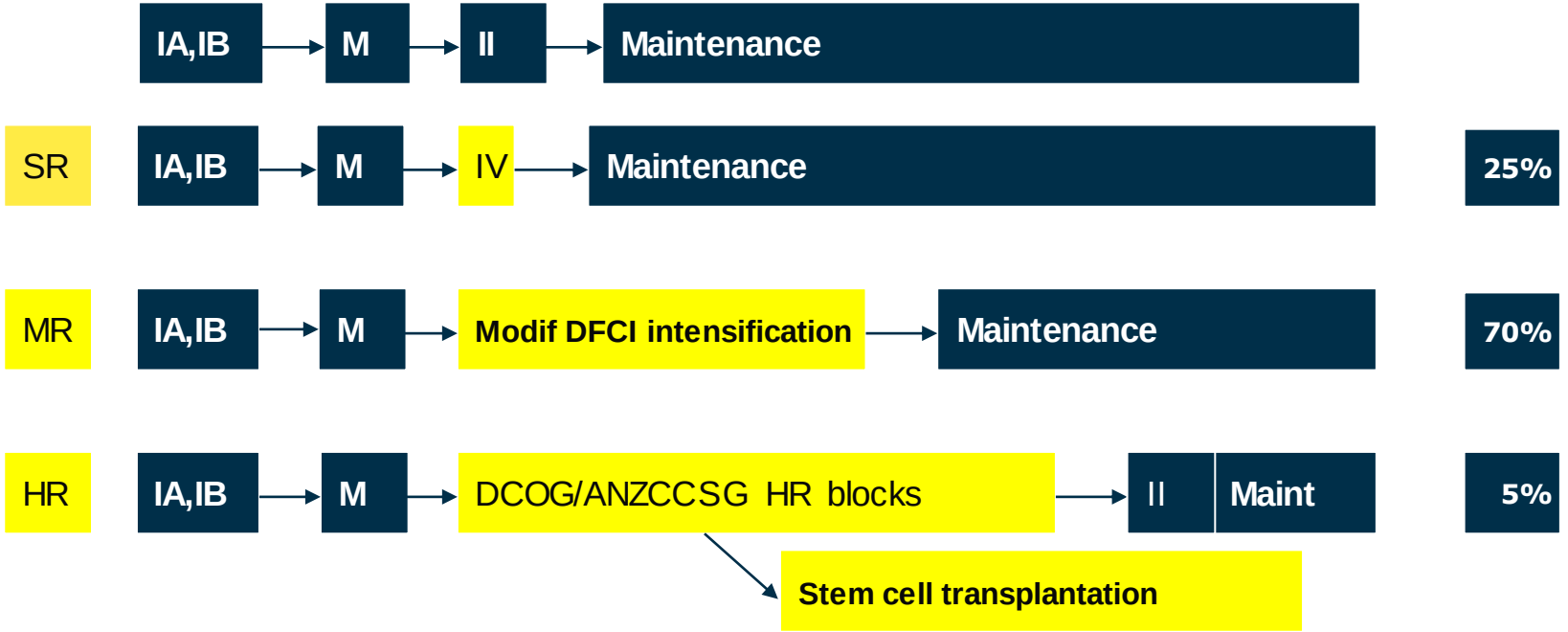
- Minimal residual disease (MRD) monitoring
- Therapeutic drug monitoring
- Genetic subclasses and pharmacology
- Specific targetable genetic lesions
- New (epi)genetic abnormalities
- Immunotherapies

Minimal residual disease and outcome in ALL



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

DCOG ALL-10 outlines (2004–2012)



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

ALL-10 protocol outcome

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

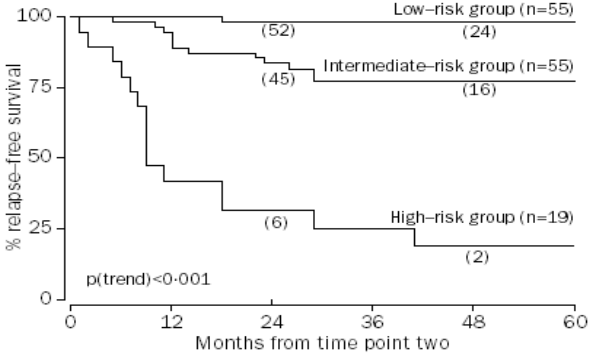
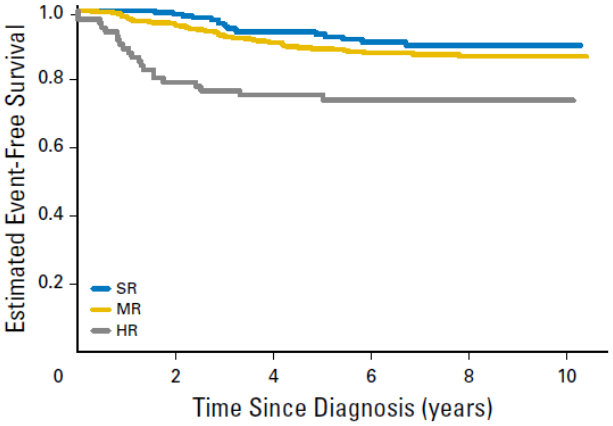
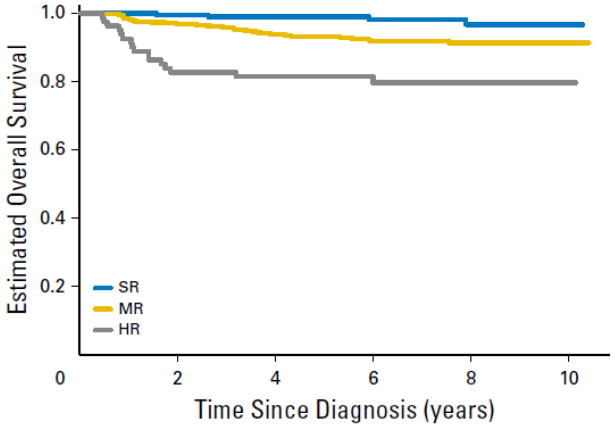


Figure 4: **Relapse-free survival of the three MRD-based risk groups, as defined by MRD information at time points one and two**

Event-free survival



Survival

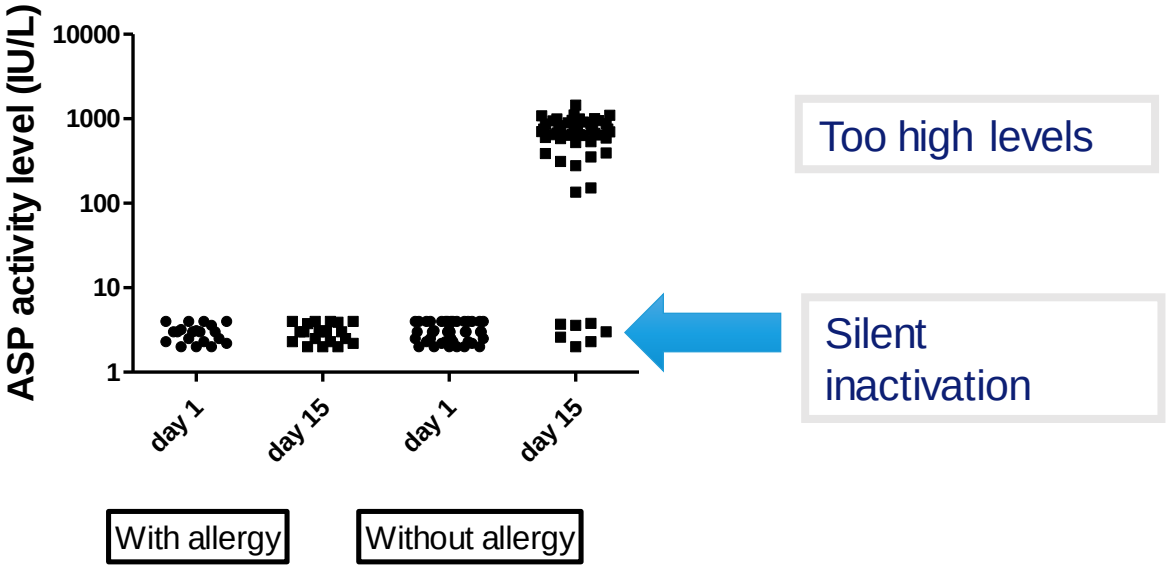


Van Dongen JJ, et al. *Lancet.* 1998;352(9142):1731-1738; Pieters R, et al. *J Clin Oncol.* 2016;34(22):2591-2601.

Targeting therapy in ALL

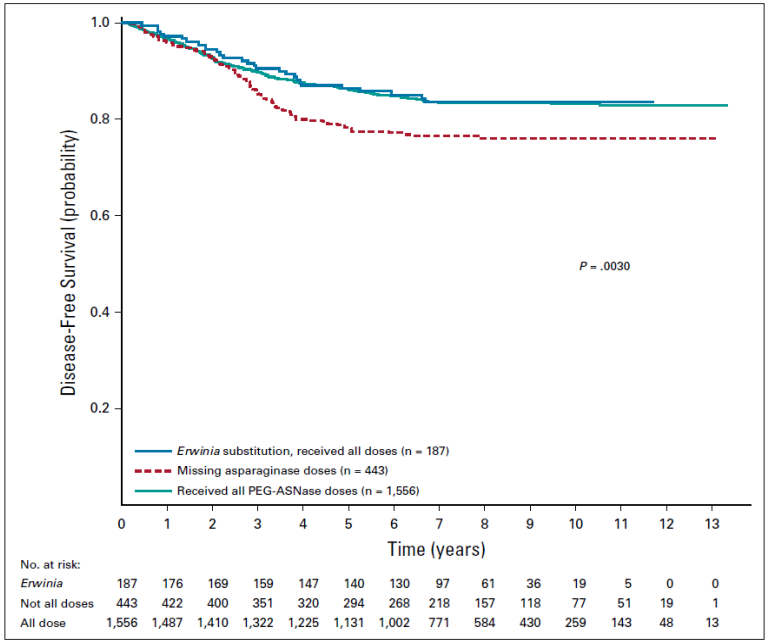
- Minimal residual disease (MRD) monitoring
- Therapeutic drug monitoring
- Genetic subclasses and pharmacology
- Specific targetable genetic lesions
- New (epi)genetic abnormalities
- Immunotherapies

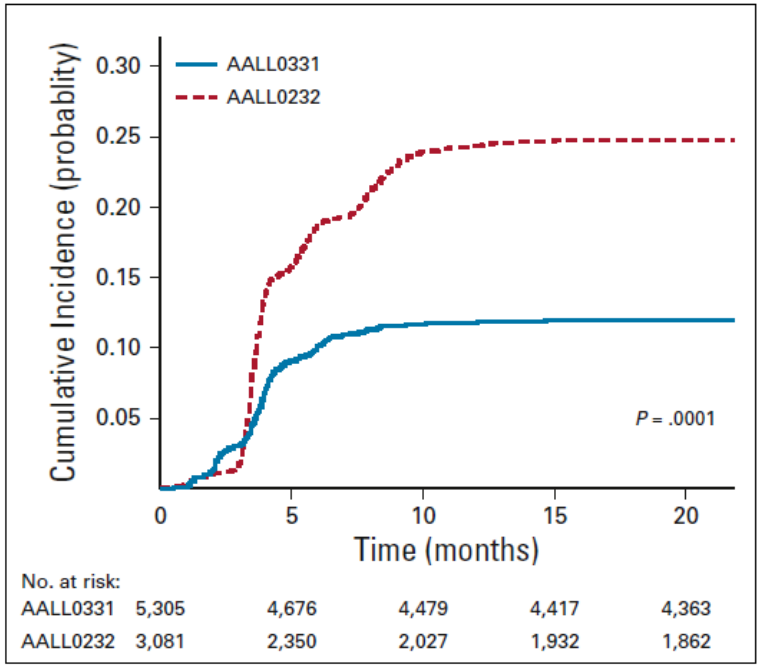
Asparaginase activity in patients with/without allergic reactions



Tong WH, et al. *Blood*. 2014;123(13):2026-2033.

DFS and CIR of NCI high-risk patients stratified by asparaginase received





Targeting therapy in ALL

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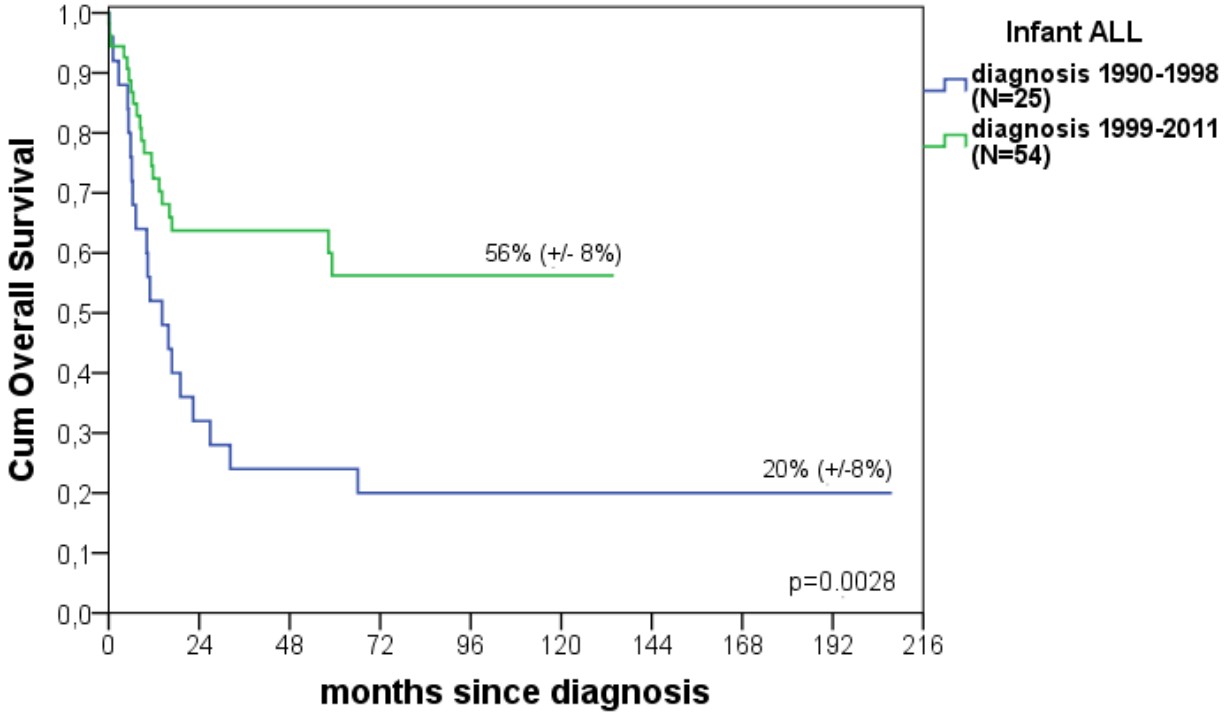
In vitro resistance/sensitivity of infant ALL

Drug	Infants <1 year median (25th–75th)	n =	c/preB ⩾1 year median (25th–75th)	n =	Resistance ratio[a]	P-value
Prednisolone	>250 (0.30–>250)	41	0.43 (0.12–12.5)	373	>581	0.001
Dexamethasone	3.61 (0.05–>6.0)	11	0.07 (0.01–0.55)	241	54.8	0.040
Vincristine	0.55 (0.10–2.54)	37	0.69 (0.24–2.52)	369	0.80	0.088
L-Asparaginase	0.96 (0.35–1.43)	29	0.08 (0.01–1.04)	361	12.0	0.001
Daunorubicin	0.07 (0.03–0.12)	33	0.09 (0.06–0.17)	386	0.83	0.090
6-Mercaptopurine	201 (95.2–321)	12	97.9 (50.4–248)	280	2.05	0.110
6-Thioguanine	6.04 (5.23–10.1)	27	5.92 (3.80–9.10)	299	1.02	0.256
Cytarabine	0.27 (0.13–0.51)	35	0.49 (0.27–1.31)	291	0.54	0.001
2-CdA[b]	0.02 (0.01–0.03)	29	0.030 (0.02–0.14)	79	0.59	<0.001
Etoposide	1.04 (0.48–2.56)	17	1.50 (0.64–2.77)	162	0.70	0.305
Teniposide	0.28 (0.16–0.75)	11	0.25 (0.18–0.58)	227	1.12	0.786
4-HOO-ifosfamide	4.08 (1.93–5.66)	20	3.07 (1.24–5.23)	221	1.33	0.185

Pieters R, et al. *Leukemia.* 1998;12(9):1344-1348; Ramakers-van Woerden NL, et al. *Leukemia.* 2004;18(3):521-529.

Survival in infant ALL before and after introduction of interfant protocol



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

Targeting therapy in ALL

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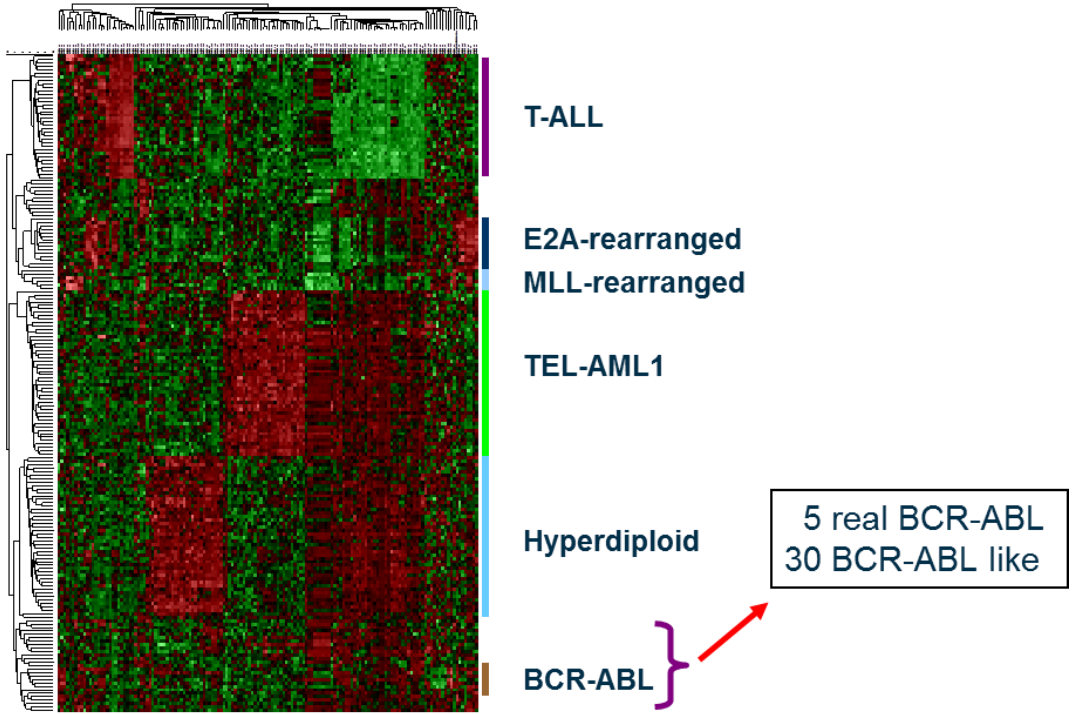
Discovery of BCR-ABL–like ALL



Den Boer ML, et al. *Lancet Oncol.* 2009;10(2):125-134.

Frequency of tyrosine kinase fusion genes in BCR-ABL–like ALL

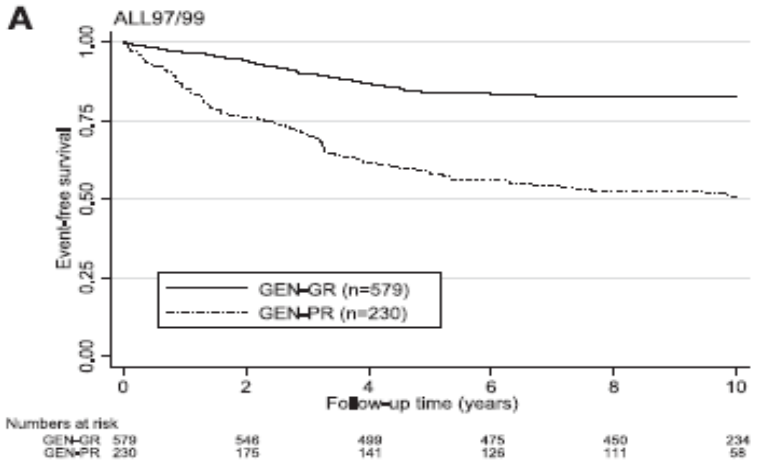
Marker	*BCR-ABL1*-like (n=77)	Remaining B-other (n=76)
***ABL1/ABL2* fusion**	**3.9%**	0%
ZMIZ1-ABL1	1	
FOXP1-ABL1	1	
RCSD1-ABL2	1	
***PDGFRB* fusion**	**5.2%**	0%
EBF1-PDGFRB	4	
***CSF1R* fusion**	**2.6%**	0%
SSBP2-CSF1R	2	
***JAK2* fusion**	**6.5%**	0%
PAX5-JAK2	3	
BCR-JAK2	1	
TERF2-JAK2	1	
CRLF2*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

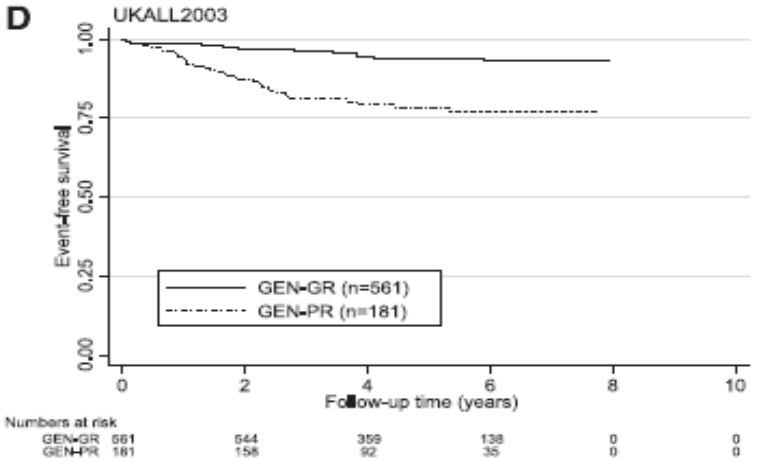
12% with *ABL-1* class fusions
Targetable with imatinib/dasatinib

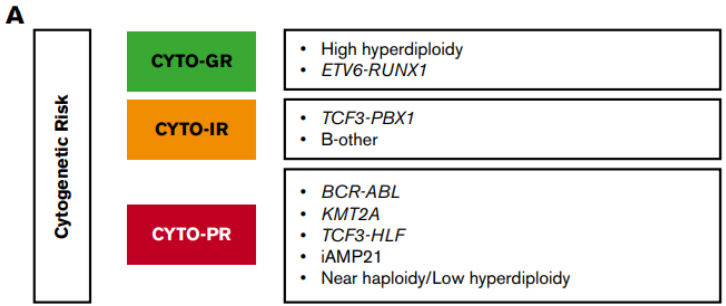
6% with *JAK2* fusions
Targetable with ruxolitinib????

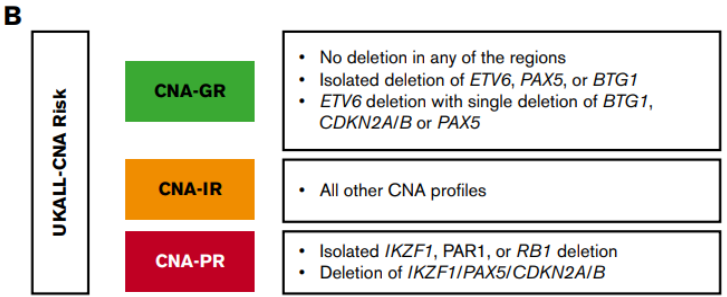
Boer JM, et al. *Oncotarget.* 2017;8(3):4618-4628.

EFS ALL97/99 and UKALL2003 by genetic risk group





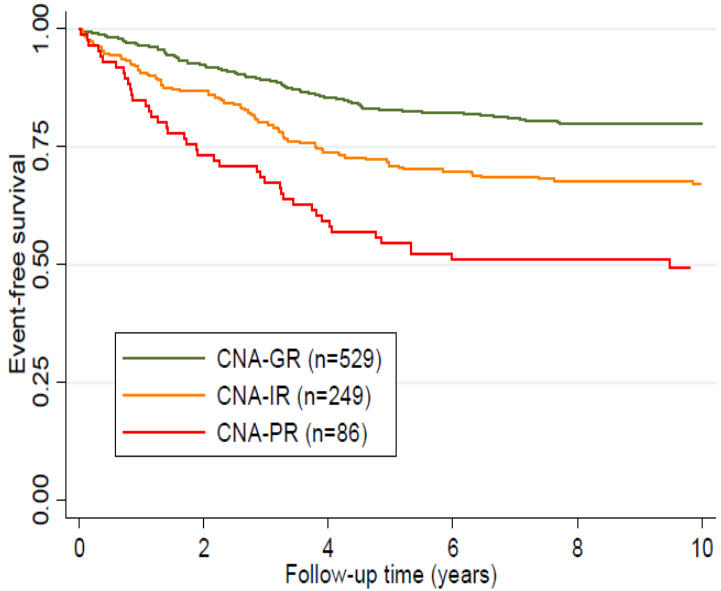




Moorman AV, et al. *Blood.* 2014;124(9):1434-1444; Hamadeh L, et al. *Blood Adv.* 2019;3(2):148-157.

UK copy number alteration (CNA) classifier in UKALL

CNA profile defines risk groups



CNA profiles by MLPA

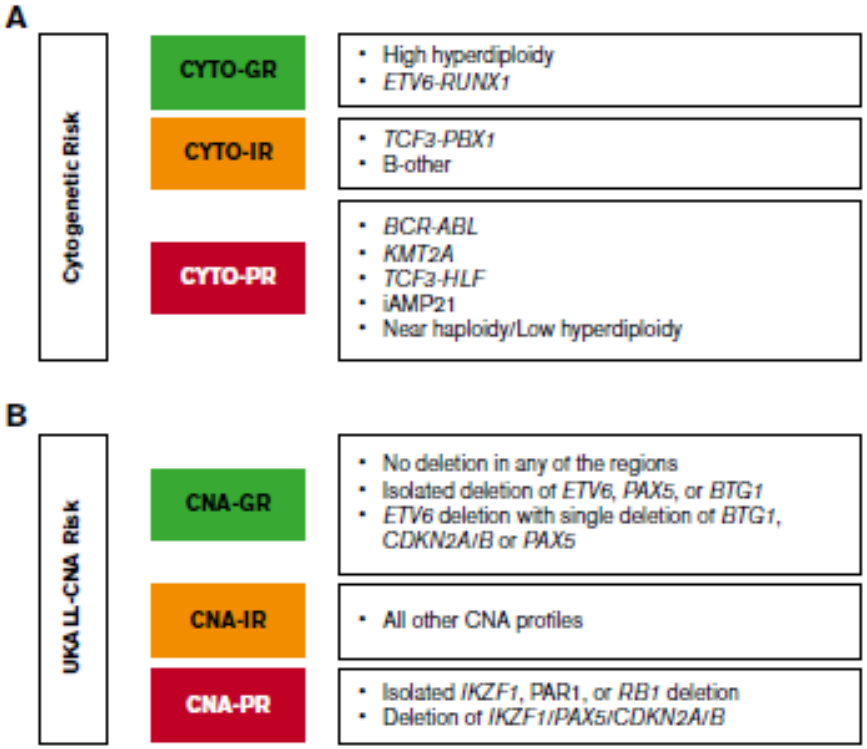
Good risk
- No deletion
- Isolated deletion of *ETV6, PAX5*, or *BTG1*
- *ETV6* deletion + *BTG1, CDKN2A/B* or *PAX5 deletion*

Intermediate risk
- All other CNA profiles

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

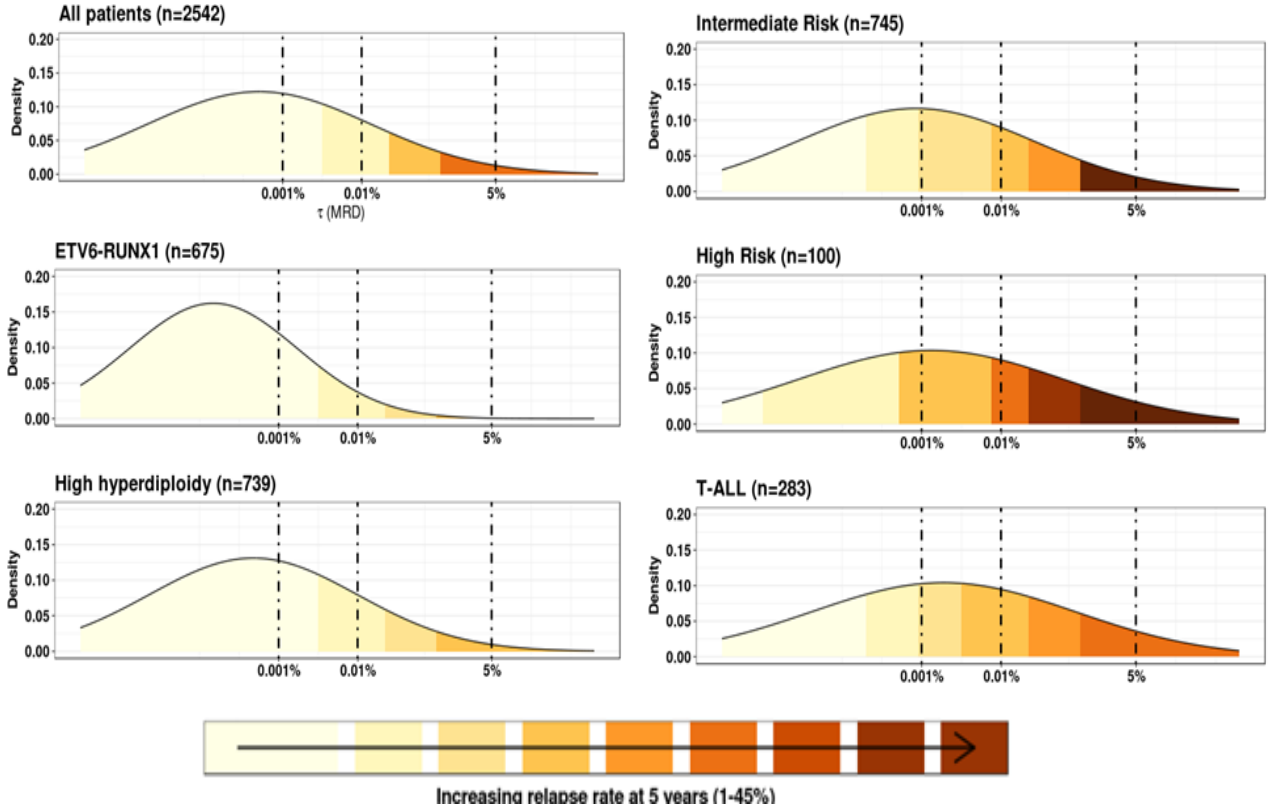
Moorman AV, et al. *Blood.* 2014;124(9):1434-1444.

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 DJ, et al. *J Clin Oncol*. 2018;36(1):34-43.

Risk groups, outcome, 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 CART T-lineage: non-random nelarabine

Personal communication from Dr Pieters.

Targeting therapy in ALL

- Minimal residual disease (MRD) monitoring
- Therapeutic drug monitoring
- Genetic subclasses and pharmacology
- Specific targetable genetic lesions
- New (epi)genetic abnormalities
- Immunotherapies: blinatumomab, inotuzumab, CAR T cells

Question 1

After listening to the presentation, which assertion is correct for first-line treatment of pediatric ALL?

a) A minority of patients with Ph+ ALL benefit from receiving allogenic SCT when receiving a tyrosine kinase inhibitor such as imatinib

b) The dose intensity of asparaginase has no impact on outcome

c) 6-mercaptopurine dose-intensity is of minor importance in maintenance therapy

d) Prednisone is a more effective drug than dexamethasone

Question 2

After listening to the presentation, which assertion is correct?

a) All children with a BCR-ABL–like ALL should be treated with a tyrosine kinase inhibitor such as imatinib or dasatinib

b) Cranial irradiation is indicated in B-lineage ALL and T-lineage ALL with a WBC >50 × 10^9/L at diagnosis

c) Copy number alterations (CNA) do not predict outcome

d) End of induction MRD and/or end of consolidation MRD is the most powerful prognostic factor

Thank you!

princess máxima center
pediatric oncology

Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

Current treatment options for relapsed ALL in children, including HSCT and COVID-19 considerations

Franco Locatelli

APTITUDE HEALTH

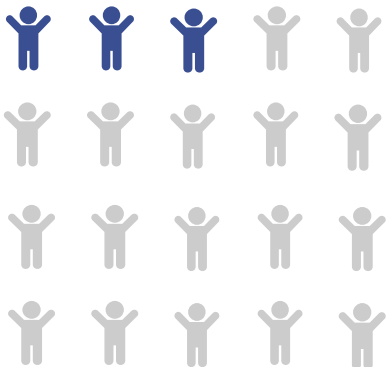
Current treatment options for relapsed ALL in children, including HSCT

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

Disclosures

Company name	Disclosure
Amgen	Honoraria, Speakers' bureau, Consultancy and Travel support
Novartis	Consultancy
Medac	Speakers' bureau
Miltenyi	Speakers' bureau
Jazz Pharmaceuticals	Honoraria, Speakers' bureau
Bluebird bio	Speakers' bureau and Consultancy
SOBI	Consultancy

Background



RELAPSE RATE:

Approximately 15-20% of children with ALL relapse after standard treatment[1]

PROGNOSIS OF RELAPSED ALL LARGELY DEPENDS ON[2-6]

- ✓ Time from diagnosis to relapse
- ✓ Site of relapse
- ✓ Blast immune-phenotype

Almost all children with relapsed T-ALL and 2/3 of those with BCP-ALL are candidates for alloHSCT after a second morphological complete remission (M1 marrow) is achieved[7-8]

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

1. Hunger SP, Mullighan CG. *N Engl J Med.* 2015;373:1541-1552. 2. Chessells JM, et al. *Br J Haematol*. 2003;123:396-405. 3. Irving JA, et al. *Blood.* 2016;128:911-922. 4. Krentz S, et al. *Leukemia.* 2013;27:295-304. 5. Malempati S, et al. *J Clin Oncol.* 2007;25:5800-7. 6. Schrappe et al. *N Engl J Med.* 2012;366:1371-1381. 7. Locatelli F, et al. *Blood.* 2012;120:2807-16. 8. Peters C, et al. *J Clin Oncol.* 2015;33:1265-1274.

Immuno-phenotype	B-cell precursor			(pre) T		
Time-Point/Site	Extra-med. Isolated	Bone marrow combined	Bone marrow isolated	Extra-med. isolated	Bone marrow combined	Bone marrow isolated
Very early	**HR**	**HR**	**HR**	**HR**	**HR**	**HR**
Early	**SR**	**SR**	**HR**	**SR**	**HR**	**HR**
Late	**SR**	**SR**	**SR**	**SR**	**HR**	**HR**

Late defined as: >6 months after cessation of frontline therapy, ie, >30 month after initial diagnosis

https://cordis.europa.eu/docs/results/278/278514/final1-intreall-278514-final-publishable-summary-whole-project-incl-figures.pdf

IntReALL-BCP 2020 – New risk stratification

VHR (15%)

Eligible to allo-HSCT or consolidation therapy

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

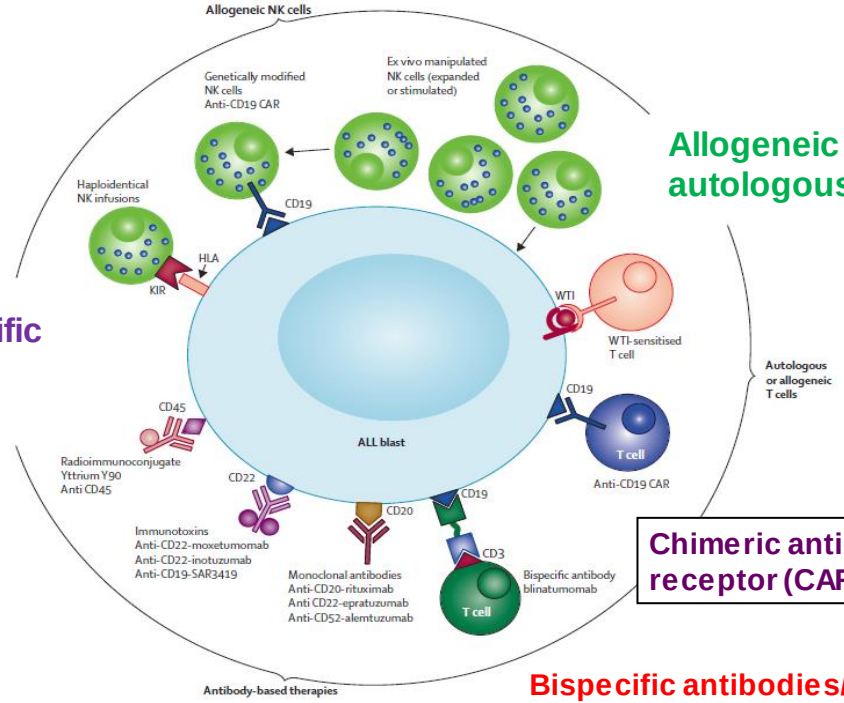
SR (60%)

- Late isolated or combined medullary/extramedullary relapse (allo-HSCT depending on MRD response at the end of induction)

HR (25%)

- Early isolated or combined medullary/extramedullary relapse (all these patients are candidates to receive allo-HSCT as final consolidation)

New immunological approaches under investigation in childhood ALL



Allogeneic and autologous NK cells

Immunotoxin-specific antibodies

Chimeric antigen receptor (CAR) T cells

Bispecific antibodies/antibody constructs

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

A phase I/II study of inotuzumab ozogamicin as a single agent and in combination with chemotherapy for pediatric CD22-positive relapsed/refractory ALL, ITCC-059 study

Stratum 1: R/R CD22 positive BCP-ALL patients, aged 1-18 years

• ***Stratum 1A***	Single agent InO	Enrolment completed
• ***Phase 2***	InO to determine preliminary activity	Open at DL2
• ***Stratum 1B***	InO in combination with adjusted R3 block	Not yet open

Stratum 2: Other CD22 positive B-cell malignancies

• ***Stratum 2***	Explorative cohort	Open at DL2

Dose level 1: 1.4 mg/m² in course 1

- C1D1: 0.6 mg/m²
- C1D8 and C1D15 (and next doses): 0.4 mg/m²

Dose level 2: 1.8 mg/m² in course 1

- C1D1: 0.8 mg/m²
- C1D8 and C1D15 (and next doses): 0.5 mg/m²

https://www.trialregister.nl/trial/5629

Patient characteristics

Characteristic	n=25
Age, years; median (range)	11 (1.7–16.9)
Age category, n (%)	
>1– ≤2 years	1 (4)
>2– ≤6 years	4 (16)
>6 years	20 (80)
Gender, n (%)	
Male	17 (68)
Female	8 (32)
Bone marrow status at screening, n (%)	
M3	22 (88)
M2	3 (12)
White blood cell count at screening, per L; median (range)	3.5×10^9 ($0.19–8.59 \times 10^9$)
Disease status at enrolment	
1st relapse after HSCT	7 (28)
≥2nd relapse	15 (60)
Refractory	3 (12)

Characteristic	n=25
Number of prior treatments; median (range)	2 (2–7)
Specific elements of prior treatment, n (%)	
Prior HSCT	14 (56)
Prior blinatumomab	6 (24)
Prior CAR-T	1 (4)
CD22 expression at screening	
CD22-positive ALL cells, MFI; median (range)	2768 (505–8370)
CD22-positive blasts; % (range)	98 (53–100)
Cytogenetic subtype, n (%)[a]	
Hypodiploid	4 (16)
Hyperdiploid	13 (52)
t[1;19](q23;p13)	2 (8)
t[4;11](q21;q23)	1 (4)
Normal cytogenetics	4 (16)
Not done	1 (4)

[a]Note: patients can have both hypodiploidy and a translocation

ALL, acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell; HSCT, hematopoietic stem cell transplant; MFI, mean fluorescence intensity

Brivio E, et al. *Blood.* 2020. DOI: 10.1182/blood.2020007848. Online ahead of print.

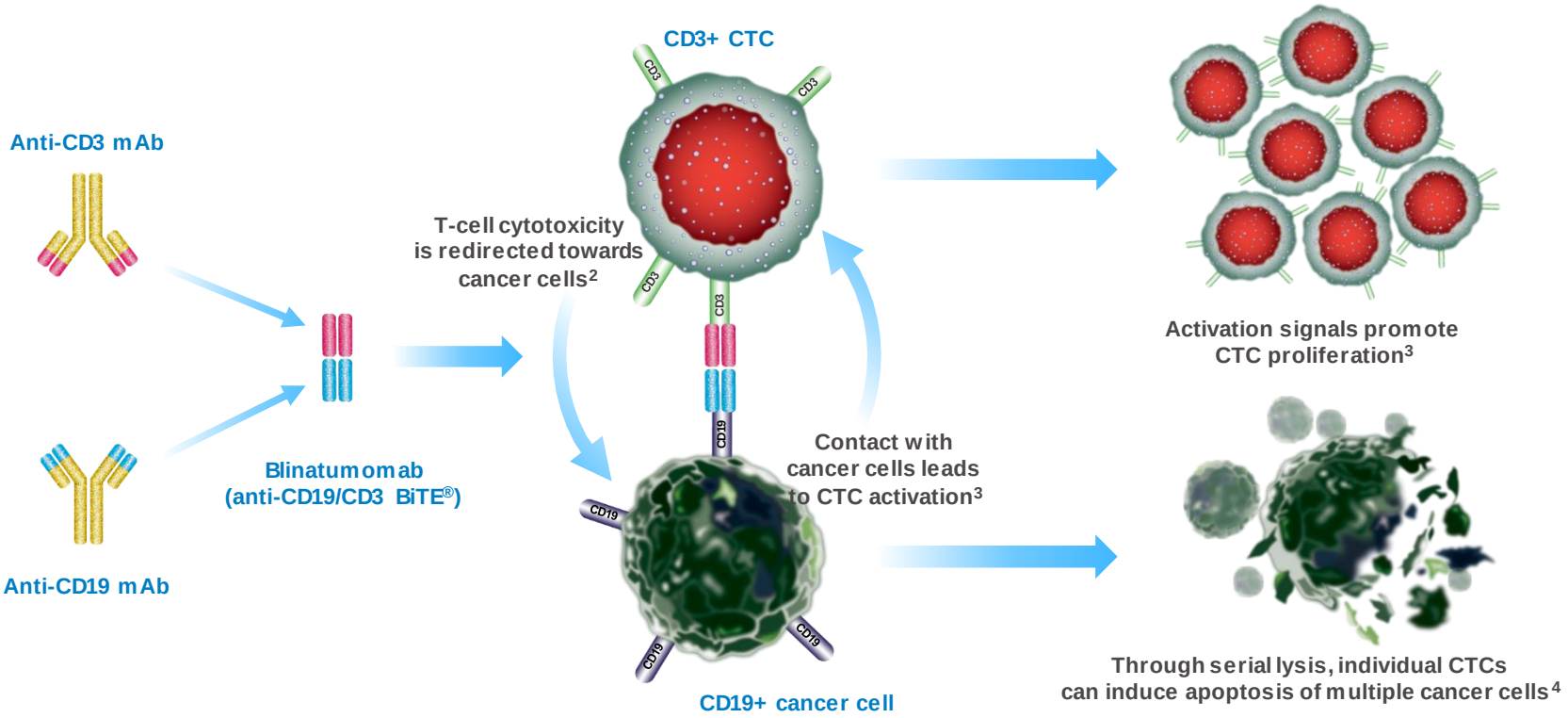
Results, n = 20

ORR after 1 course	80% 75% at DL1 85% at DL2 (CR n = 15, CRp n = 1, CRi n = 4)
Achievement of MRD neg	79% (n = 15)
Median FU	13.3 months (range 1.1–14.0)
Median duration of response	8 months (range 1.1–14.0)
6-m EFS/OS	63.3% (95% CI: 45.8–87.6) 66.7% (95% CI 47.9-93.0)
12 m EFS/OS	33.4% (95% CI: 16.5–67.4) 38.7% (95% CI: 21.3–70.4)

- 8 patients received a consolidation treatment with HSCT (n = 6) or CAR T cells (n = 2) (median of 61 days [range 23-125] after the last InO dose)
- 2/13 patients with available samples showed CD22-negativity at relapse

Brivio E, et al. ASH Annual Meeting 2019. *Blood*. 2019;134(suppl_1):2629.

The BiTE® blinatumomab: Designed to bridge cytotoxic T cells (CTCs) to CD19-expressing cancer cells, resulting in cancer cell death[1]



BiTE®, bispecific T-cell engager; mAb, monoclonal antibody.

1. Baeuerle PA, Reinhardt C. *Cancer Res.* 2009;69:4941-4944; 2. Bargou R, et al. *Science.* 2008;321:974-977; 3. Klinger M, et al. *Blood.* 2012;119:6226-6233; 4. Hoffmann P, et al. *Int J Cancer.* 2005;115:98-104.

High Remission Rates In Pediatric Patients With Resistant Acute Lymphoblastic Leukemia Treated With Blinatumomab: Updated Analysis Of An Expanded Access Study (RIALTO)

Franco Locatelli[1], Gerhard Zugmaier[2], Peter Bader[3], Sima Jeha[4], Paul-Gerhardt Schlegel[5], Jean-Pierre Bourquin[6], Rupert Handgretinger[7], Benoit Brethon[8], Claudia Rossig[9], Christiane Chen-Santel[10]

[1]Department of Hematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Sapienza, University of Rome, Italy; [2]Amgen Research (Munich) GmbH, Munich, Germany; [3]Department for Children and Adolescents, University Hospital Frankfurt, Frankfurt, Germany; [4]St Jude Children's Research Hospital, Memphis, TN; [5]University Children's Hospital Würzburg, Würzburg, Germany; [6]Department of Pediatric Oncology, Children's Research Centre, University Children's Hospital Zurich, Zurich, Switzerland; [7]Hematology/Oncology, University Children's Hospital Tübingen, Tübingen, Germany; [8]Pediatric Hematology and Immunology Department, Robert Debré Hospital, APHP, Paris, France; [9]University Children's Hospital Münster, Münster, Germany; [10]Charité University Medicine Berlin, Berlin, Germany

Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Patient eligibility

Key inclusion criteria	• Age >28 days and <18 years • CD19-positive B-precursor ALL with ≥5% blasts in the bone marrow, or <5% blasts but with minimal residual disease (MRD) level $\geq 10^{-3}$ • Relapsed/refractory disease defined as – ≥2 relapses – Relapse after alloHSCT – Refractory to prior treatments • Prior treatment with blinatumomab was allowed, provided the patient was not blinatumomab-refractory or intolerant, and leukemic cells were CD19 positive
Key exclusion criteria	• Clinically relevant CNS pathology • Chemotherapy within 2 weeks, radiotherapy within 4 weeks, or immunotherapy within 6 weeks • Grade 2–4 acute GvHD or active chronic GvHD • Immunosuppressive agents to prevent or treat GvHD within 2 weeks

CNS, central nervous system; GvHD, graft-versus-host disease; alloHSCT, allogeneic haematopoietic stem cell transplantation.
Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Best response during first 2 cycles of blinatumomab

Response	Patients with ≥5% blasts at baseline (N = 98)	
	n (%)	95% CI
CR in first 2 cycles, n (%)	58 (59)	48.8–69.0
CR with full recovery of peripheral blood counts	39 (67)	30.0–50.2
CR with incomplete recovery of peripheral blood counts	6 (10)	2.3–12.9
CR without recovery of peripheral blood counts	13 (22)	7.3–21.6
MRD response	46 (47)	36.8–57.3
MRD non-responsive	19 (19)	21.1–28.6
Proceeded to HSCT, n (%)	36 (62)	48.4–74.5
Hypoplastic or acellular bone marrow	1 (1)	0.0–5.6
Partial remission	0	0.0–3.7
Non-CR		
Stable disease	5 (5)	1.7–11.5
Progressive disease	20 (20)	12.9–29.7
Not evaluable	1 (1)	0.0–5.6
No response data	13 (13)	7.3–21.6
Prior HSCT	45 (46)	35.9–56.3
Genetic abnormality	30 (31)	21.9–40.9

Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Response within first 2 cycles of blinatumomab

Patient Subgroup	CR		CR with full haematological recovery		MRD	
	n/N1	%	n/N1	%	n/N1	%
Baseline blast category						
<5%	11/12	92	3/12	25	11/12	92
5-49%	39/55	71	26/55	47	33/55	60
≥50%	19/42	45	13/42	31	13/42	31
Genetic abnormality						
Yes	17/32	53	11/32	34	11/32	34
No	52/78	67	31/78	40	46/78	59
t(17;19)	2/2	100	2/2	100	2/2	100
Down syndrome	4/4	100	2/4	50	4/4	100
Prior HSCT						
Yes	28/45	62	19/45	42	22/45	49
No	41/65	63	23/65	35	35/65	54
Prior blinatumomab	4/4	100	4/4	100	3/4	75
Prior relapses						
1	17/30	57	12/30	40	13/30	43
≥2	42/63	67	24/63	38	36/63	57

alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; MRD, minimal residual disease. n/N1, number of responders/total number of patients with evaluable data under each category.

Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Superior Event-free Survival With Blinatumomab Versus Chemotherapy in Children With High-risk First Relapse of B-cell Precursor Acute Lymphoblastic Leukemia: A Randomized, Controlled Phase 3 Trial

Franco Locatelli, Gerhard Zugmaier, Carmelo Rizzari, Joan Morris, Bernd Gruhn, Thomas Klingebiel, Rosanna Parasole, Christin Linderkamp, Christian Flotho, Arnaud Petit, Concetta Micalizzi, Noemi Mergen, Abeera Mohammad, Cornelia Eckert, Anja Moericke, Mary Sartor, Ondrej Hrusak, Christina Peters, Vaskar Saha, and Arend von Stackelberg

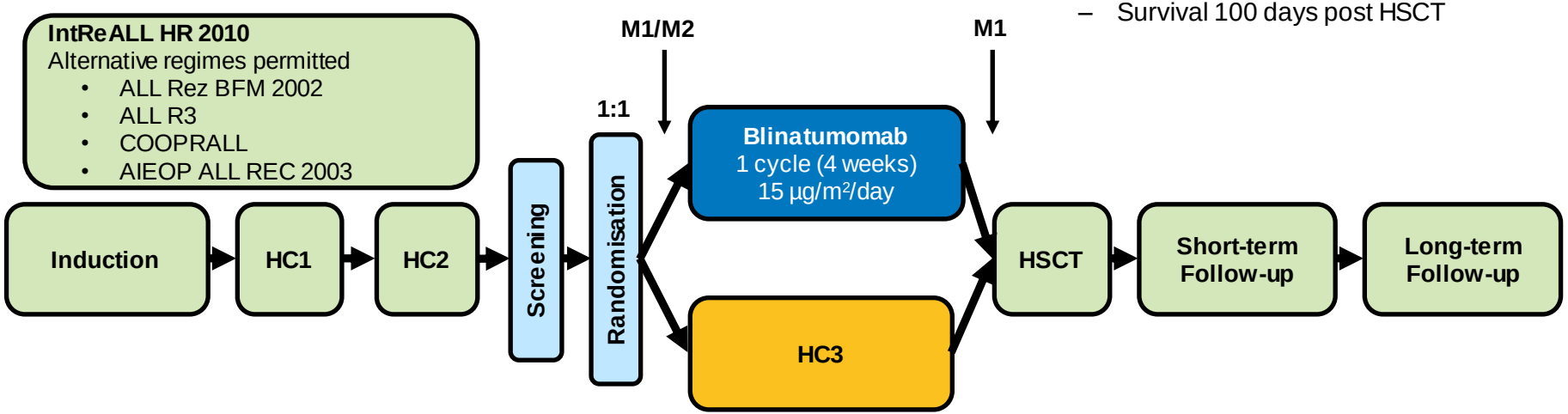
Locatelli F, et al. EBMT 2020. Abstract GS2-5 and oral presentation.

Open-label, randomised, phase III trial: 47 centres, 13 countries

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

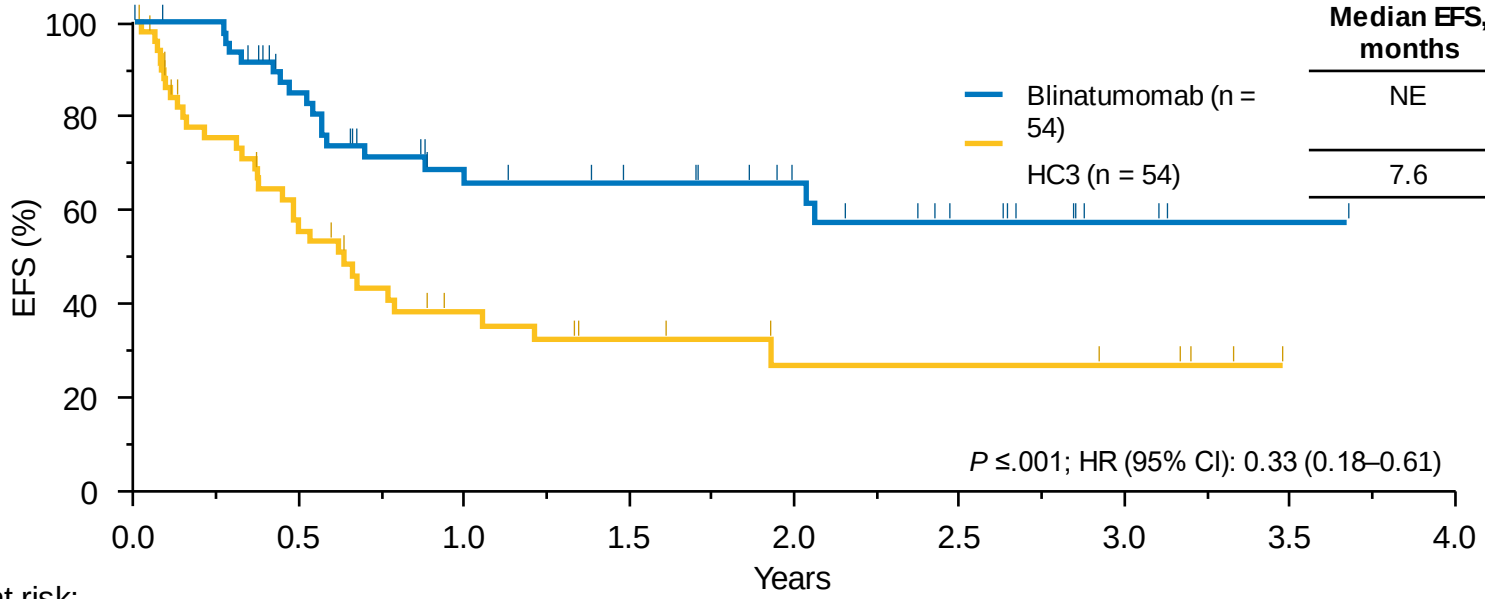
Stratification
- Age: <1 year, 1 to 9 years, >9 years
- BM status at end of HC2
  - M1 with MRD >10^{-3}
  - M1 with MRD <10^{-3}
  - M2

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



BCP, B-cell precursor; EFS, event-free survival; HC, high-risk consolidation.
Locatelli F, et al. EBMT 2020. Abstract GS2-5.

Superior EFS in the blinatumomab arm



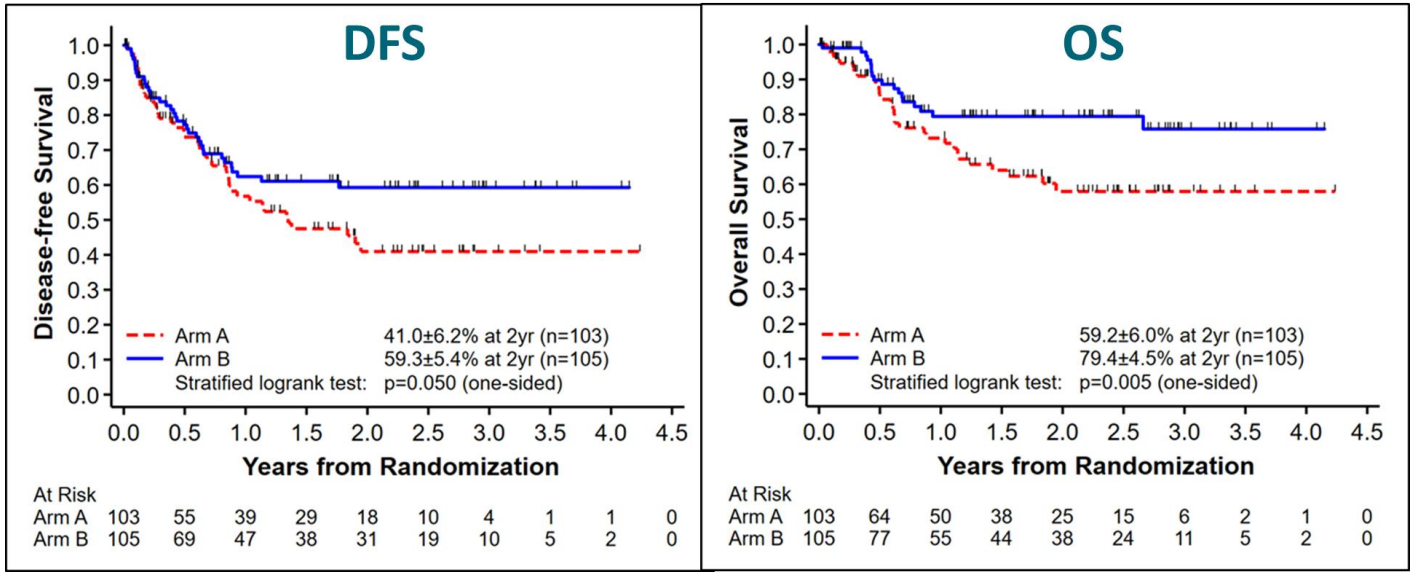
	Median EFS, months	95% CI
Blinatumomab (n = 54)	NE	24.4–NE
HC3 (n = 54)	7.6	4.5–12.7

Subjects at risk:

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

P, stratified log rank P-value; HR, hazard ratio from stratified Cox regression.
Adapted from Locatelli F, et al. EBMT 2020. Abstract GS2-5 and oral presentation.

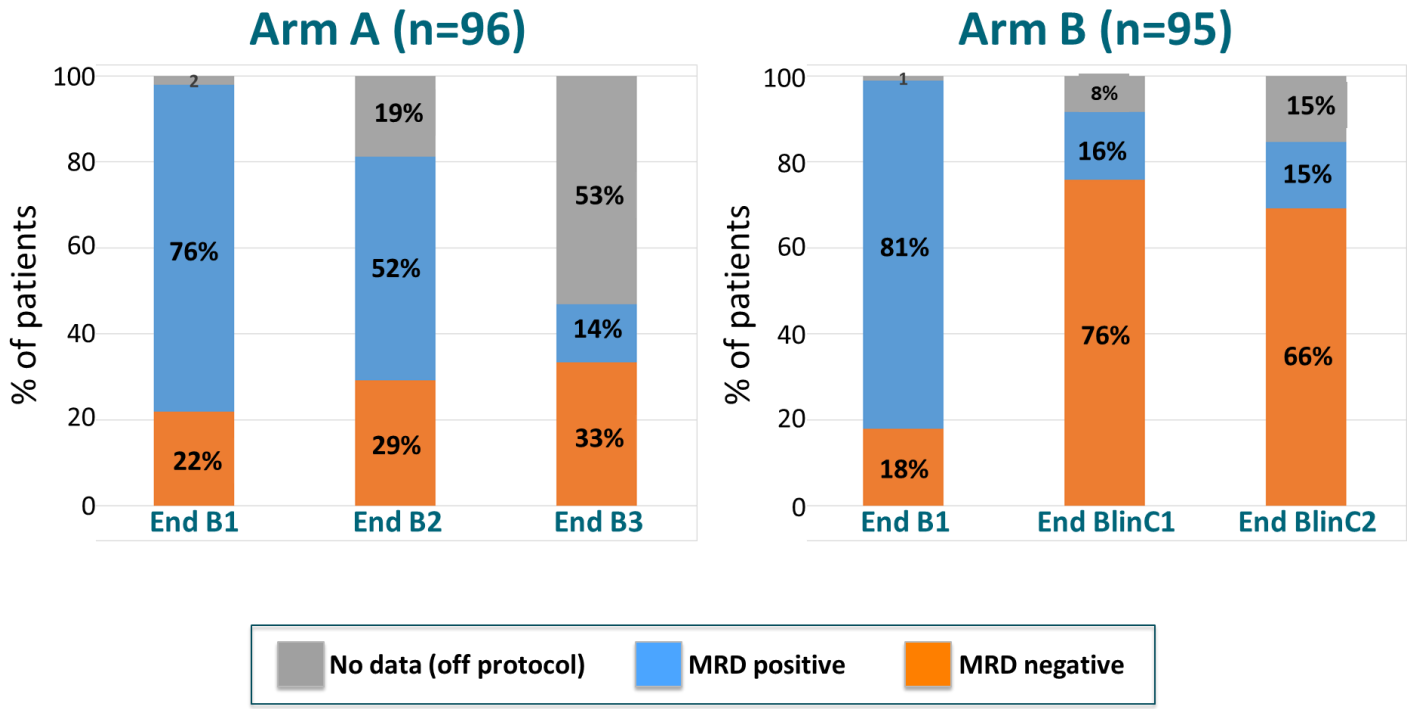
COG AALL1331 HR/IR ALL relapse, Blina vs Ctx design



Arm A = Chemotherapy
Arm B = Blinatumomab
Median follow-up = 1.4 years

Brown, PA, et al. *Blood*. 2019;134(suppl_2): LBA-1.

COG AALL1331 HR/IR ALL relapse, Blina vs Ctx MRD clearance



Brown, PA, et al. *Blood.* 2019;134(suppl_2): LBA-1.

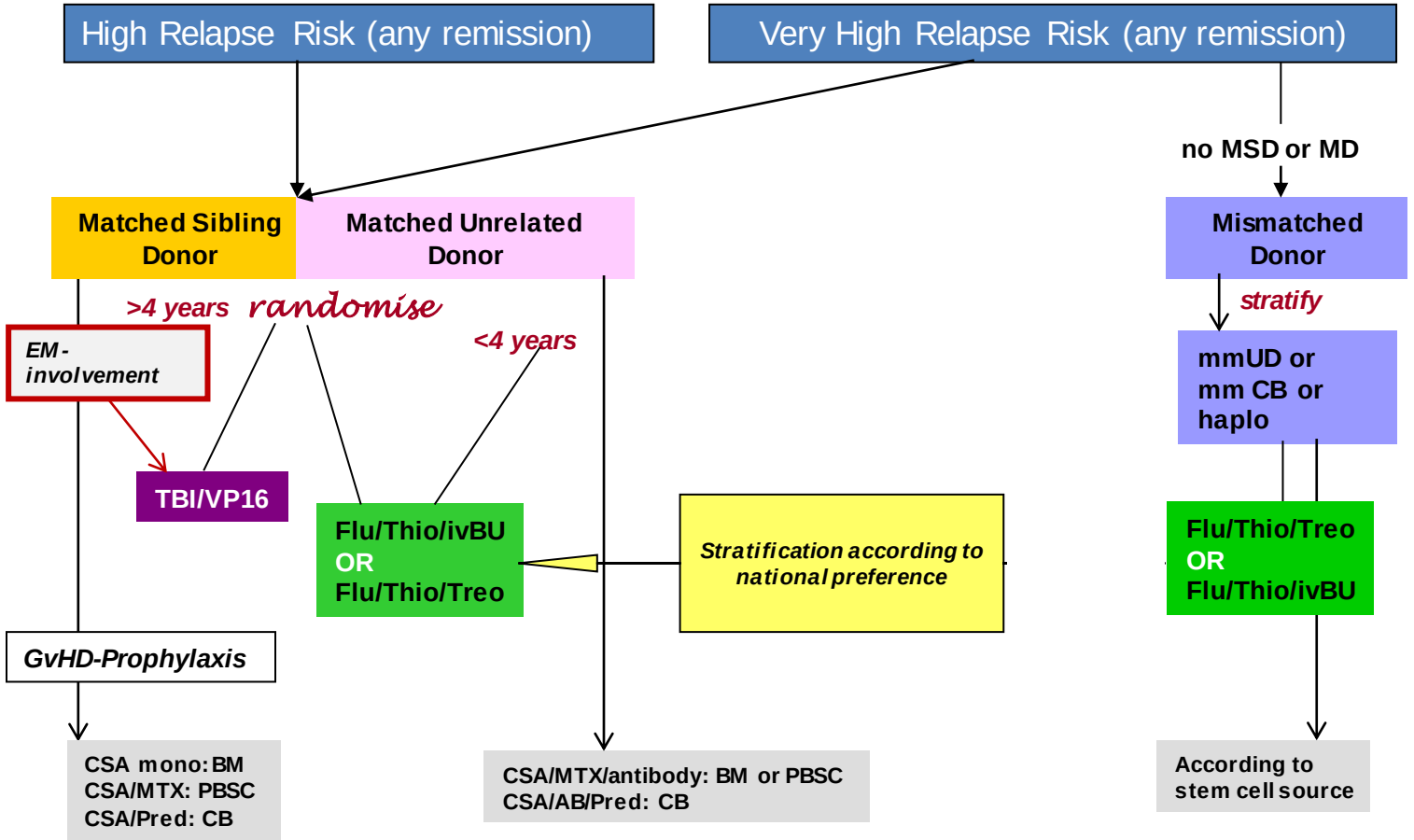
TBI or Chemotherapy-Based Conditioning for Children and Adolescents with ALL: the **FORUM** Trial on Behalf of the AIEOP-BFM-ALL SG, IBFM-SG, INTREALL-SG and EBMT-PD WP

Christina Peters

Vienna, Austria

Date: June 12, 15.00 – 17.00
Program section: Presidential Symposium

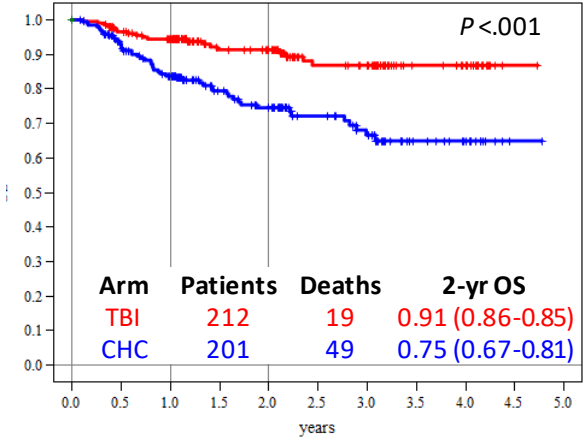
Study design ALL SCTped FORUM



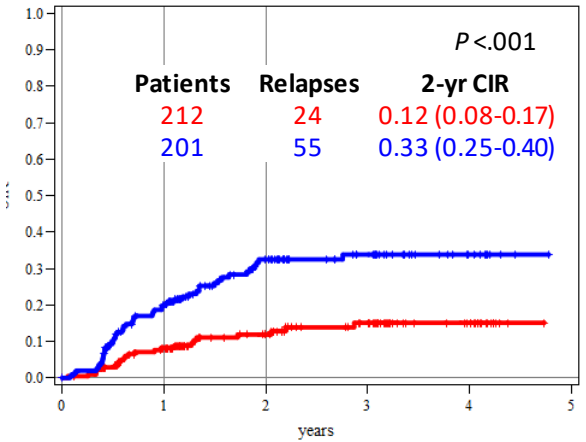
Peters C, et al. EHA 2020. Abstract S102.

Results: Intention to treat

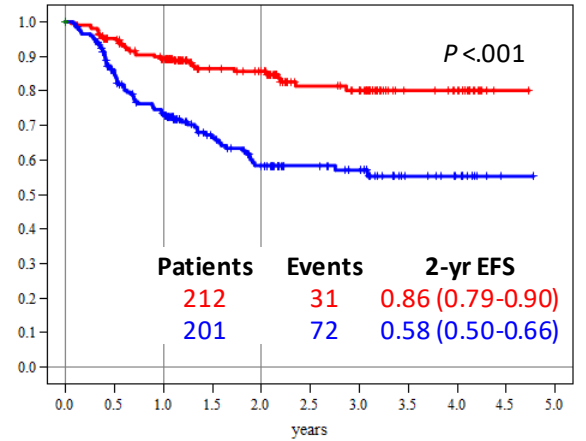
Overall Survival



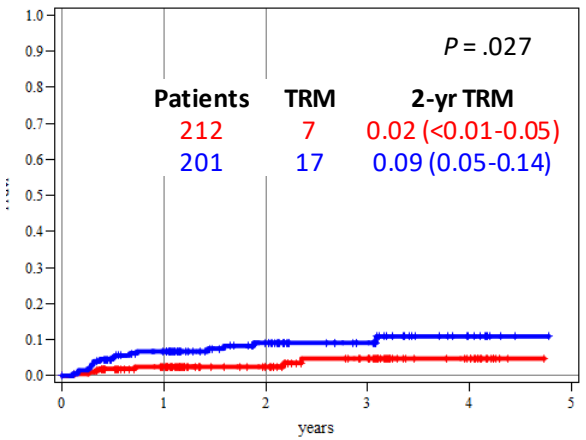
Relapses (CIR)



EFS



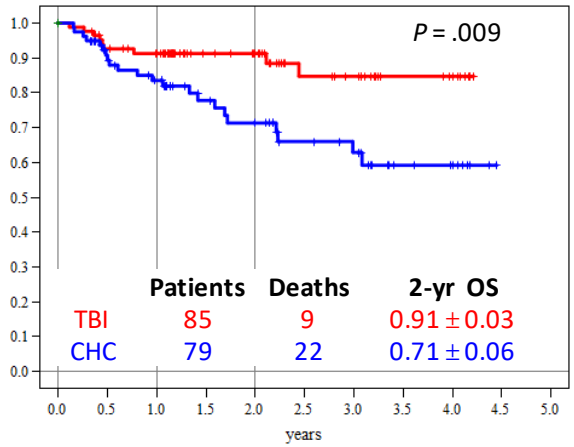
TRM



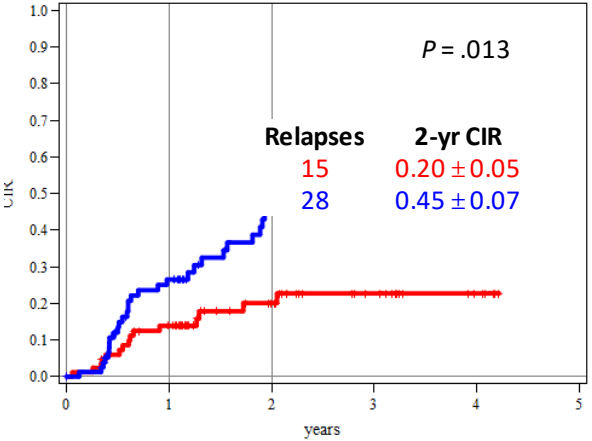
Peters C, et al. EHA 2020. Abstract S102.

Results: CR2 Intention to treat

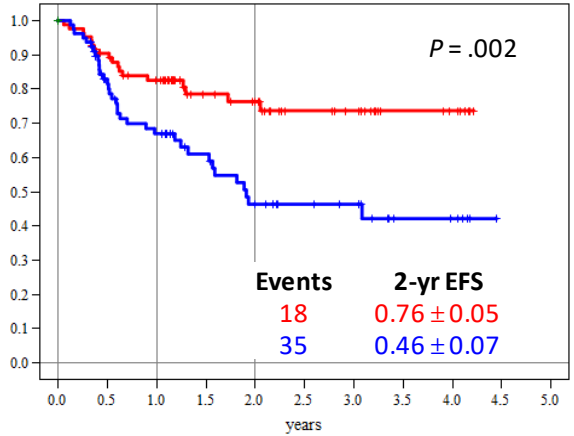
Overall Survival



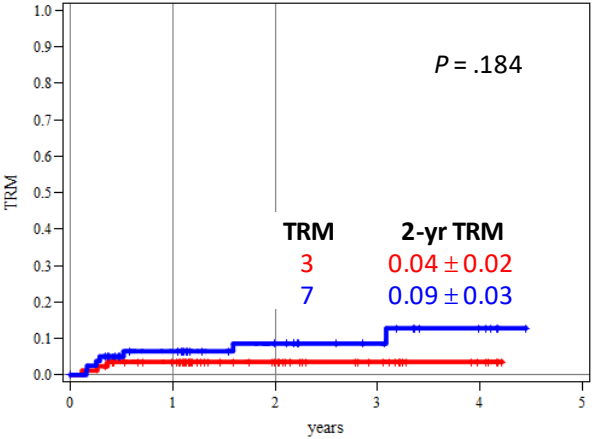
Relapses (CIR)



EFS



TRM



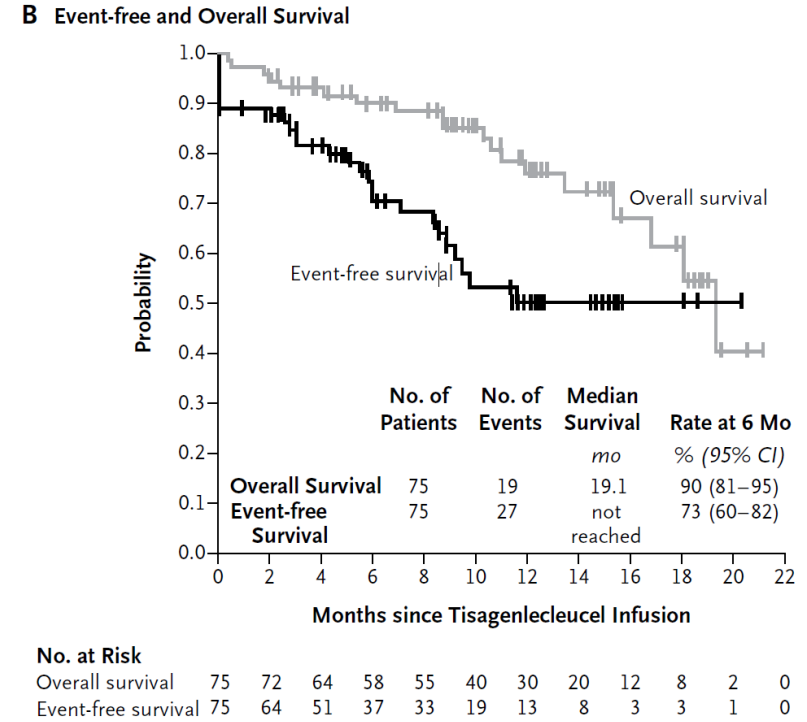
Peters C, et al. EHA 2020. Abstract S102.

Summary of ELIANA study

ORIGINAL ARTICLE

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

- 92 patients enrolled, 75 treated
- 73% Grade 3–4 AEs related to CAR T
- **81% → CR/CRi, all MRD negative; 66% in intention-to-treat analysis**
- 1-year EFS 50%
- **Demonstrates feasibility of delivery in multiple centres**
- **FDA approval for R/R pediatric ALL: August 2017**
- **Also approved in the EU, Canada, and Switzerland**



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

Frequency of high-risk cytogenetic abnormalities in ELIANA and ENSIGN

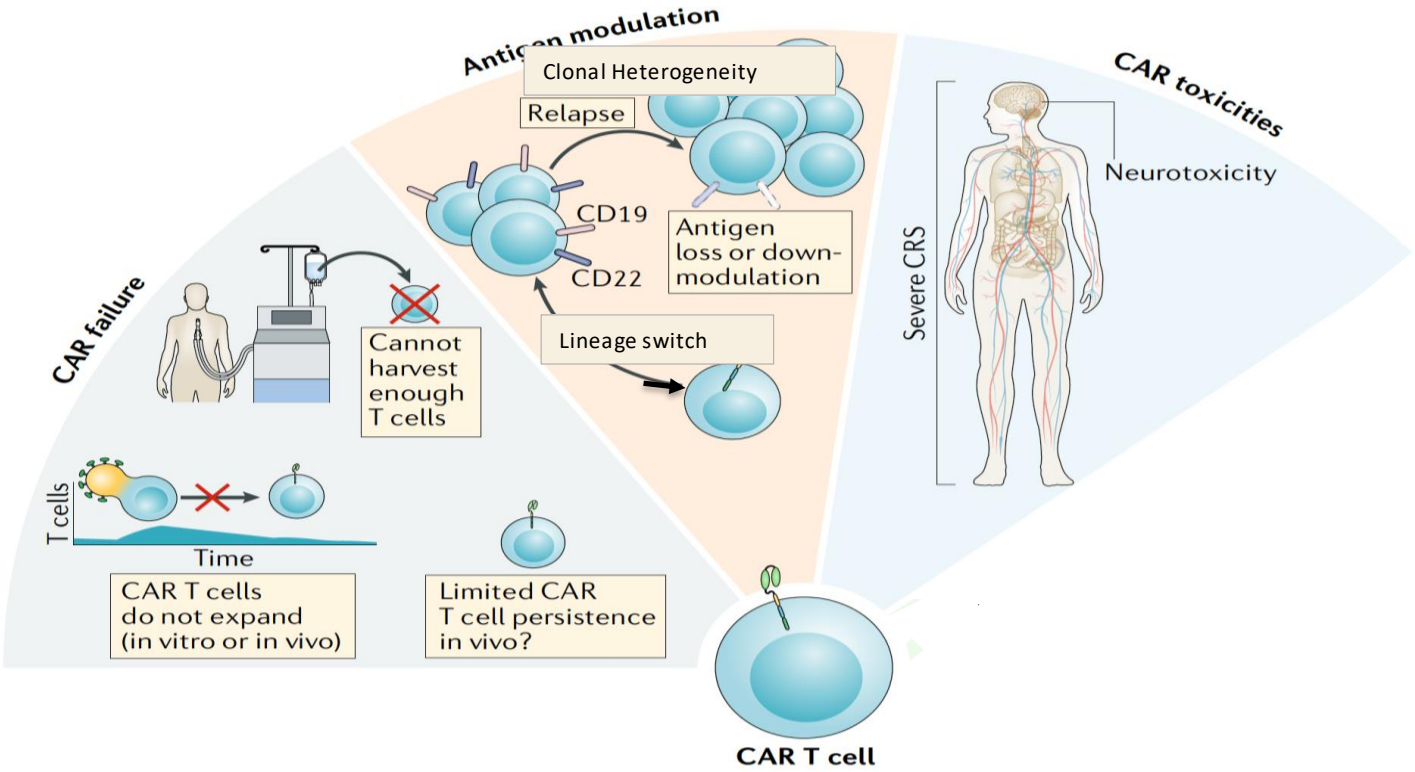
- 29 of 137 infused patients had high-risk cytogenetic abnormalities

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

[a]<46 chromosomes.

Grupp S, et al. *HemaSphere.* 2019 3(S1):746-747.

Current limitations of CAR T cells



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

Global Leukemia Academy

Q&A

APTITUDE HEALTH

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Bispecific T-cell engagers for pediatric ALL

Patrick Brown

APTITUDE HEALTH

BiTE Immunotherapy for Pediatric ALL

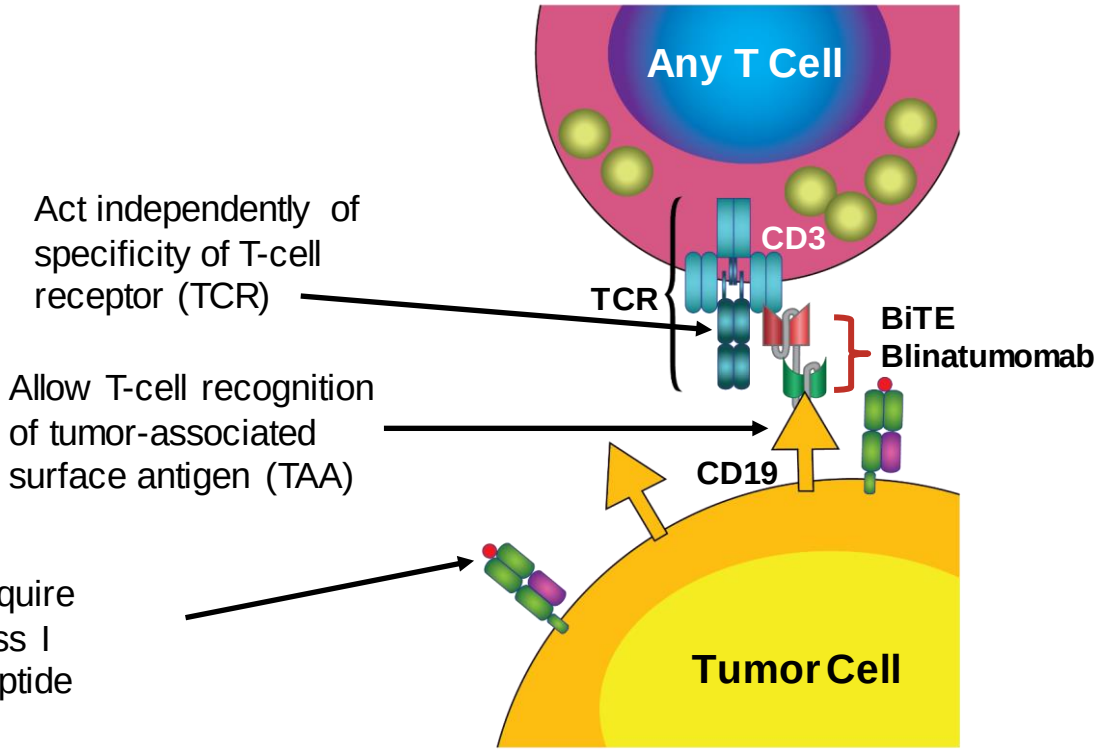
Patrick Brown, MD

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

Blinatumomab Mechanism of Action

Bispecific anti-CD19/CD3 BiTE antibody blinatumomab designed to kill autologous tumor cells

Relies on *functional endogenous cytotoxic T-cell response*

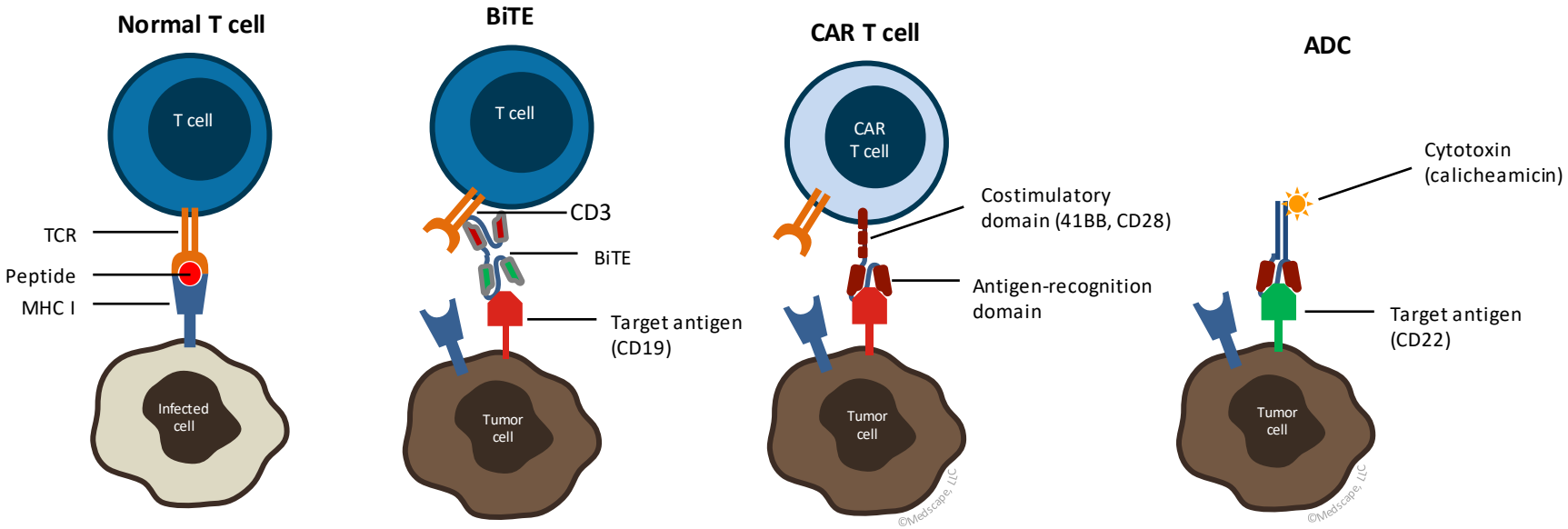


Given as 28-day continuous infusion IV; bag changes q 4-7 days

BiTE, Bispecific T-Cell Engager

Adapted from/courtesy of Amgen.

Normal vs BiTE vs CAR vs ADC



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

Response Rates and Survival in Relapsed/Refractory B-ALL

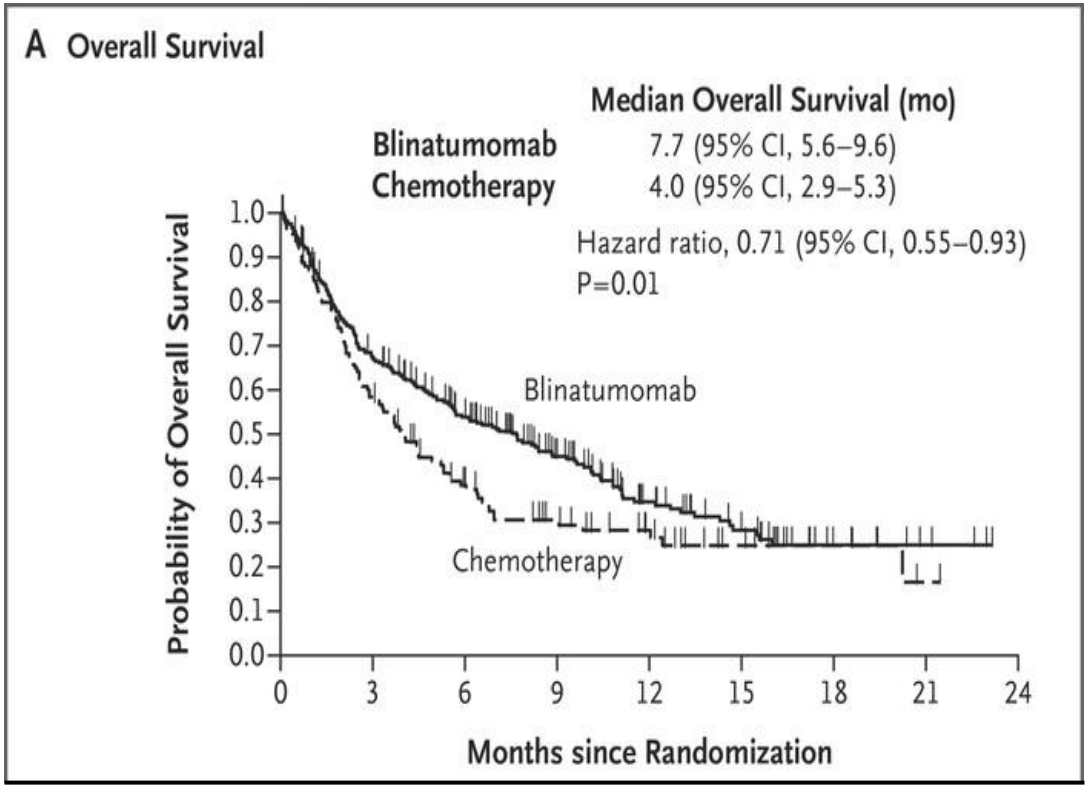
Agent	Type	Target	Responses (CR / MRD–)	Toxicities	FDA indication	Cost
Blinatumomab[1,2]	BiTE	CD19	42-44% / 22-33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	$180K
Inotuzumab[3]	Immuno-conjugate	CD22	81% / 63%	Hepatotoxicity	Adult R/R B-ALL	$168K
Tisagenlecleucel[4]	CAR T cell	CD19	81% / 81%	CRS, neurotoxicity	Refractory or 2nd/greater relapse; age up to 26 years	$475K

Unprecedented initial response rates . . . BUT . . .

1. Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847; 2. von Stackelberg A, et al. *J Clin Oncol.* 2016;34:4381-4389; 3. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; 4. Maude SL, et al. *N Engl J Med.* 2018;378:439-448.

Survival in R/R ALL (adult)

Blinatumomab

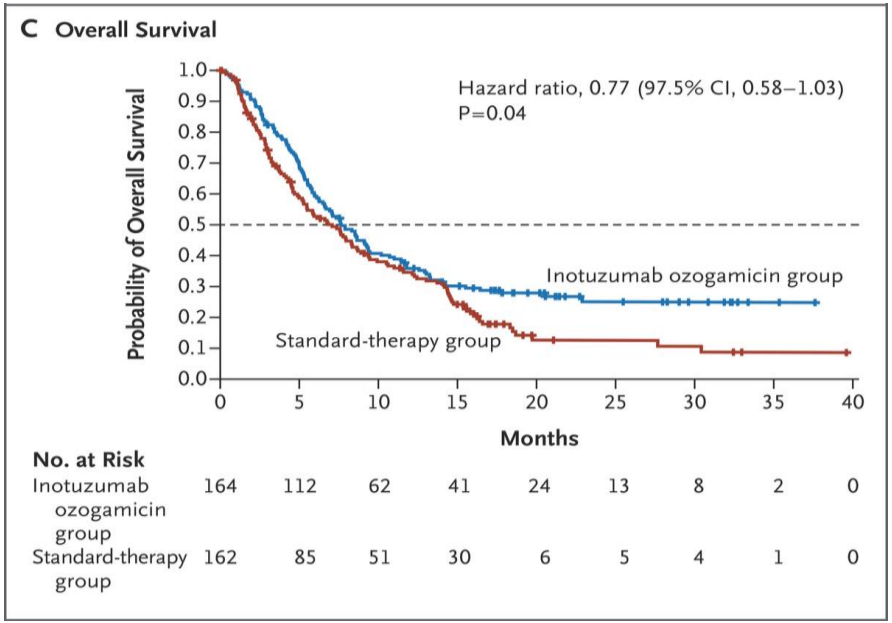


Blina: Improved survival initially, but not durable

Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

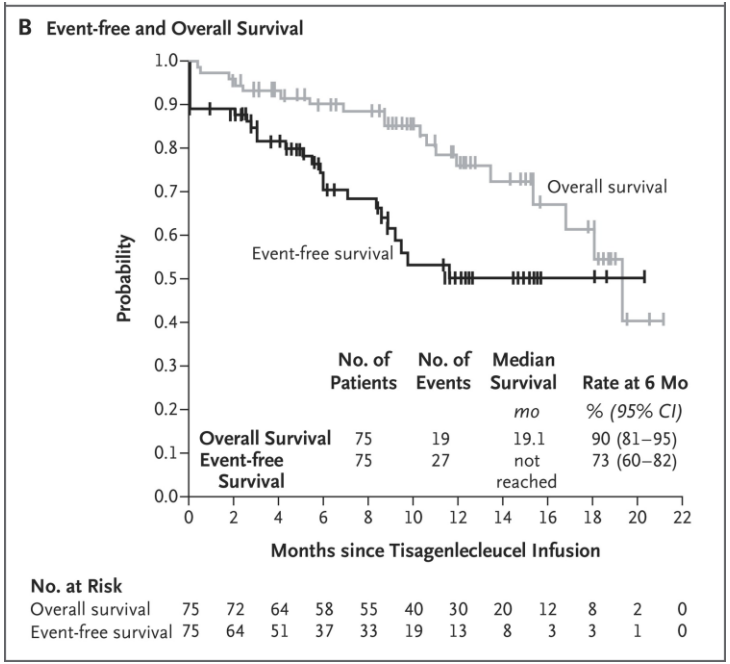
Survival in R/R ALL

Inotuzumab Ozogamicin[1]



Ino: Improved survival initially, but not durable

Tisagenlecleucel[2]



N Engl J Med 2018;378:439-448

Tisa: Durable survival improvement, but long-term EFS is in the 50% range

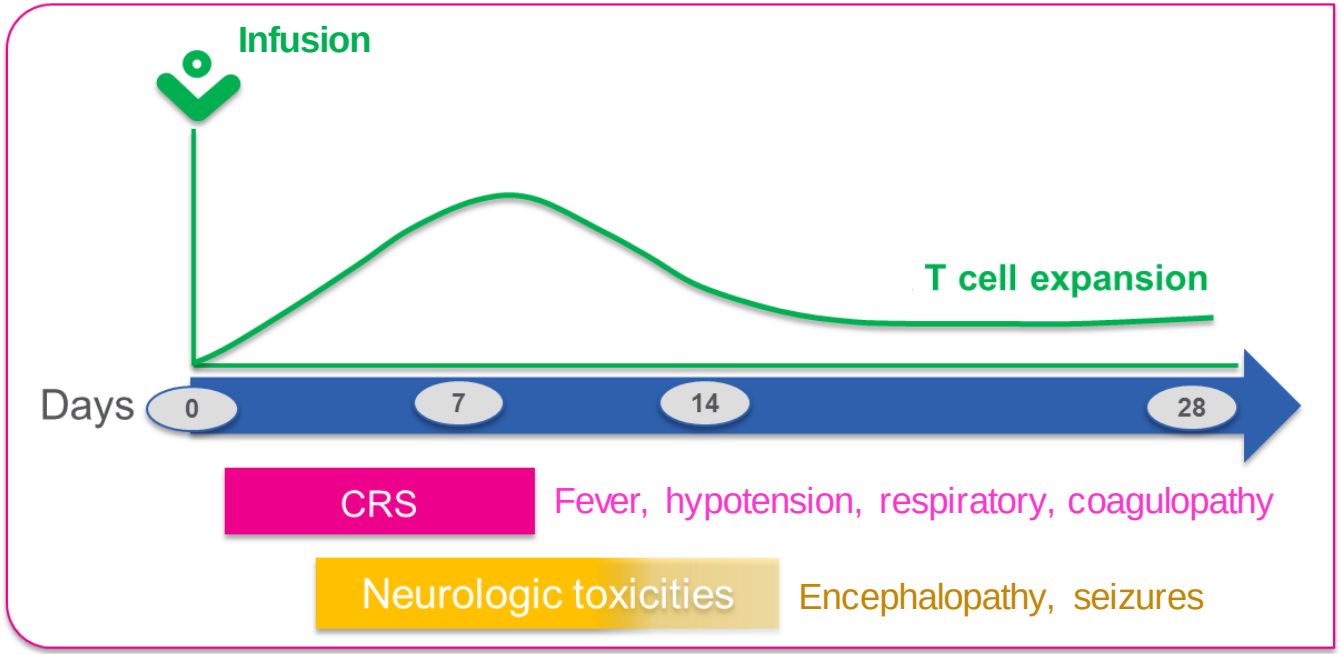
1. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; 2. Maude SL, et al. *N Engl J Med.* 2018;378:439-448.

Adverse Events in Relapsed/Refractory B-ALL

Agent	Type	Target	Responses (CR / MRD–)	Toxicities	FDA indication	Cost
Blinatumomab[1,2]	BiTE	CD19	42-44% / 22-33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	$180K
Inotuzumab[3]	Immuno-conjugate	CD22	81% / 63%	Hepatotoxicity	Adult R/R B-ALL	$168K
Tisagenlecleucel[4]	CAR T cell	CD19	81% / 81%	CRS, neurotoxicity	Refractory or 2nd/greater relapse; age up to 26 years	$475K

1. Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847; 2. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389; 3. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; 4. Maude SL, et al. *N Engl J Med.* 2018;378:439-448.

AEs After Blinatumomab and CAR T Cells



- CRS 40%–80% (20%–40% Gr 3+), Neuro 10%–30% (5%–10% Gr 3+)
- CRS and neuro may **not** correlate
- CRS -> IVF, tocilizumab (anti-IL6R), steroids
- Neuro -> self-limiting, reversible; steroids (toci not effective)

MRD+

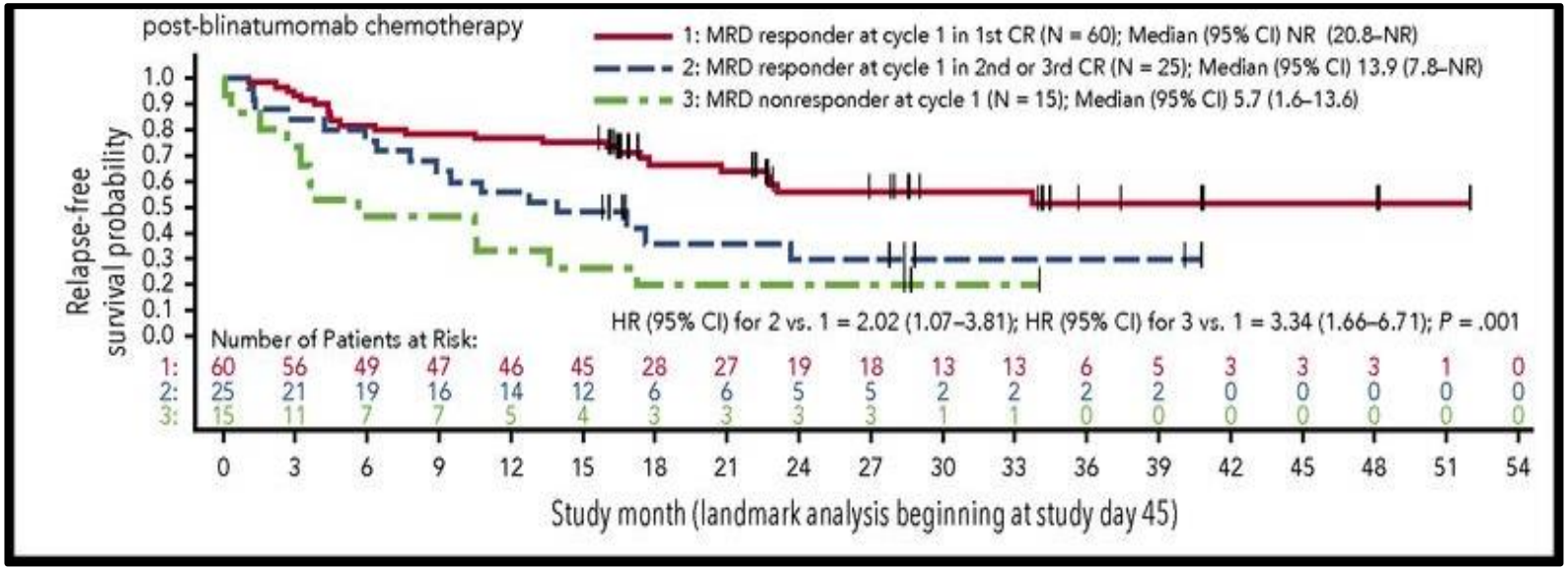
*Incidence of CRS strikingly lower in MRD+ setting; neurotox is similar

Adapted from/courtesy of Novartis.

Response Rates and Survival in MRD+ B-ALL (Adults)

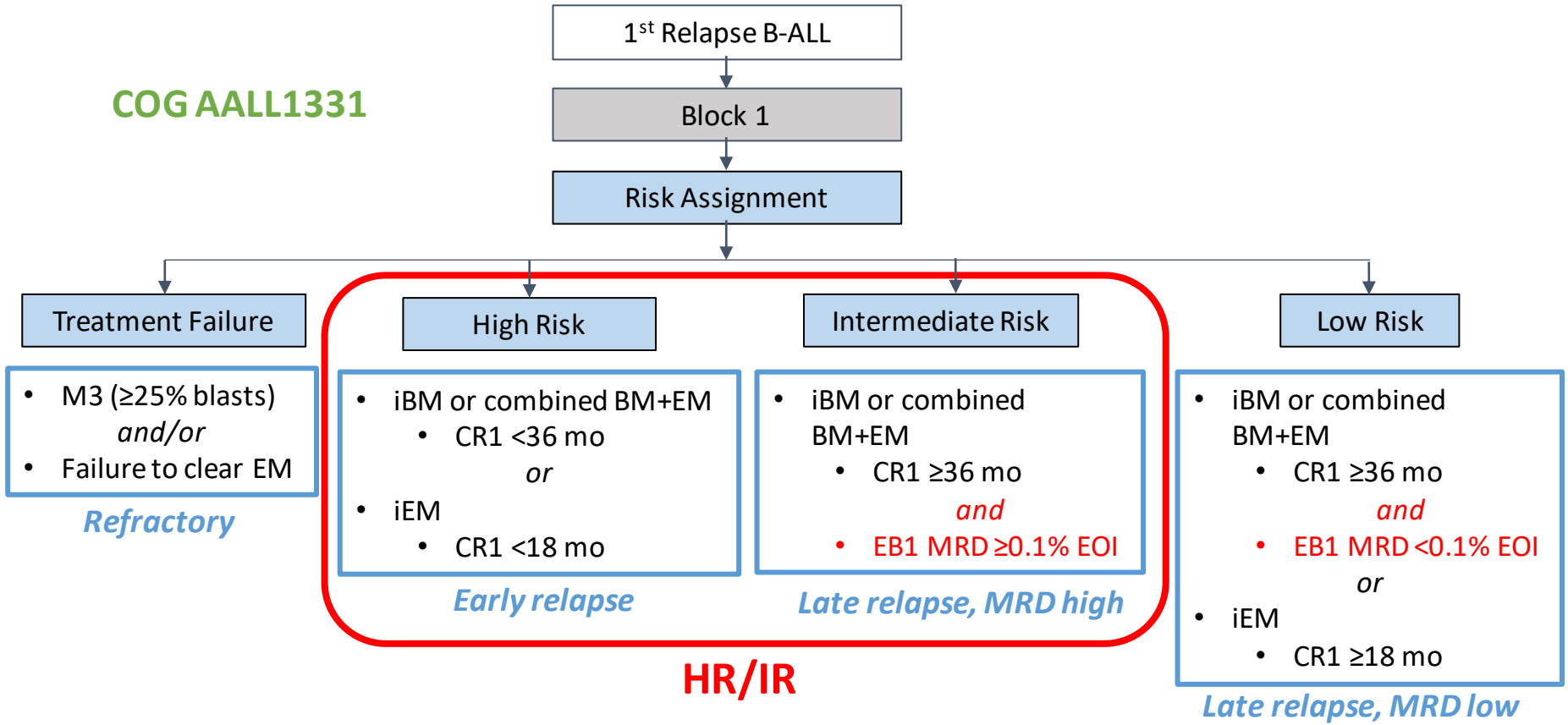
- N = 116 adults, international multicenter single-arm Ph 2
- MRD+ (>10^{-3})
- 65% in CR1 (rest CR2+)
- MRD cleared in 78% after 1 cycle

- 67% proceeded to HSCT
- Significant percentage of those who did not remain in prolonged remission
- 20 of 74 proceeding to HSCT (27%) died of TRM

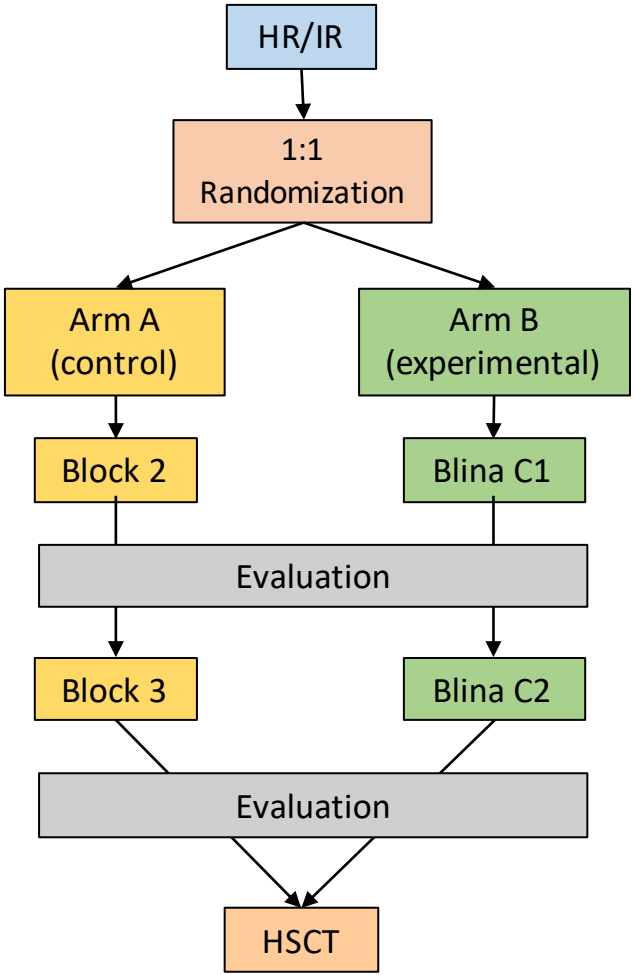


Gokbuget N, et al. *Blood.* 2018;131(14):1522-1531.

Response Rates and Survival in MRD+ B-ALL (Children/AYA)



Brown P, et al. *Blood.* 2019;134(suppl_2):LBA-1.

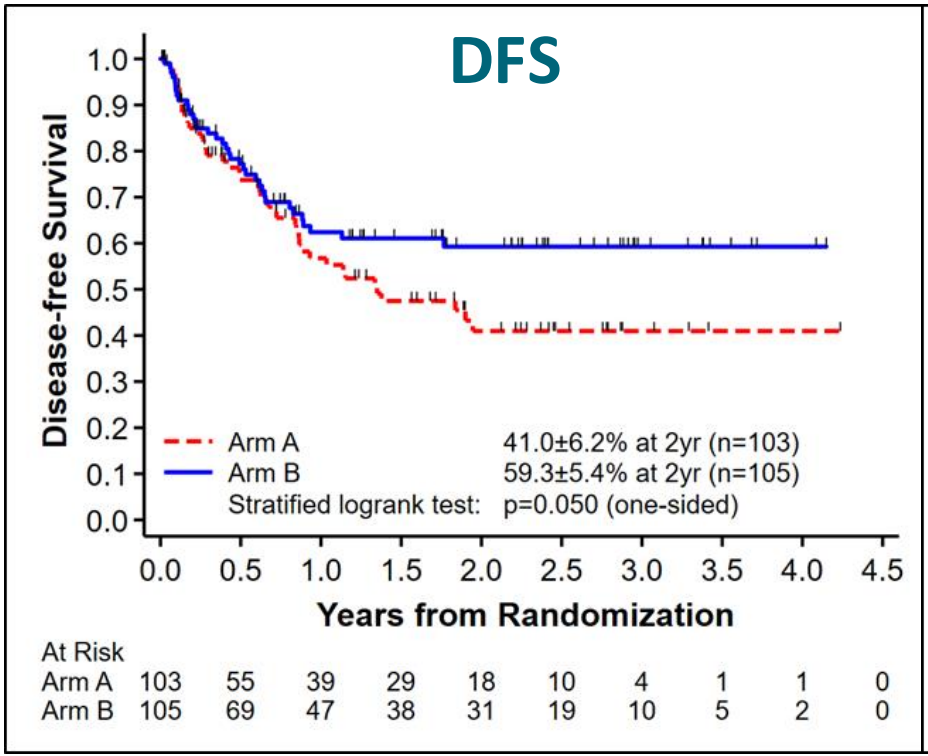


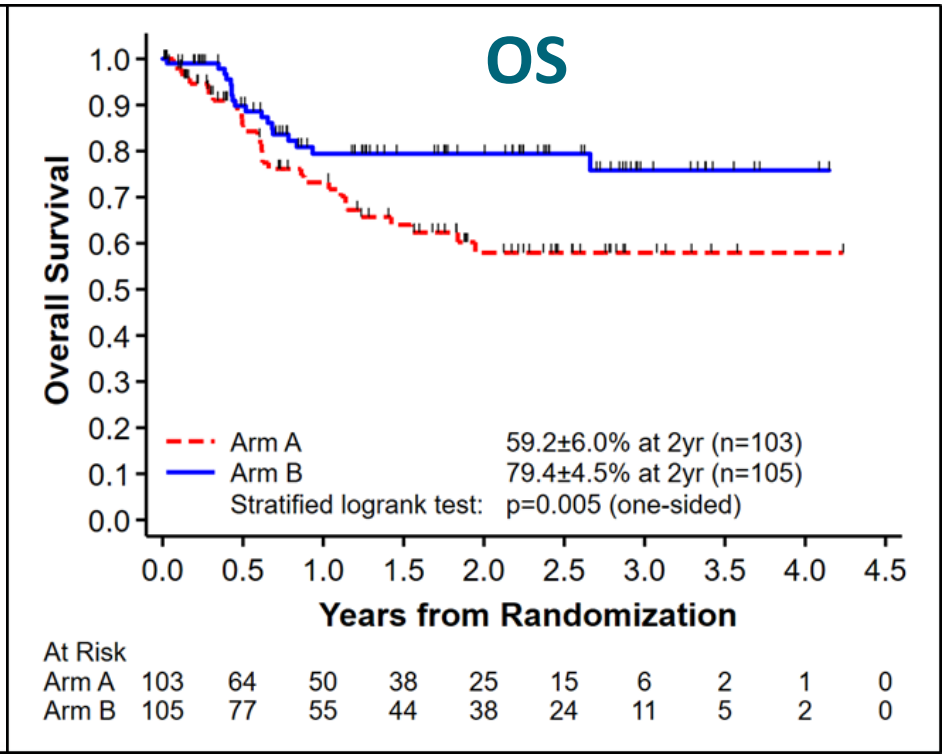
COG AALL1331

- Serious AE rates: 40%–60% vs 0%–10%
- MRD clearance rate: 30% vs 81%
- Proceed to HSCT: 45% vs 73%

Brown P, et al. *Blood.* 2019;134(suppl_2):LBA-1.

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





CHILDREN'S ONCOLOGY GROUP

Median follow-up 1.4 years

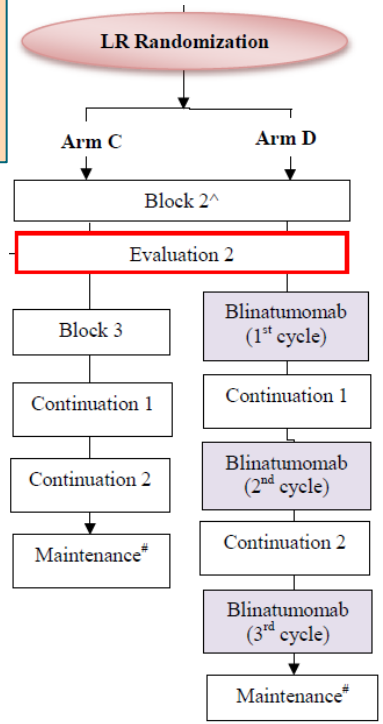
Brown P, et al. *Blood.* 2019;134(suppl_2):LBA-1.

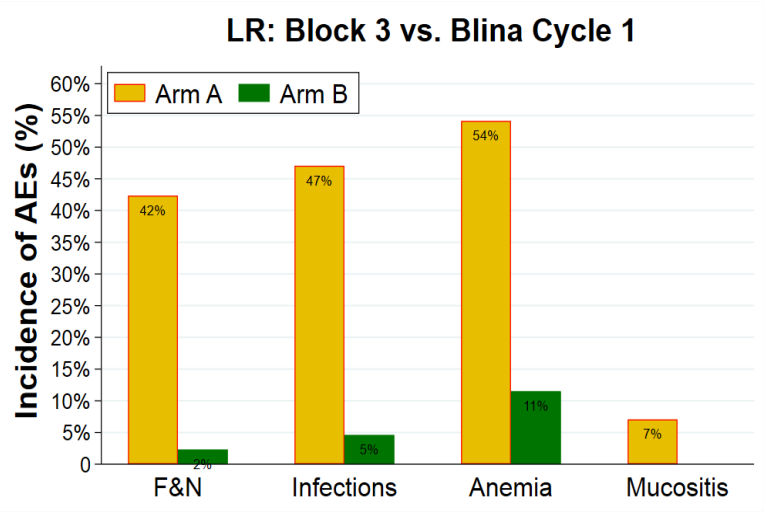
COG AALL1331: LR Randomization

LR

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

- Blinatumomab 15 µg/m²/day × 28 days, then 7 days off
- Dex 5 mg/m²/dose × 1 premed





Other outcomes pending release by DSMC

CHILDREN'S ONCOLOGY GROUP

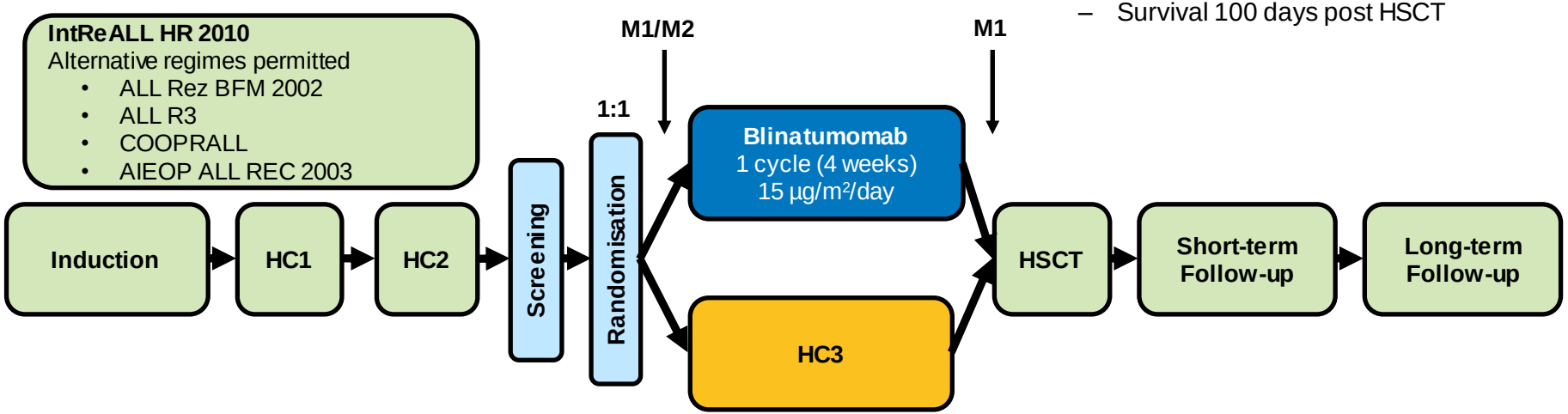
Unpublished data.

Open-label, randomised, phase III trial: 47 centres, 13 countries

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

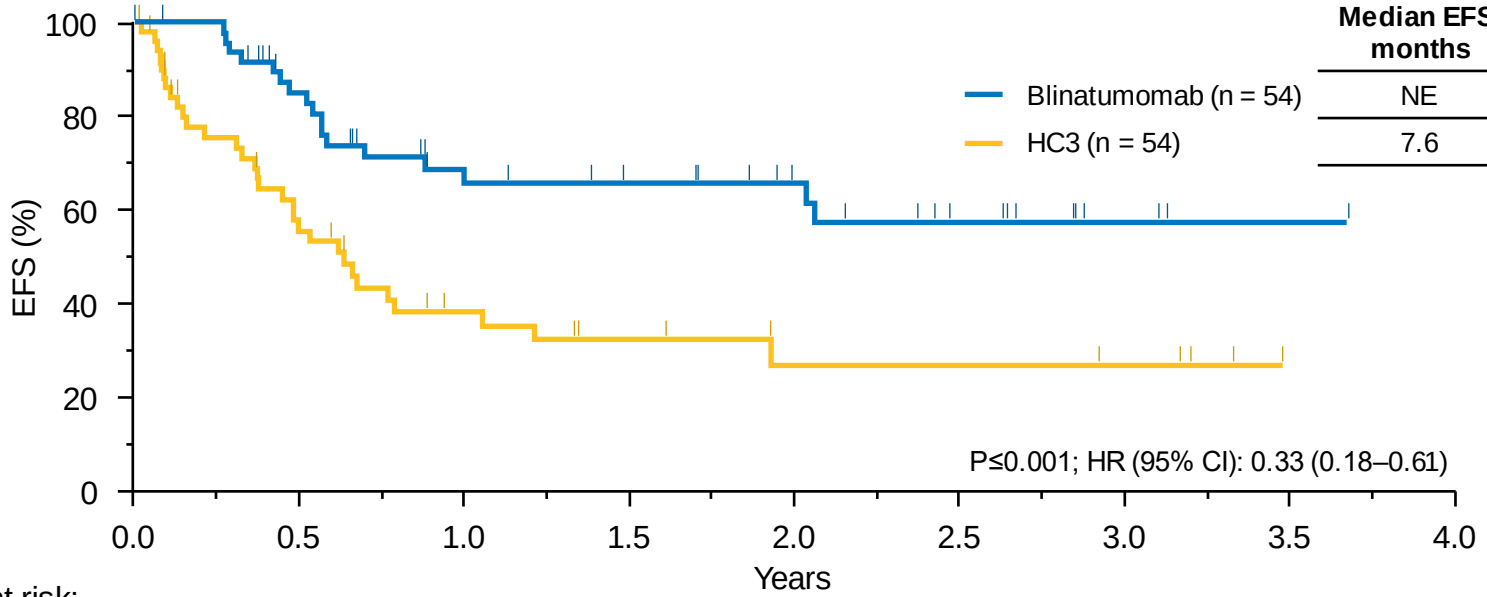
Stratification
- Age: <1 year, 1 to 9 years, >9 years
- BM status at end of HC2
  - M1 with MRD >10^{-3}
  - M1 with MRD <10^{-3}
  - M2

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



BCP, B-cell precursor; EFS, event-free survival; HC, high-risk consolidation.
Locatelli F, et al. EBMT 2020. Abstract GS2-5.

Superior EFS in the blinatumomab arm



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

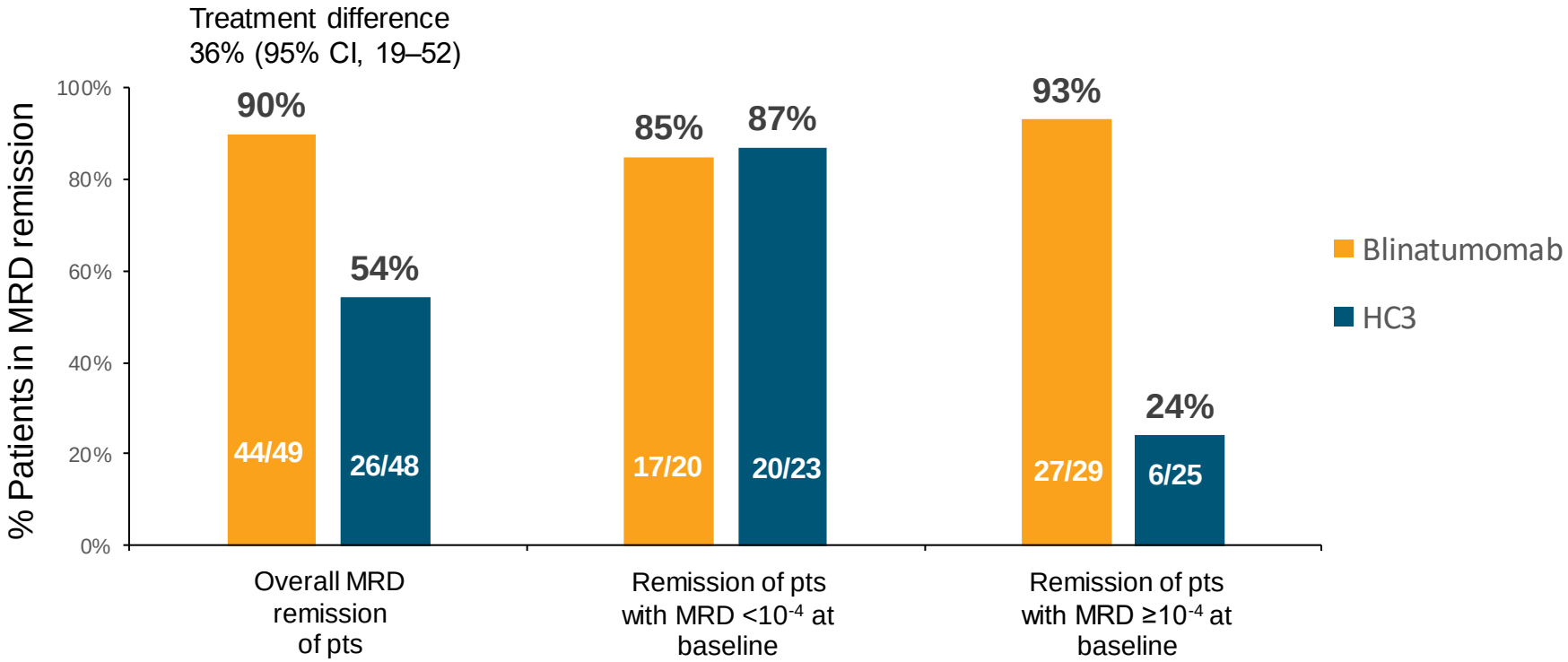
Subjects at risk:

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

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

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

Superior MRD remission by PCR in the blinatumomab arm (overall and by baseline* MRD status)



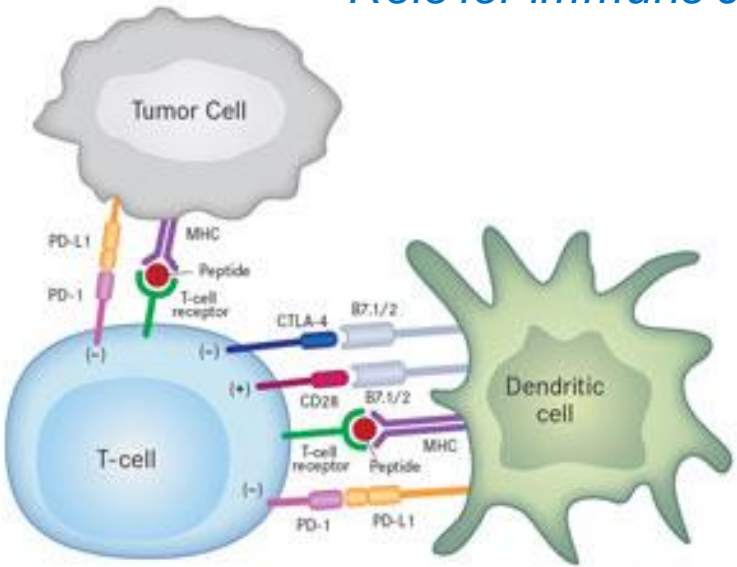
*Baseline: end of HC2 (screening sample before enrollment) PCR, polymerase chain reaction

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

What Happens When Blinatumomab Doesn't Work?

- EARLY: Endogenous T-cell "exhaustion"

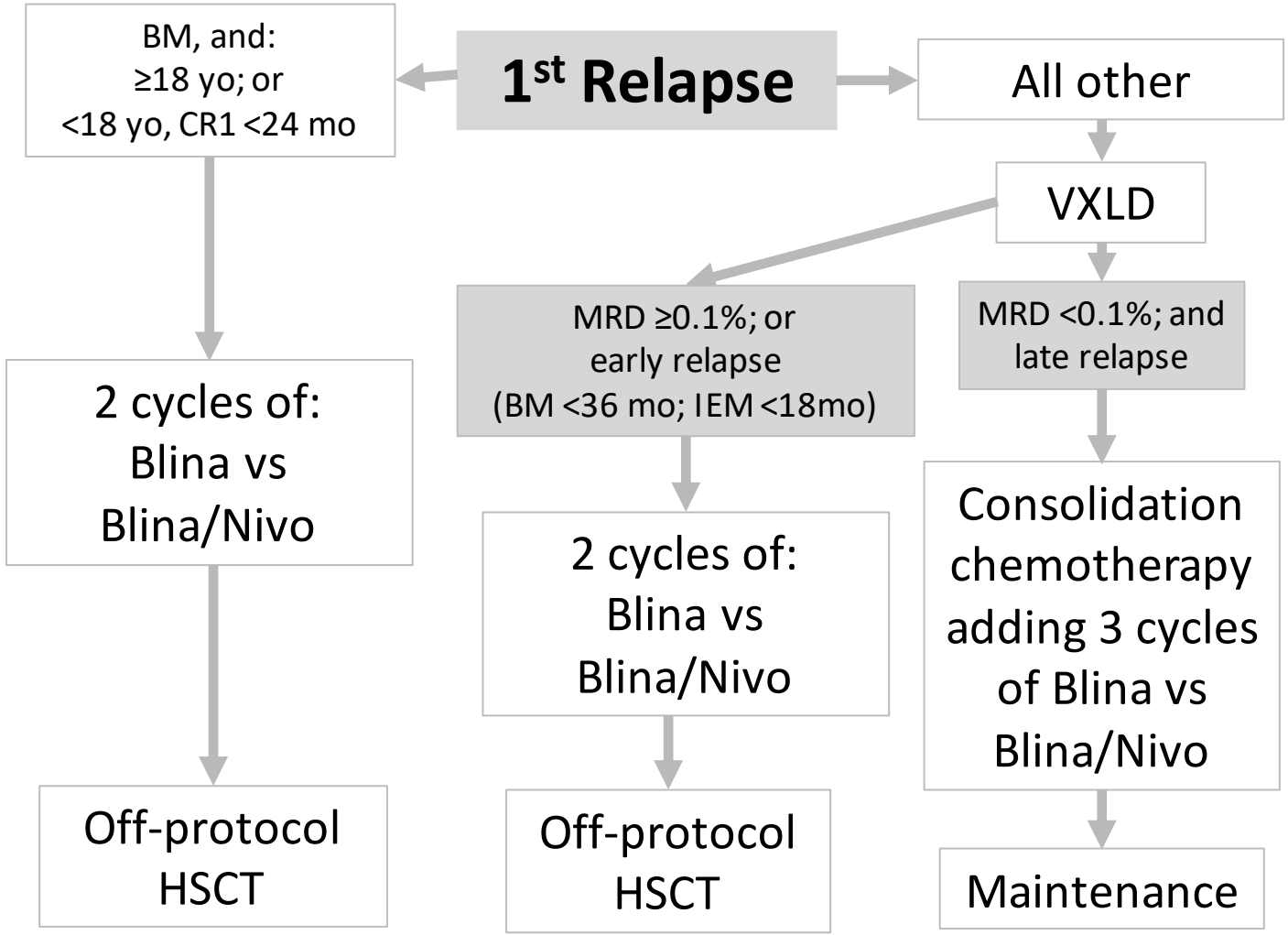
Role for immune checkpoint inhibitors (eg, anti–PD-1)?



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

Reports of efficacy in patients relapsing after blina/CAR T cells
- Feucht, et al. *Oncotarget.* 2016;7(47):76902-76919

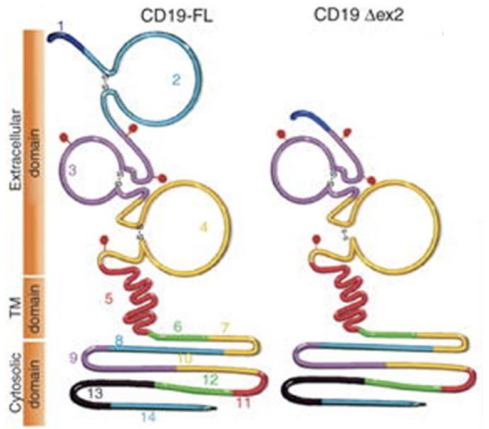
Adapted from Zaravinos A. *Oncotarget.* 2014;5(12):3956-3969.



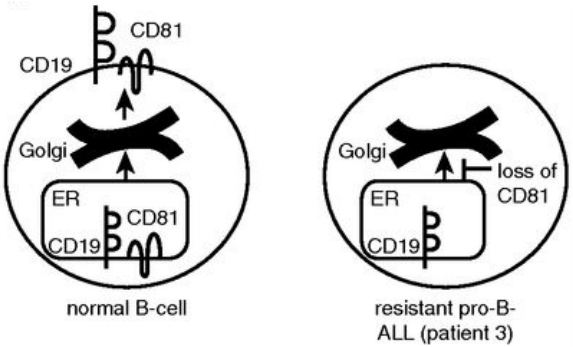
Unpublished data.

What Happens When Blinatumomab Doesn't Work?

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



Multiantigen targeting?



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

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

Question 1

A 14-year-old male began an infusion of blinatumomab 36 hours ago. He has developed acute onset of fever, hypotension, respiratory distress, hypoxia, and diffuse edema. Which of the following is the most likely explanation?

a. Gram-negative bacterial sepsis
b. Disseminated adenoviral infection
c. Cytokine release syndrome (CRS)
d. Macrophage activation syndrome (MAS)
e. Hemophagocytic lymphohistiocytosis (HLH)

Question 2

True or False: The most effective treatment for blinatumomab-associated neurotoxicity is tocilizumab (anti-IL6R antibody).

a. True

b. False

Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients

APTITUDE HEALTH

Global Leukemia Academy

Overview of long-term toxicities

Rob Pieters

APTITUDE HEALTH

Long-term toxicities in pediatric ALL

Rob Pieters
Chief Medical Officer

Question 1

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

a) The anthracyclines daunorubicin and/or doxorubicin in a cumulative dose of >300 mg/m^2 in a child aged 5 years at diagnosis

b) Methotrexate in a cumulative dose of 20,000 mg/m^2 in a child aged 8 years at diagnosis

c) Cranial radiotherapy in a child aged 2 years at diagnosis

d) Dexamethasone in a female child aged 14 years at diagnosis

Question 2

Which assertion is NOT correct?

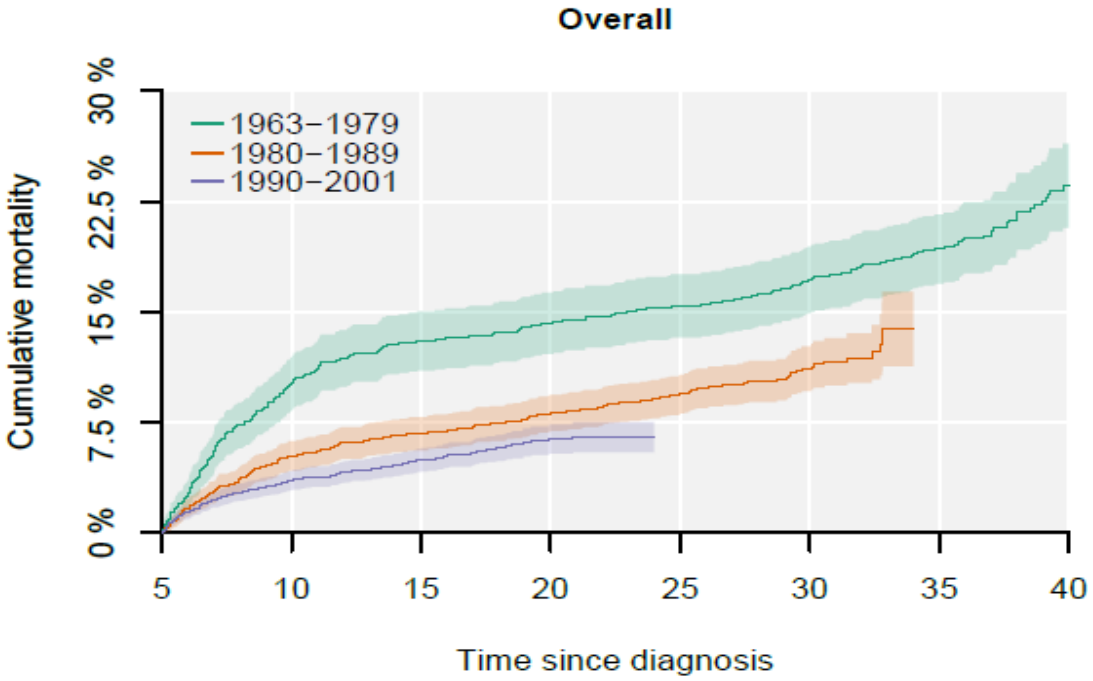
a) Dexamethasone and prednisone can cause osteonecrosis

b) The risk of osteonecrosis is lowest in children <10 years of age

c) The risk of osteonecrosis depends on age and is highest in adults with ALL

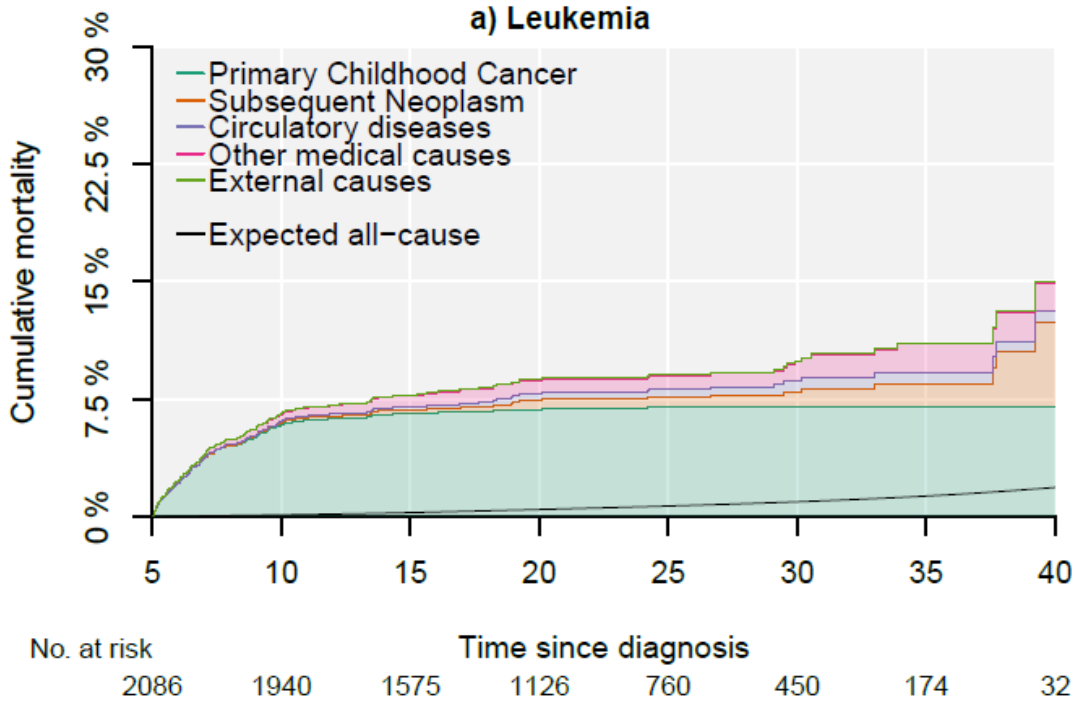
d) The risk of osteonecrosis is higher with a continuous schedule of glucocorticoids than with a discontinuous schedule in the same cumulative dose

Cumulative late mortality of childhood cancer survivors by year of diagnosis



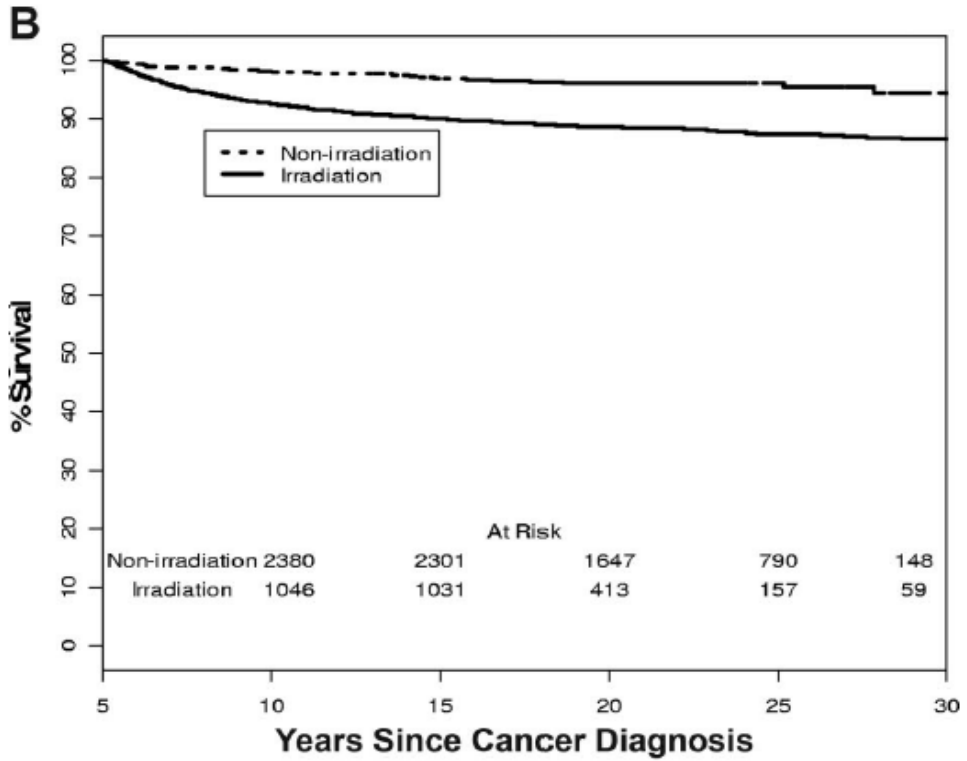
Kilsdonk E, et al. 2020 (submitted manuscript).

Cumulative late mortality of survivors of childhood leukemia



Kilsdonk E, et al. 2020 (submitted manuscript).

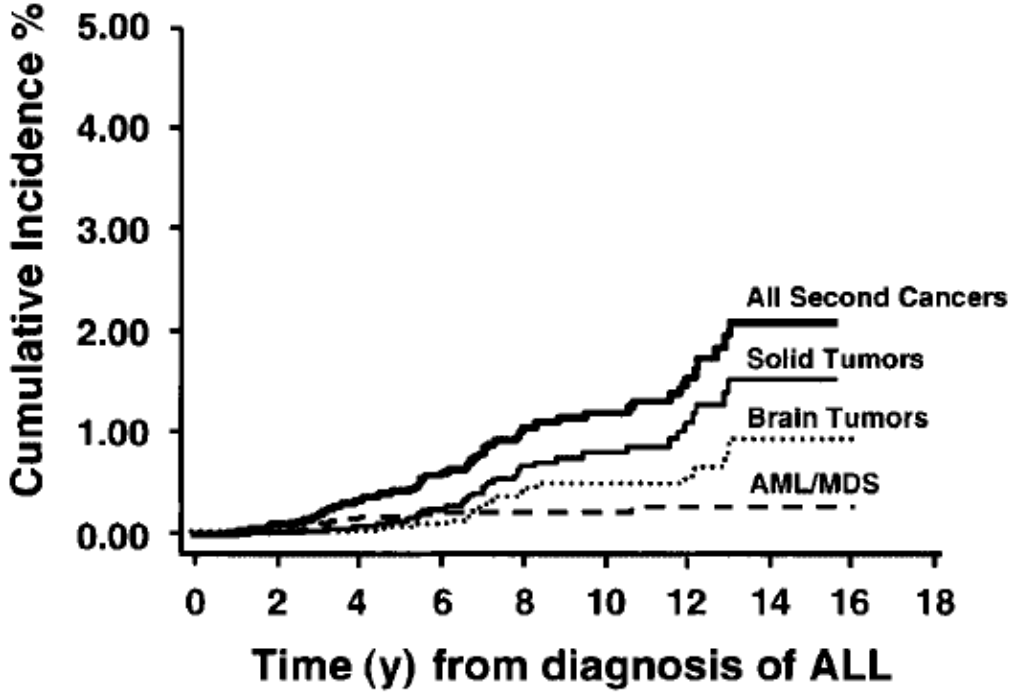
Survival of 5-year ALL survivors: irradiated vs nonirradiated



Late effects of treatment in ALL

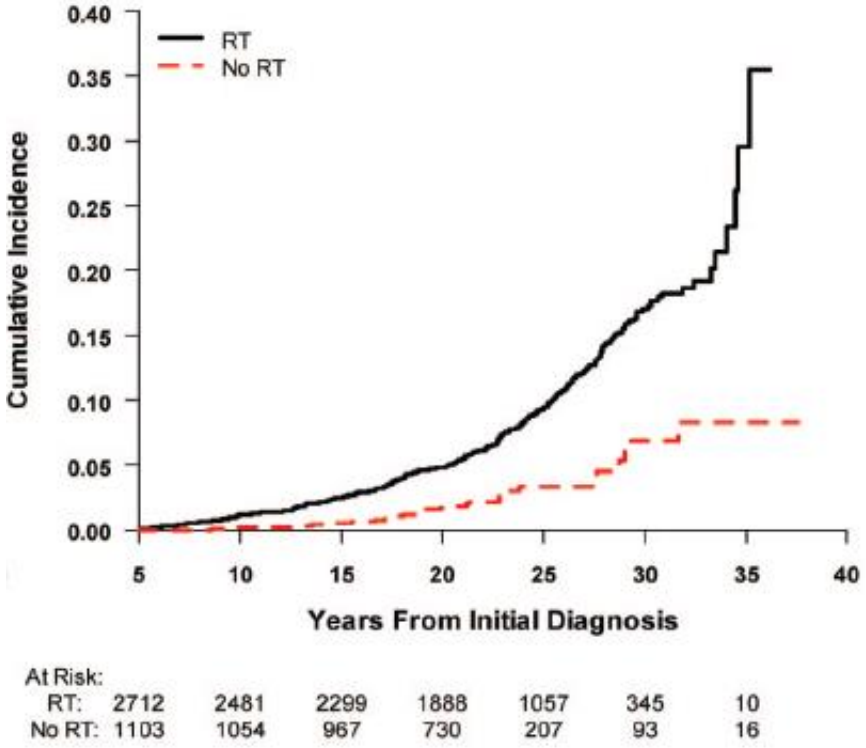
- Second malignancies
- Osteonecrosis
- Neurocognitive sequelae
- Cardiomyopathy
- Insulin dependent diabetes (pancreatitis)
- Chronic GvH
- Chronic immune deficiency (CD19-directed CAR T cells)

Cumulative incidence of second neoplasms in 8831 children with ALL



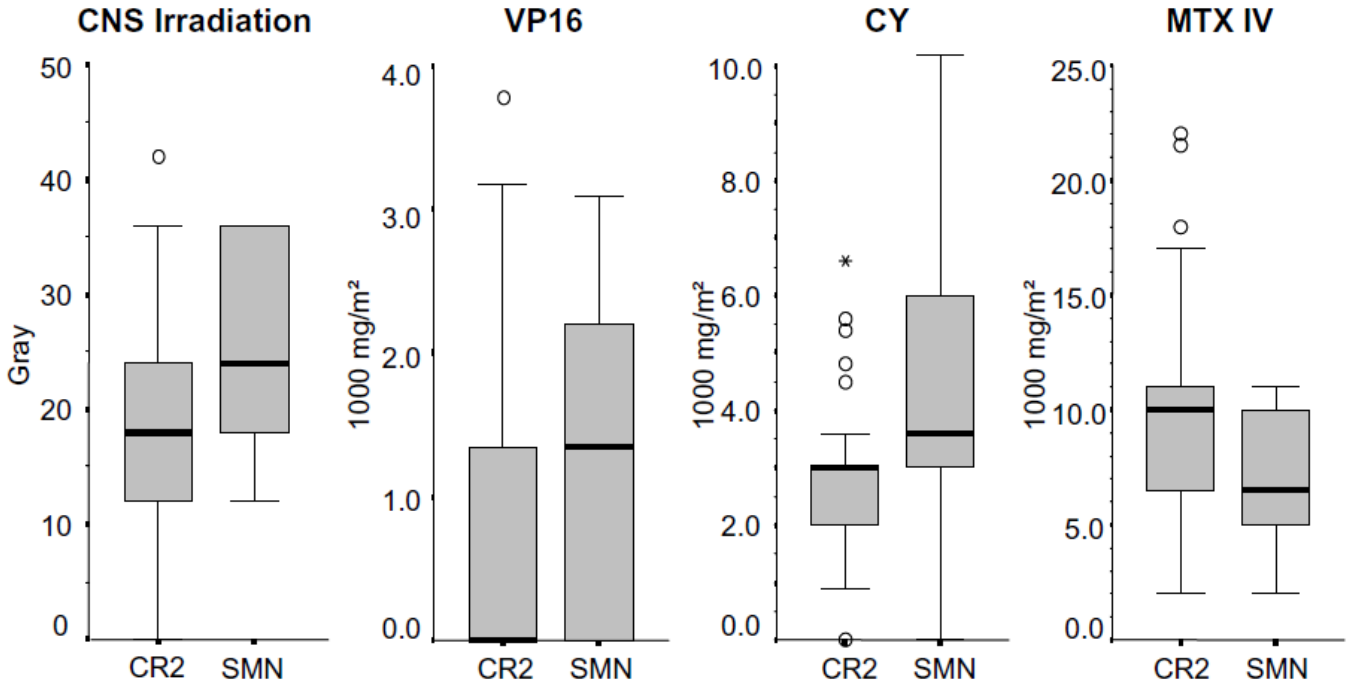
Bhatia S, et al. *Blood*. 2002;99(12):4257-4264.

Second neoplasms among 5-year survivors of childhood ALL in the CCSS cohort: role of radiotherapy



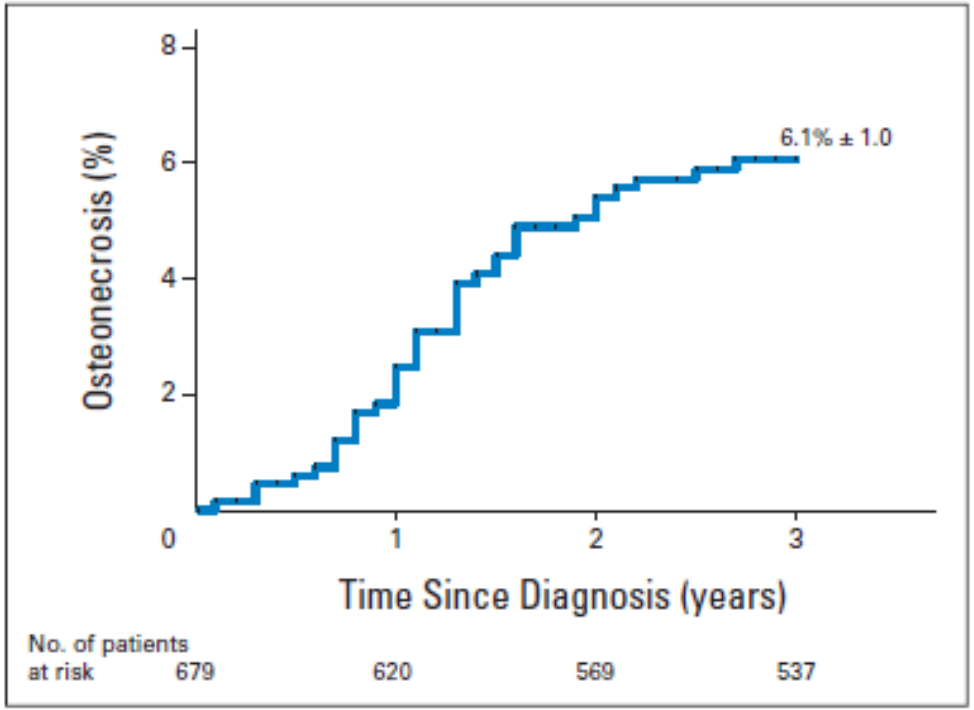
Robison LL, et al. *Hematology Am Soc Hematol Educ Program*. 2011;2011:238-242.

Cumulative dose of cranial irradiation and chemotherapeutic agents vs second malignancies in patients with first relapse of ALL, treated with ALL-REZ BFM 83–96



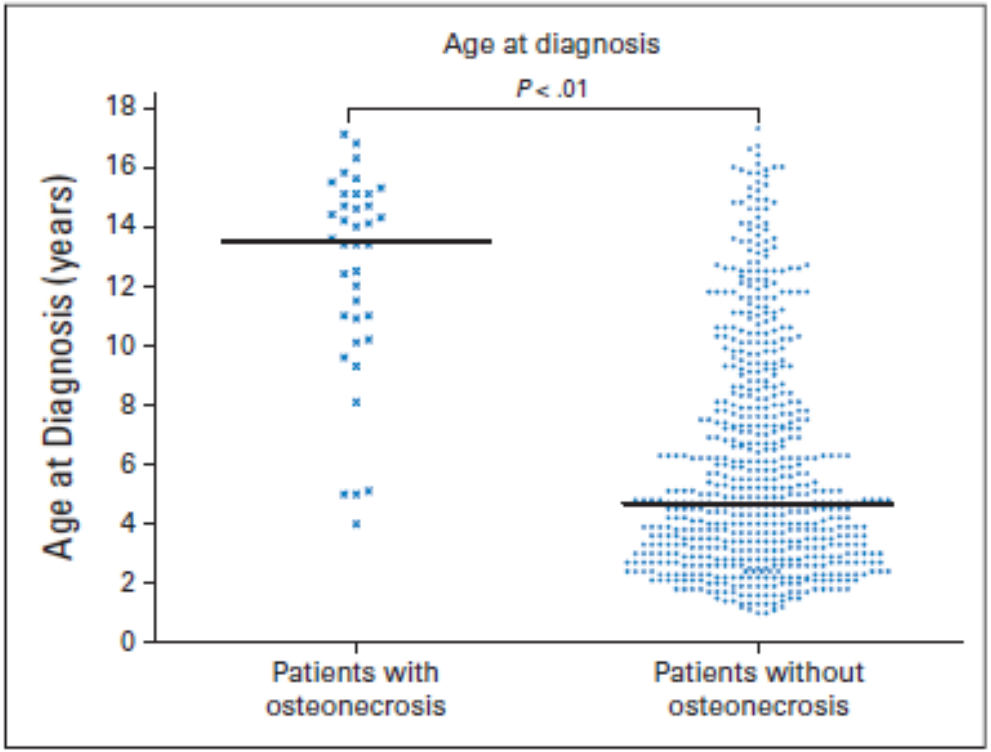
Borgmann A, et al. *Eur J Cancer.* 2008;44(2):257-268.

Cumulative incidence of symptomatic osteonecrosis in pediatric ALL



Te Winkel ML, et al. *J Clin Oncol.* 2011;29(31):4143-4150.

Age at diagnosis in patients with and without symptomatic osteonecrosis

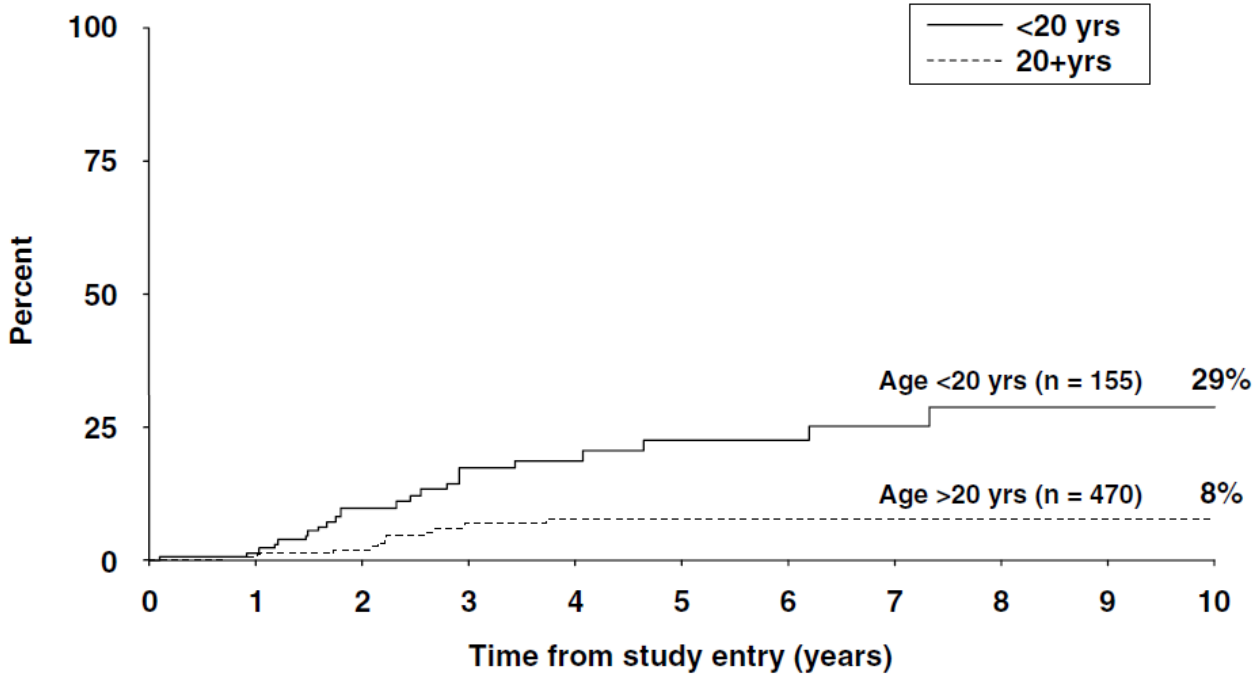


Te Winkel ML, et al. *J Clin Oncol.* 2011;29(31):4143-4150.

Multivariate logistic regression analysis of symptomatic osteonecrosis in relation to age, sex, and treatment arm

Risk Factor	Initial Model		
	OR	95% CI	*P*
Age at diagnosis of ALL, years	1.47	1.33 to 1.63	< .001
BMI at diagnosis, sds	0.88	0.64 to 1.20	.41
Sex			
Male	1.00		
Female	2.13	0.99 to 4.62	.05
Risk group			
Non–high risk	1.00		
High risk	0.69	0.30 to 1.60	.39

Osteonecrosis by age in ALL: UKALL XII study

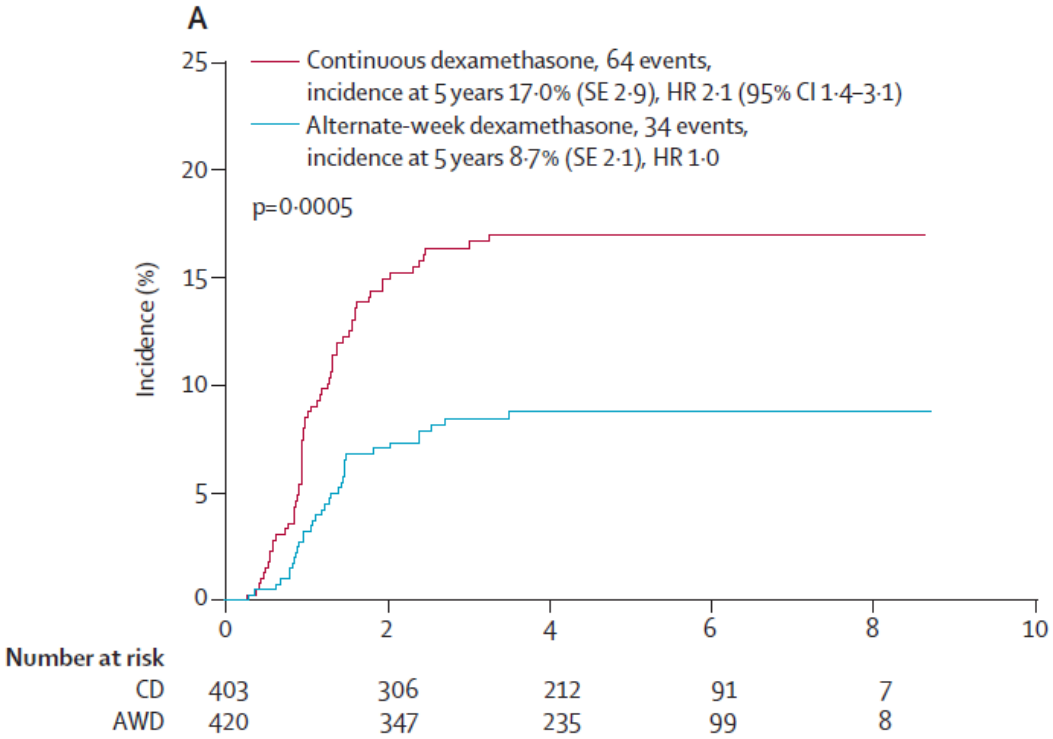


At risk:

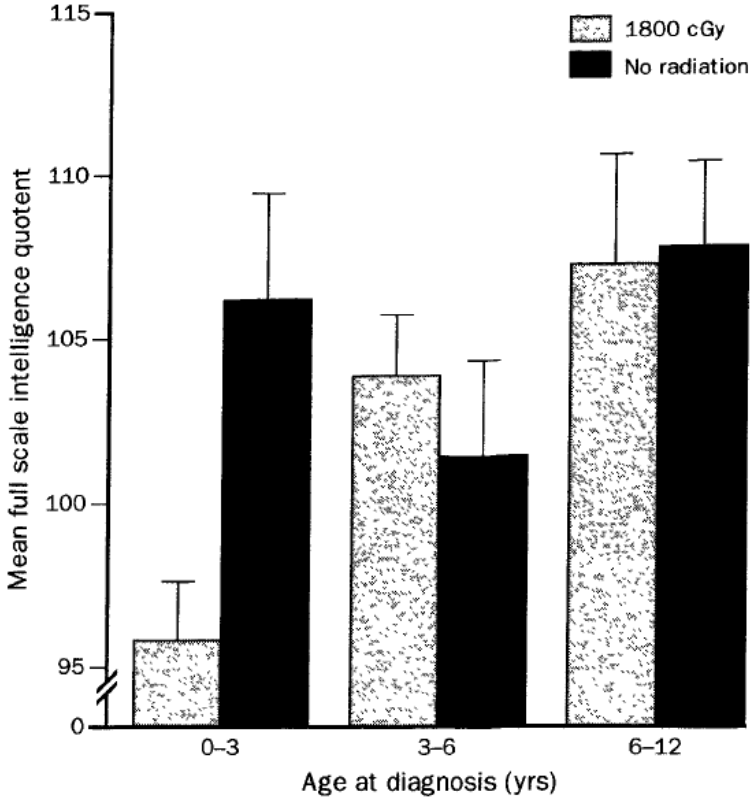
<20 yrs	155	126	93	61	46	34	28	23	18	16	9
20+ yrs	470	264	161	109	86	66	54	43	30	23	21

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

Osteonecrosis: continuous vs alternate-week dexamethasone

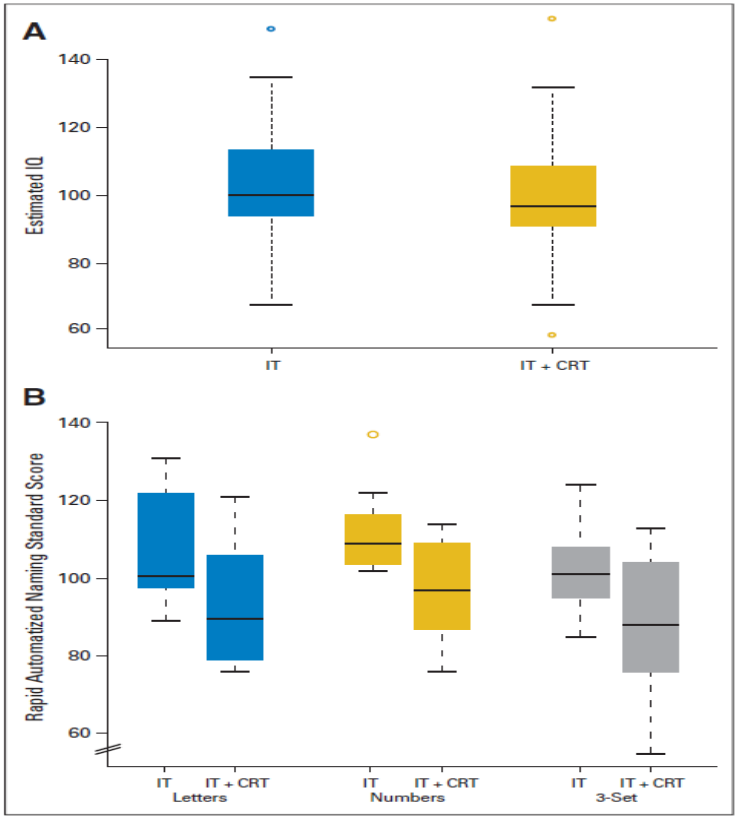


Effects of 1800 cGy cranial radiation on intellectual performance as a function of age at diagnosis



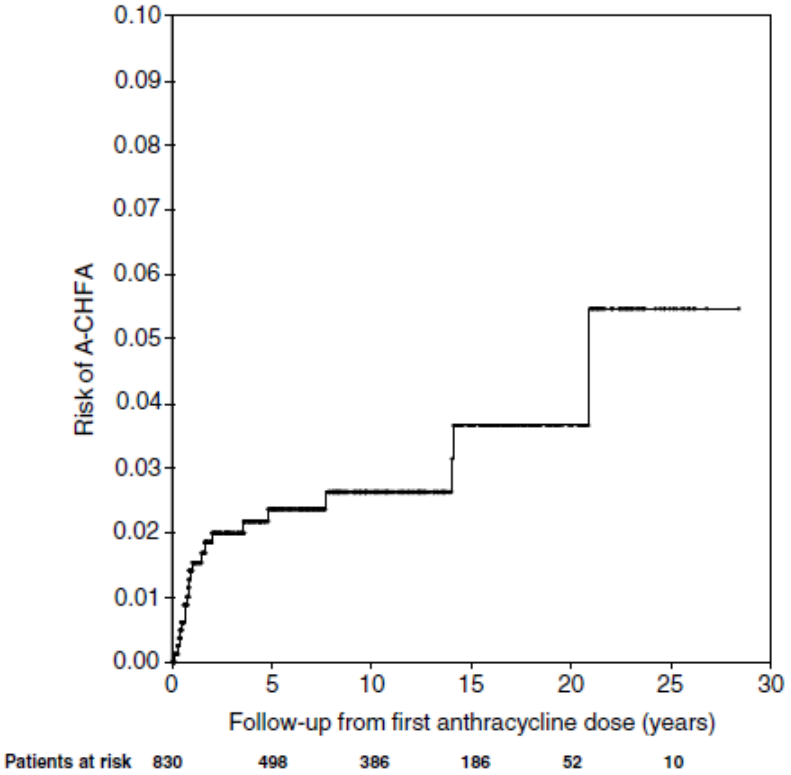
Jankovic M, et al. *Lancet.* 1994;344(8917):224-227.

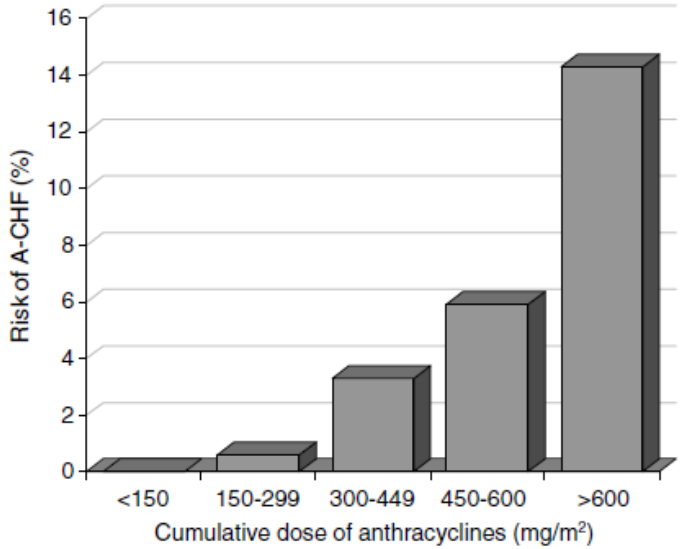
IQ and rapid naming tasks: intrathecal (IT) vs IT plus cranial radiation therapy (CRT)



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

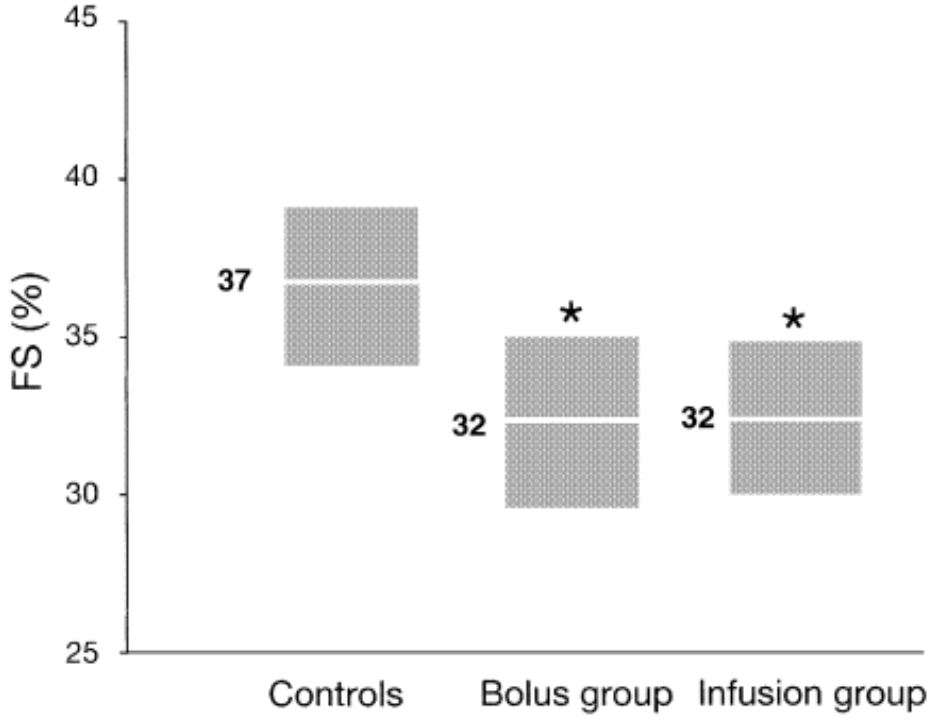
Risk of anthracycline-induced clinical heart failure in childhood cancer





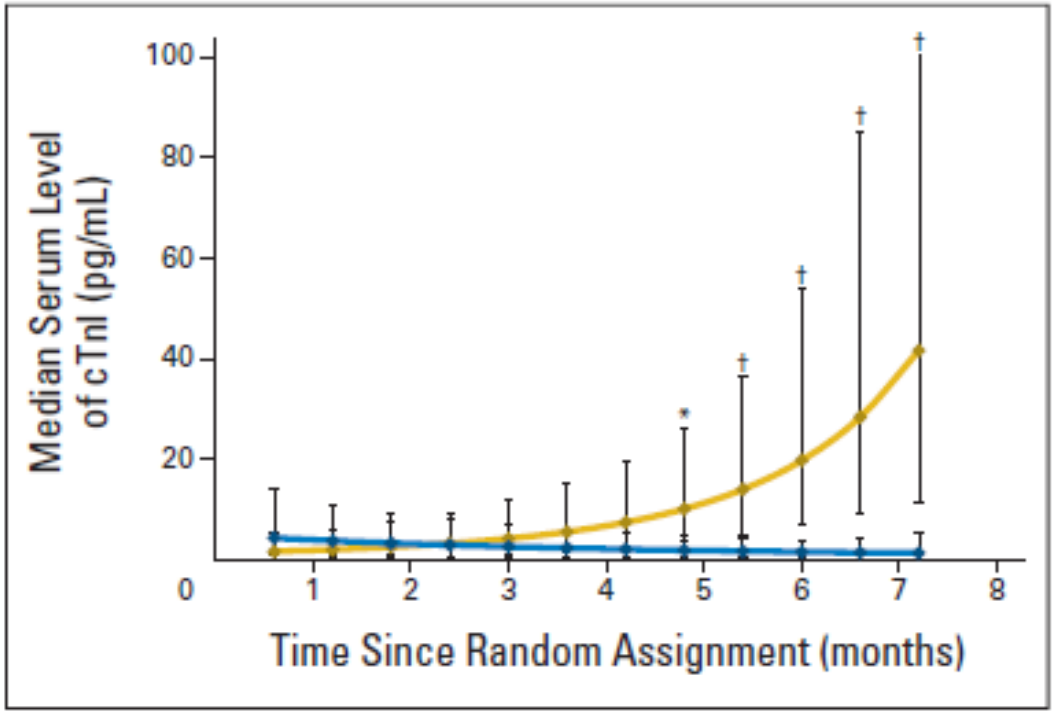
Van Dalen EC, et al. *Eur J Cancer.* 2006;42(18):3191-3198.

Shortening fraction by bolus or 6-hour infusion of daunorubicin



Levitt GA, et al. *Br J Haematol.* 2004;124(4):463-468.

Cardiac troponin during doxorubicin therapy in ALL with (blue) or without (red) dexrazoxane

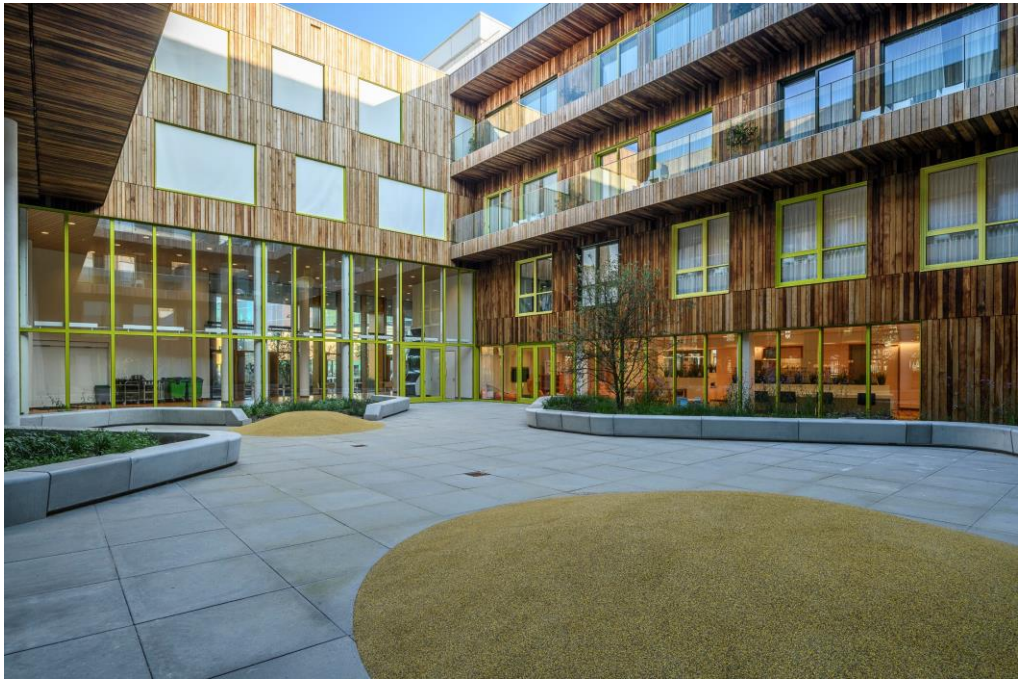


Late effects of treatment in ALL

- Second malignancies
- Osteonecrosis
- Neurocognitive sequelae
- Cardiomyopathy
- … Others …

- Large series
- Long follow-up
- Structured follow-up
- Feedback to current protocols

Late effects outpatient clinic



Question 1

After listening to the presentation, which factor has the lowest probability of causing significant long-term toxicity in pediatric ALL?

a) The anthracyclines daunorubicin and/or doxorubicin in a cumulative dose of >300 mg/m^2 in a child aged 5 years at diagnosis

b) Methotrexate in a cumulative dose of 20,000 mg/m^2 in a child aged 8 years at diagnosis

c) Cranial radiotherapy in a child aged 2 years at diagnosis

d) Dexamethasone in a female child aged 14 years at diagnosis

Question 2

After listening to the presentation, which assertion is NOT correct?

a) Dexamethasone and prednisone can cause osteonecrosis

b) The risk of osteonecrosis is lowest in children <10 years of age

c) The risk of osteonecrosis depends on age and is highest in adults with ALL

d) The risk of osteonecrosis is higher with a continuous schedule of glucocorticoids than with a discontinuous schedule in the same cumulative dose

Thank you!

Global Leukemia Academy

Patient case presentation

Patrick Brown

APTITUDE HEALTH

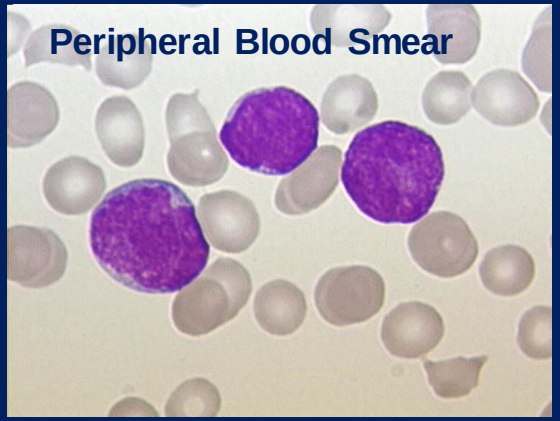
Patient Case Presentation: Acute Toxicities in Pediatric ALL

Patrick Brown, MD

Director, Pediatric Leukemia Program
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Chair, NCCN ALL Guideline Committee

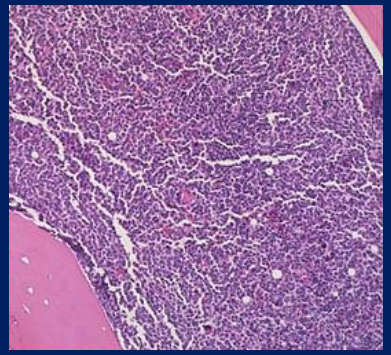
Case Presentation

- 15 y/o female presents to outside ER with 2-week history of progressive diffuse bone pain and fatigue; in last week, developed intermittent low-grade fevers and nosebleeds
- PE: Pallor, diffuse lymphadenopathy and hepatosplenomegaly, scattered petechiae
- CBC
  - WBC 69,000 per uL, 94% blasts; ANC 950 per uL; Hgb: 6.6 gm/dl; PLT: 33,000 per uL

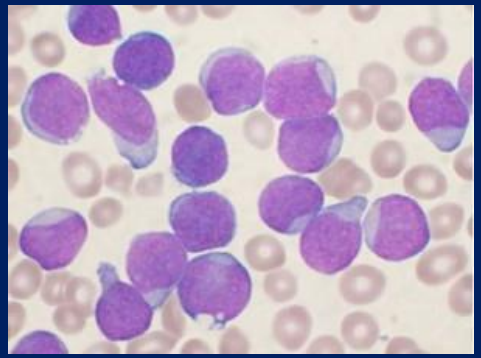


Suspected diagnosis: Acute lymphoblastic leukemia

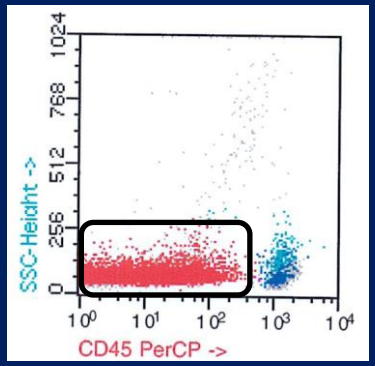
Case Presentation (continued)

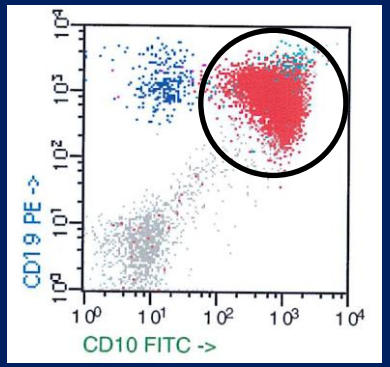


Bone Marrow Biopsy



Bone Marrow Aspirate





Flow Cytometry Plots

- LDH 488
- Uric Acid 5.9
- K 4.1, Phos 3.6, Ca 9.3
- DIC panel normal

- CSF: WBC 1, RBC 0, no blasts on cytospin

- Normal echo, EKG

Diagnosis: B-lymphoblastic leukemia

Case Presentation (continued)

- Initial treatment: standard induction for pediatric “high-risk” ALL
  - 4 weeks of vincristine (days 1,8,15 and 22), prednisone (days 1-28), PEG asparaginase (day 4), daunorubicin (days 1, 8, 15 and 22), intrathecal methotrexate (days 1, 8 and 29)
- On day 11 of treatment, patient develops acute onset of severe frontal headache, blurry vision, and vomiting
- The headache is the same whether lying, sitting, or standing

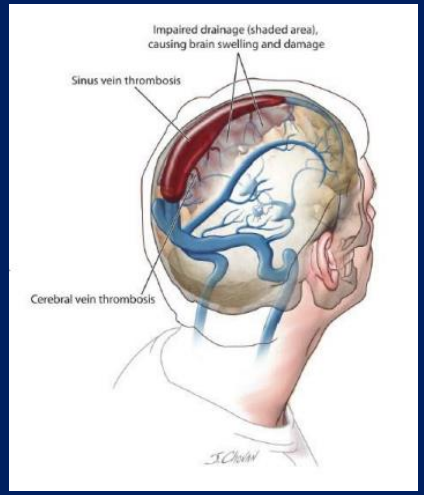
Question 1

Of the following, which is MOST likely cause of this patient's headache?

a) Spinal headache due to CSF leak
b) Intrathecal methotrexate-related neurotoxicity
c) Cerebral venous sinus thrombosis
d) Progressive CNS leukemia
e) Subarachnoid hemorrhage

Cerebral Venous Sinus Thrombosis (CVST)

- Incidence: Venous thromboembolism (VTE) occurred in 59 of 778 (8%) on DCOG ALL-10 study, of which 26 (44%) were CVST
- Risk factors
  - PEG + steroid co-administration
  - Compared with other VTE, CVST occurs earlier in therapy (induction) and earlier after PEG (median 3 days)
- Diagnosis: MRV
- Treatment: LMWH



Klaassen ILM, et al. *Res Pract Thromb Haemost.* 2019;3(2):234–241.

Case Presentation (continued)

- End induction marrow
  - Complete morphologic remission
  - Flow cytometry for residual B-lymphoblasts negative -> no minimal residual disease (MRD negative)
- Patient proceeds to consolidation chemotherapy: cyclophosphamide, cytarabine, 6MP, PEG, vincristine, and IT methotrexate
- Approximately 1 minute after beginning the day 15 IV PEG infusion, she develops severe anxiety, diffuse flushing, abdominal pain, nausea, and decreased blood pressure
- The infusion is stopped, and patient is given diphenhydramine and a normal saline bolus, with resolution of symptoms

Question 2

Which of the following would be your next step for this patient?

a) Bring the patient back to clinic the following day and rechallenge with PEG after premedication with diphenhydramine and hydrocortisone and a slower initial infusion rate

b) Discontinue PEG permanently due to hypersensitivity; attempt to obtain Erwinia asparaginase as a substitute

c) Draw a serum asparaginase activity level and use results to determine whether to rechallenge with PEG or not

d) Discontinue PEG permanently and substitute with etoposide

PEG Infusion Reactions

- IV PEG: 2 types of AEs have been described
  - True hypersensitivity reactions due to the production of neutralizing antibodies
  - Infusion-related reactions, not associated with neutralization
- These 2 AEs can be difficult or impossible to distinguish, since
  - Reactions occur very early (seconds/minutes into infusion), have overlapping signs/symptoms, and are extremely distressing for patient, family, and staff, resulting in immediate cessation of infusion
  - Since TDM is <u>not interpretable</u> when patients have received <5% of planned dose, SAA assays not useful

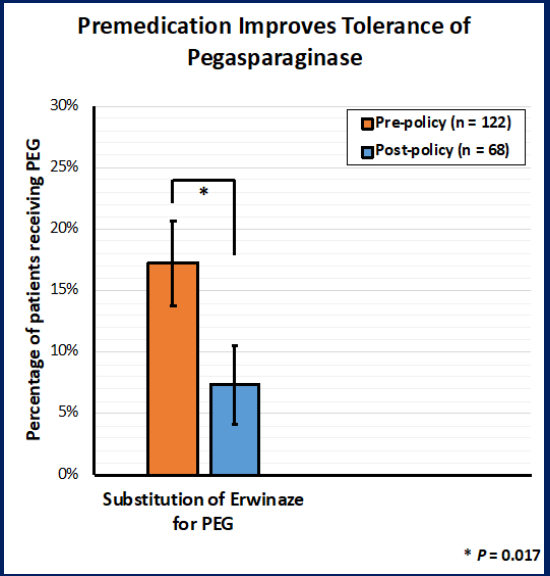
Burke MJ, et al. *Leuk Lymph.* 2017;58(3):540-551.

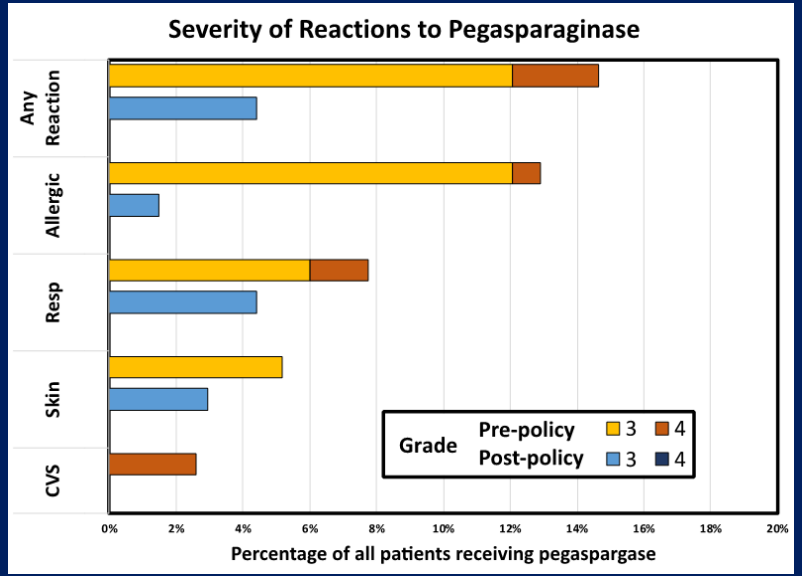
PEG Premeds and TDM

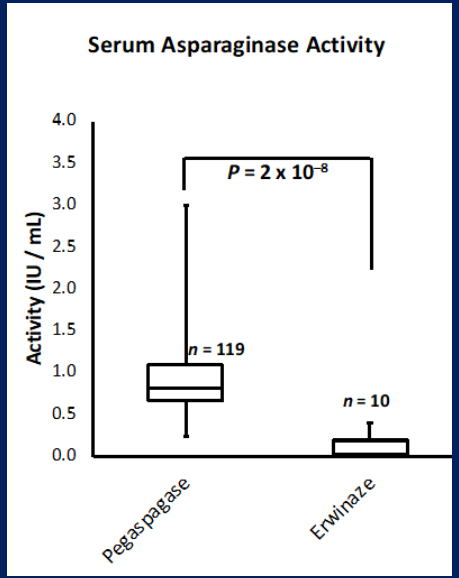
- ***Premedicate*** all patients receiving asparaginase products 20-30 minutes prior to dose
  - Diphenhydramine 1 mg/kg (PO or IV)
  - Famotidine (0.5 mg/kg) or ranitidine (2 mg/kg) PO or IV
  - Hydrocortisone 2 mg/kg IV for those with previous reactions
- ***Manage*** clinically significant reaction
  - Diphenhydramine first-line, steroids second, epi for airway involvement
- ***Test*** (SAA)
  - PEG: 7 (4-10) days later (every dose)
  - Erwinaze: 2 days later
- ***Interpret*** SAA
  - ≤0.1 units/mL despite having received a reasonable dose, change to Erwinaze
  - ≥0.1 units/mL and reaction not severe, prefer rechallenge with PEG

Cooper SL, et al. *Pediatric Blood and Cancer.* 2019;66(8):e27797.

PEG Premeds and TDM







- *Savings per patient not changed to Erwinaze:* **$106,967**
- *Savings per patient premedicated (NNT 10.1):* **$10,547**

Cooper SL, et al. *Pediatr Blood Cancer.* 2019;66(8):e27797.

Case Presentation (continued)

- Patient completed consolidation chemotherapy and moved on to interim maintenance, consisting of vincristine, 6MP, and high-dose IV methotrexate every 2 weeks (days 1, 15, 29, and 43), plus IT methotrexate on day 1 and 29

- On day 39, developed acute onset of right arm and leg weakness

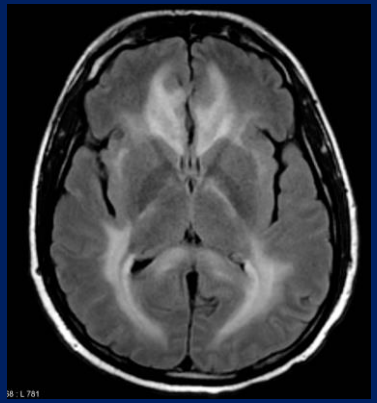
Question 3

Of the following, which is MOST likely cause of this patient's weakness?

a) Acute cerebrovascular accident (stroke)
b) Intrathecal methotrexate-related neurotoxicity
c) Cerebral venous sinus thrombosis
d) Hypertensive crisis
e) Vincristine-related neurotoxicity

Acute methotrexate neurotoxicity

- Can be a complication of either intrathecal or high-dose IV methotrexate
- Typically occurs 9-11 days after exposure
- MRI must be done urgently to rule out CVA – most likely finding is leukoencephalopathy
- Complete and rapid resolution is typical
- Most patients will tolerate reintroduction of IT methotrexate as follows
  - Substitute with cytarabine for 1 treatment
  - Give methotrexate with leucovorin rescue for 1 treatment
  - Resume standard IT methotrexate



Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 4438

Other important acute toxicities

- **Vincristine**: peripheral neuropathy, constipation, SIADH
- **PEG asparaginase**: pancreatitis, hepatotoxicity, dyslipidemia
- **Steroids**: hyperglycemia, hypertension, psychosis, AVN, gastritis

Global Leukemia Academy

Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients

APTITUDE HEALTH

Global Leukemia Academy

Educational ARS questions

Franco Locatelli

Global Leukemia Academy

APTITUDE HEALTH

Question 1:

After listening to the breakout session, which assertion is correct for children with ALL??

a) All patients with *MLL*-rearranged ALL should be transplanted

b) All patients with *BCR-ABL*–positive ALL should be transplanted

c) No patient with *BCR-ABL*–positive ALL should be transplanted

d) AlloSCT is part of treatment for children with early relapsed ALL

Answer to Question 2:

After listening to the breakout session, which assertion is correct for children with ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment

b) Blinatumomab and inotuzumab cannot be administered sequentially

c) Therapeutic drug monitoring of asparaginase improves outcome

d) Dexamethasone and vincristine are standard components of maintenance therapy

Global Leukemia Academy

Session close

Franco Locatelli

APTITUDE HEALTH

Thank you!

- Please complete the **evaluation survey** that will be sent to you by email
- The meeting recording and slides presented today will be shared on the www.globalleukemiaacademy.com website
- You will also receive a certificate of attendance by email by October 30

THANK YOU!

AMGEN

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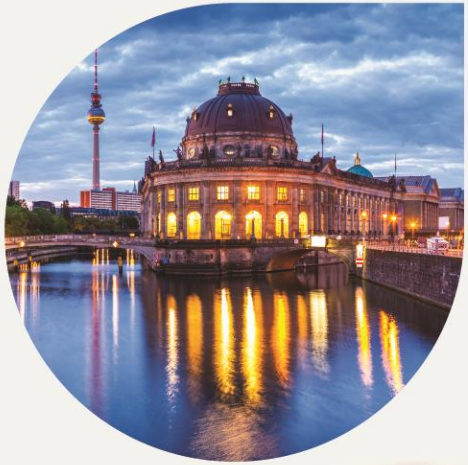

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

THANK YOU FOR YOUR PARTICIPATION!

APTITUDE HEALTH