AMGEN Adaptive biotechnologies®

Global Leukemia Academy

Global Leukemia Academy Virtual Breakout: Pediatric ALL patients

Emerging and Practical Concepts and Controversies in Leukemias

8–9 July 2020

APTITUDE HEALTH®

Global Leukemia Academy

Virtual Breakout: Pediatric ALL patients Session Opening

Rob Pieters

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Meet the Faculty

Rob Pieters, MD, PhD
Chief Medical Officer,
Princess Máxima Center for
Pediatric Oncology

Hale Ören, MD
Professor of Pediatrics,
Dokuz Eylul University

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

Sema Anak, MD
Faculty member at Istanbul Medipol
University International School of
Medicine, Head of the Department of
Pediatric Hematology/Oncology

Akif Yesilipek, MD
Head of pediatric bone marrow transplant
units in Medicalpark Antalya and Göztepe
Hospitals. Faculty of Medicine, Pediatric
Hematology Department, Bahcesehir
University, Antalya, Turkey

Objectives of the Program

- Understand current treatment patterns for ALL including incorporation of new technologies
- Uncover when genomic testing is being done for ALL, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in ALL as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring ALL
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies in ALL
- Review promising novel and emerging therapies in ALL

Virtual Breakout: Pediatric ALL Patients

Chair: Rob Pieters

TIME UTC+3	TITLE	SPEAKER
15.00 – 15.15	Session opening • Educational ARS questions for the audience	Rob Pieters
15.15 – 15.35	First-line treatment of pediatric ALL • Presentation • Q&A	Rob Pieters
15.35 – 15.55	Current treatment options for relapsed ALL in children including HSCT considerations • Presentation • Q&A	Hale Ören
15.55 – 16.15	Bispecific T-cell engagers for pediatric ALL • Presentation • Q&A	Patrick Brown
16.15 – 16.55	Case-based panel discussion: Management of long- and short-term toxicities • Overview of long-term toxicities • Patient case presentation Panelists: Rob Pieters, Hale Ören, Patrick Brown, Sema Anak, Gülyüz Öztürk, Akif Yesilipek	Rob Pieters Hale Ören Discussion
16.55 – 17.10	Session close • Educational ARS questions for the audience	Rob Pieters

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Educational ARS Questions

Rob Pieters

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Educational questions Pediatric ALL
Question 1: which assertion is correct for children with ALL?

1. All patients with MLL rearranged ALL should be transplanted
2. All patients with BCR-ABL positive ALL should be transplanted
3. No patient with BCR-ABL positive ALL should be transplanted
4. AlloSCT is part of treatment for children with early relapsed ALL

Educational questions Pediatric ALL
Question 2: which assertion is correct for children with ALL?

1. Blinatumomab and inotuzumab are part of first-line treatment
2. Blinatumomab and inotuzumab can not be administered sequentially
3. Therapeutic drug monitoring of asparaginase improves outcome
4. Dexamethasone and vincristine are standard components of maintenance therapy

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First-Line Treatment of Pediatric ALL

Rob Pieters

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First-line treatment of ALL

Rob Pieters
Chief Medical Officer

Question 1:

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

1. A minority of patients with Ph+ ALL benefit from receiving allogenic SCT when receiving a tyrosine kinase inhibitor such as imatinib
2. The dose intensity of asparaginase has no impact on outcome
3. 6-thioguanine has to be preferred over 6-mercaptopurine in maintenance therapy
4. Prednisone is a more effective drug than dexamethasone

Question 2:

Which assertion is correct?

1. All children with a BCR-ABL–like ALL should be treated with a tyrosine kinase inhibitor such as imatinib or dasatinib
2. Cranial irradiation is indicated in B-lineage ALL and T-lineage ALL with a WBC >50 × 10^9/L at diagnosis
3. Copy number alterations (CNA) do not predict outcome
4. 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)

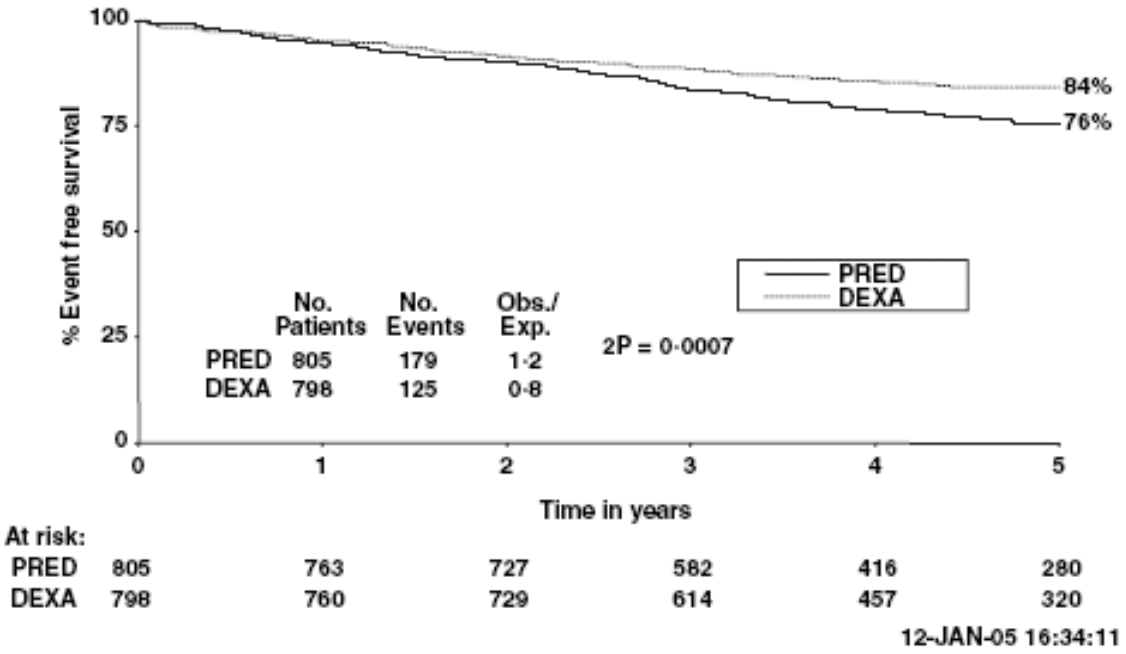
- (cranio[spinal] radiotherapy)
- (allogenic hematopoietic stem cell transplantation [HSCT])

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
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Maintenance/reinduction therapy

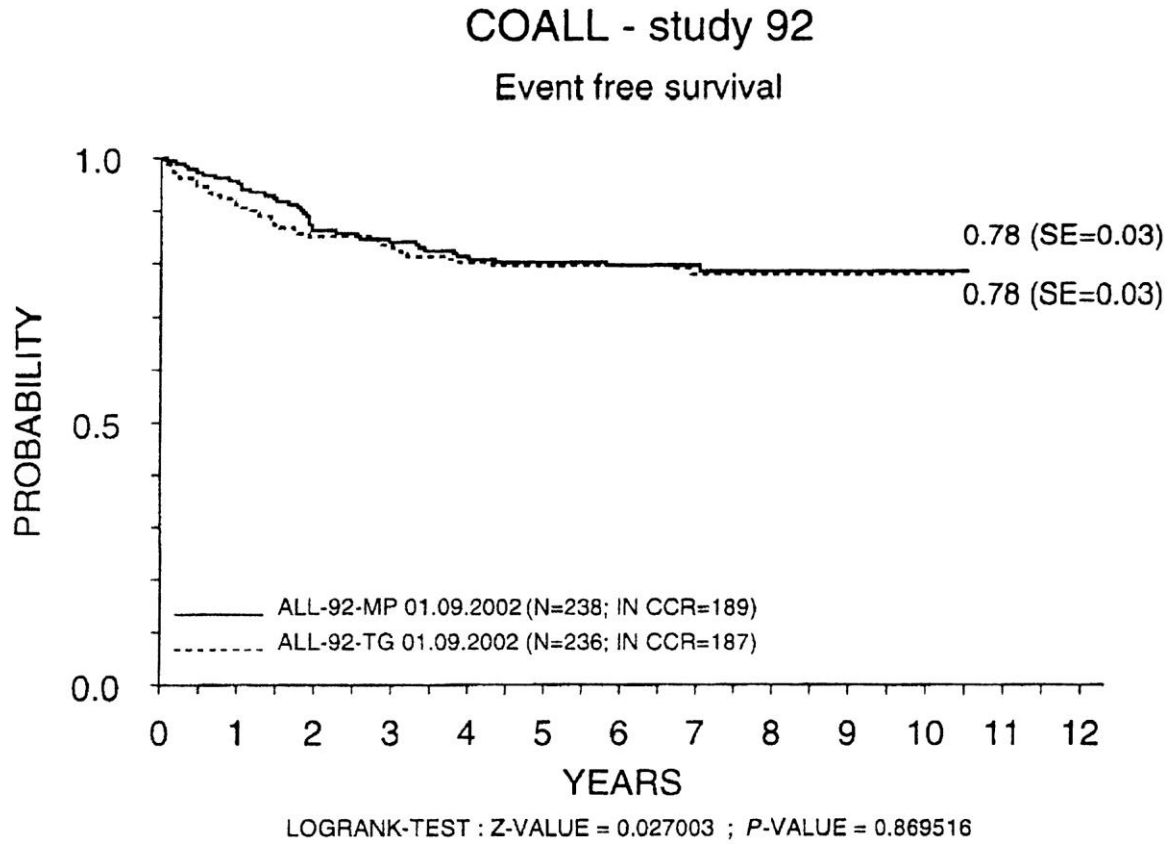
Events (relapse/toxic deaths) reduced by

▪ Longer maintenance	3-yr vs 2-yr	23% vs 28%
▪ Intensive reinduction/intensification	yes vs no	28% vs 36%
▪ VCR/Pred pulses	yes vs no	31% vs 40%

Multivariate: survival significantly improved by intensification

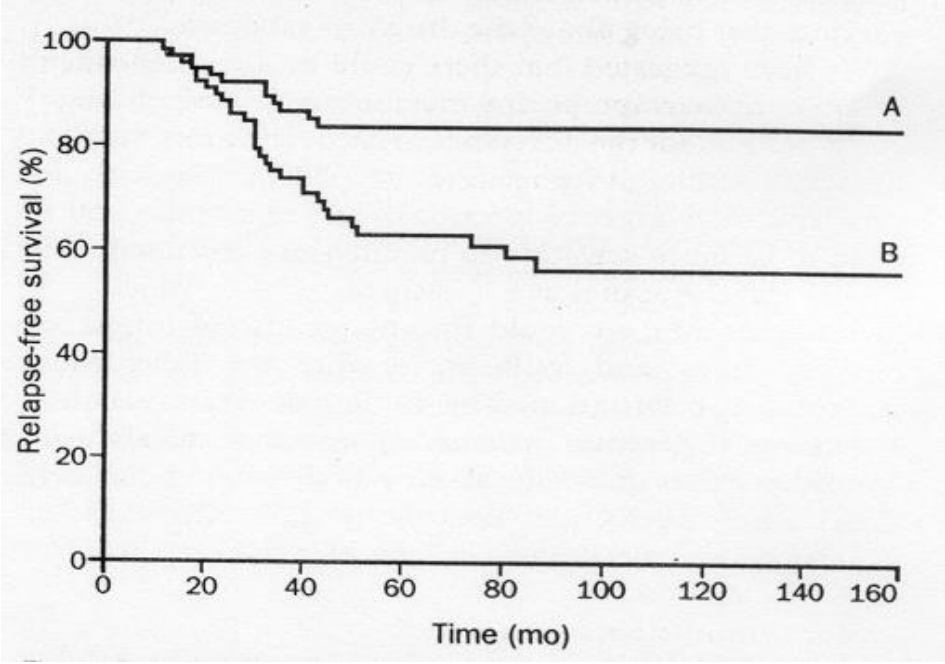
Childhood ALL Collaborative Group. *Lancet.* 1996;347(9018):1783-1788.

EFS by randomization of 6-MP vs 6-TG in maintenance



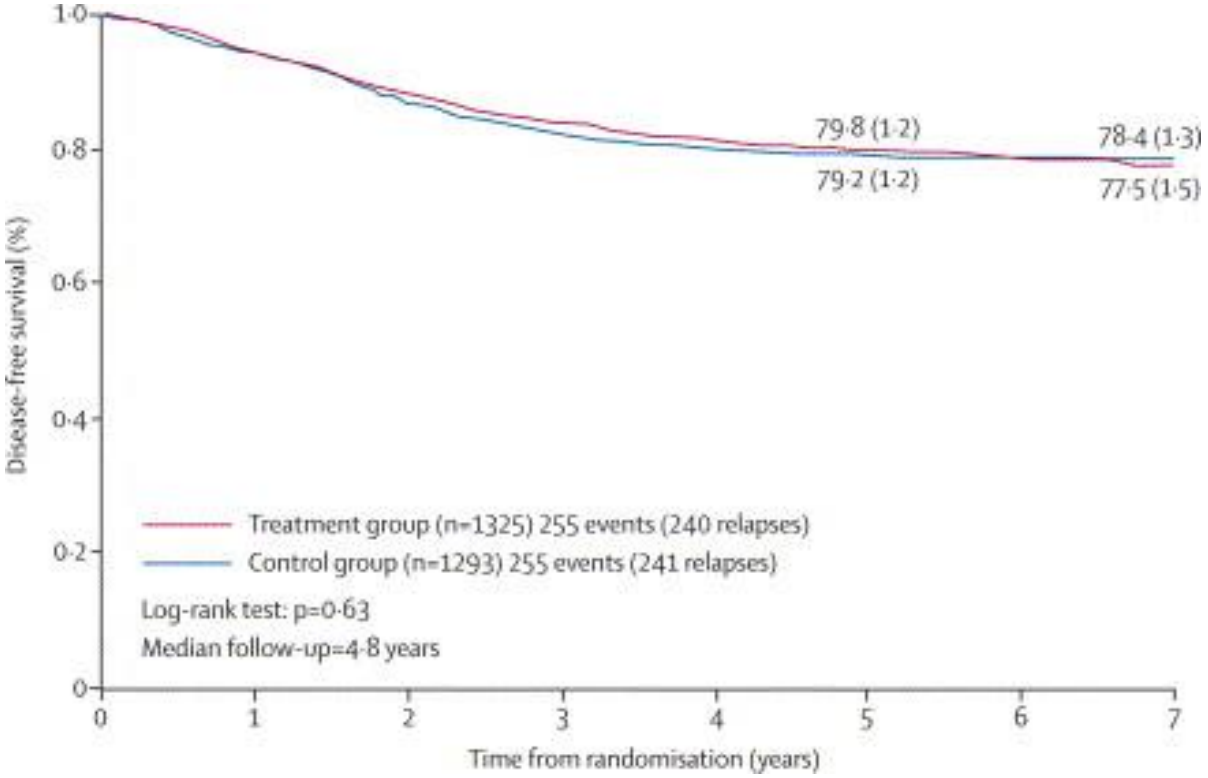
Harms DO, et al. *Blood.* 2003;102(8):2736-2740.

6-MP pharmacodynamics: Erythrocyte 6-TGN concentration vs relapse-free survival in ALL

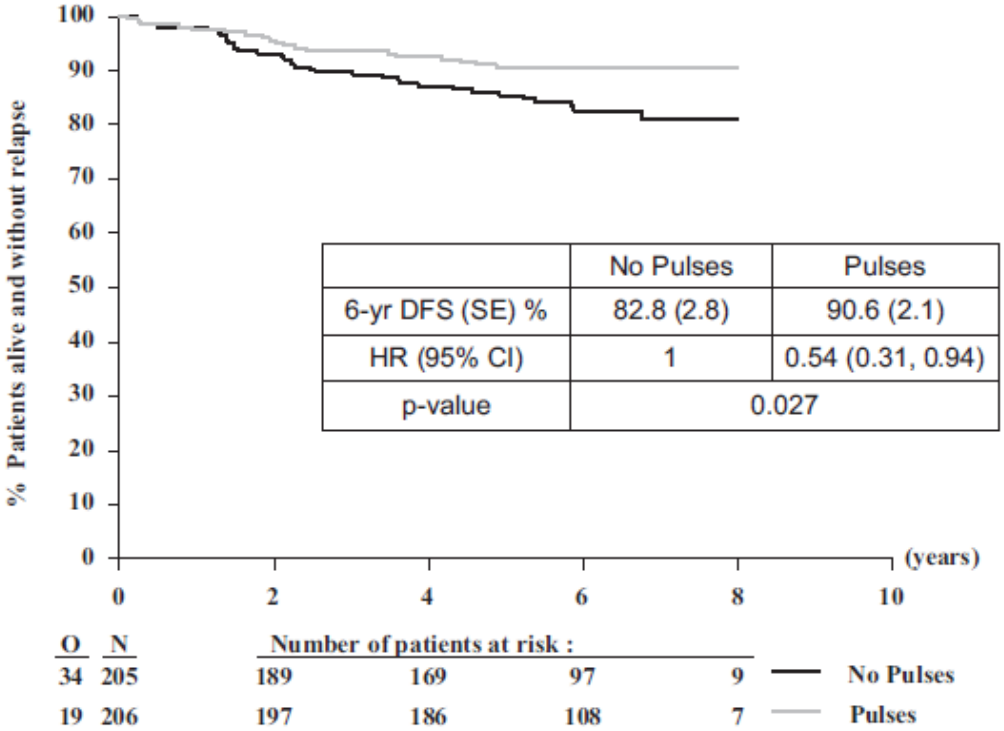


Group A = values above the median; group B = values below the median

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



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	

De Moerloose B, et al. *Blood.* 2010;116(1):36-44.

ALL

- Therapy elements
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CNS treatment

- Radiotherapy + ith therapy vs extra ith therapy: EFS not different
- Radiotherapy vs IV MTX: EFS not different

  (Radiother: less CNS relapses; IV MTX less systemic relapses)
- Radiotherapy dose: 24 Gy = 18 Gy (= 12 Gy?)

Conclusions

- Radiotherapy can be replaced by long-term intrathecal therapy
- IV MTX reduces non-CNS relapses

Clarke M, et al. Childhood ALL Collaborative Group. *J Clin Oncol.* 2003;21(9):1798-1809.

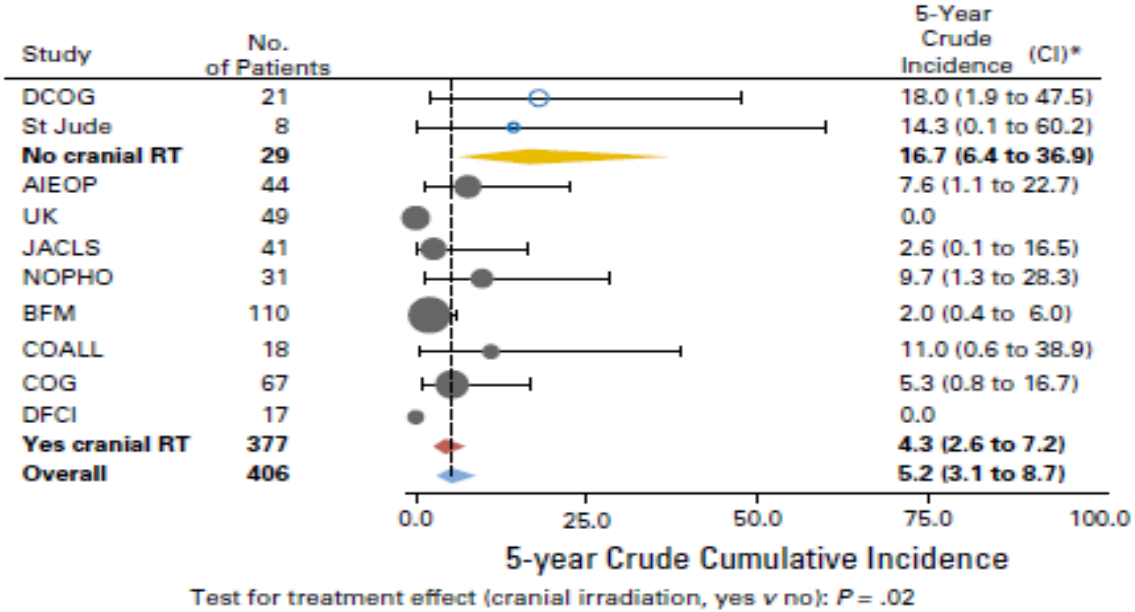
5-year outcomes to pre-emptive cranial radiotherapy (CRT) for ALL subgroups other than CNS3

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 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)



ALL

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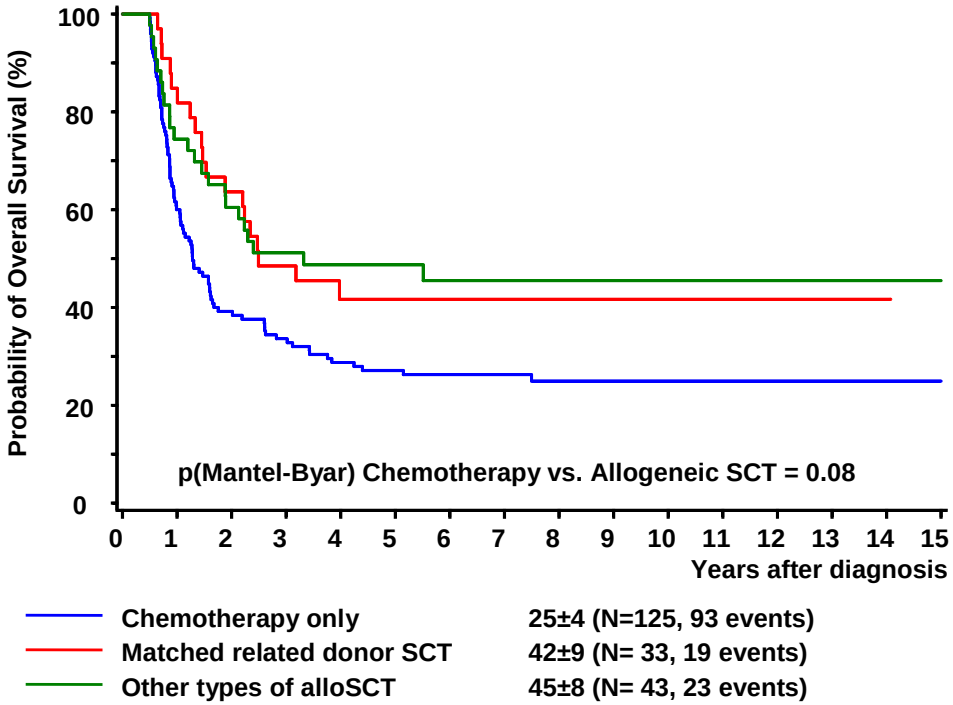
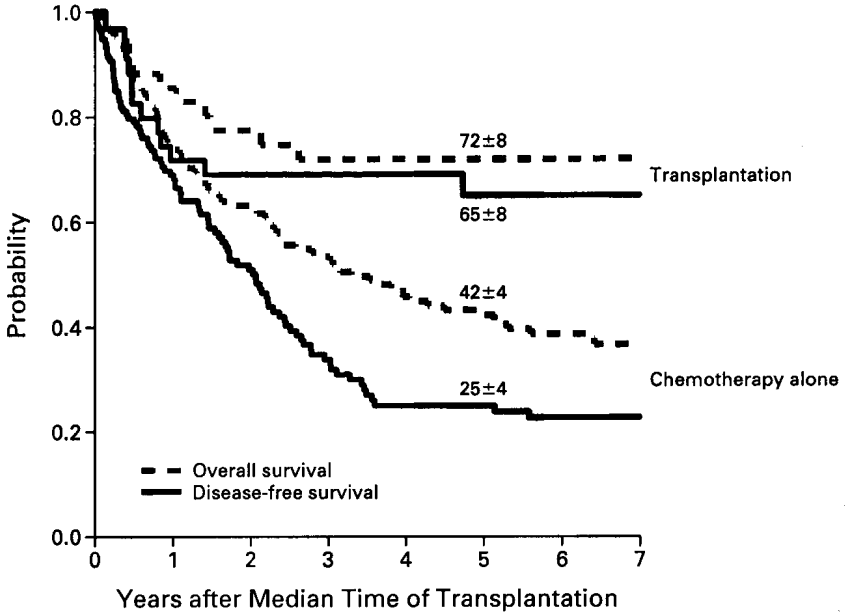
No CR after induction AND T-ALL: better survival with alloSCT



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

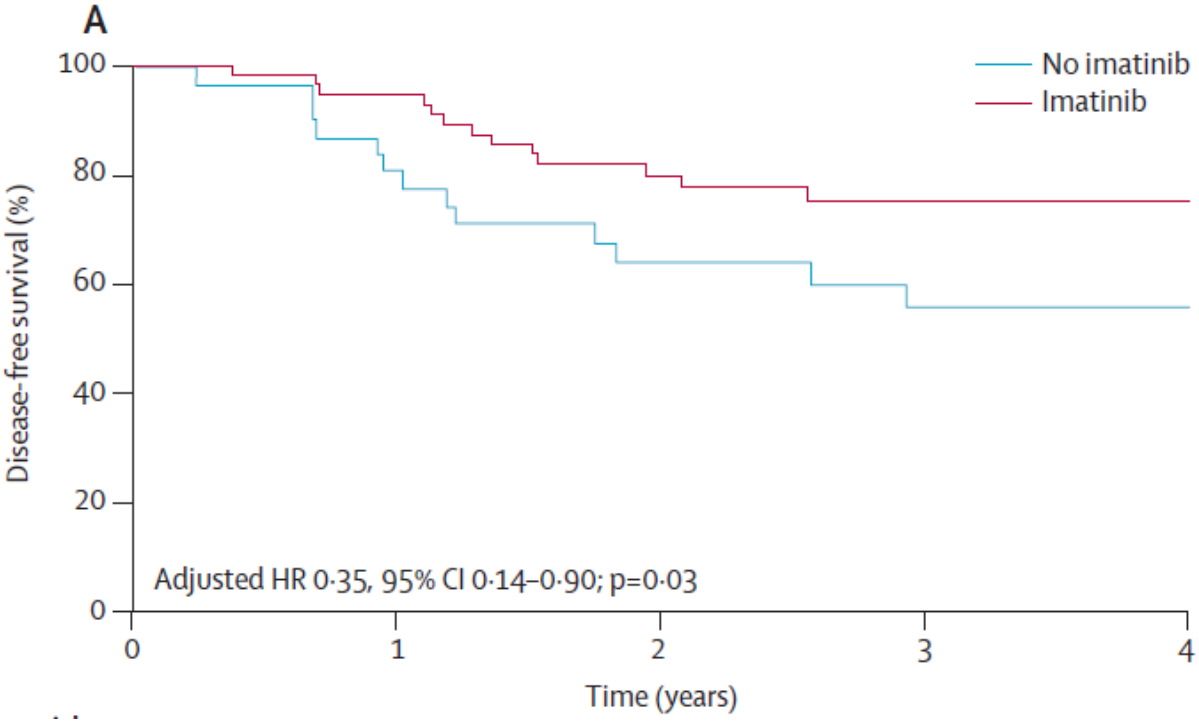


PATIENTS AT RISK

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.

DFS for good-risk Ph+ ALL patients as treated with imatinib (EsPhALL)



Biondi A, et al. *Lancet Oncol.* 2012;13(9):936-945.

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

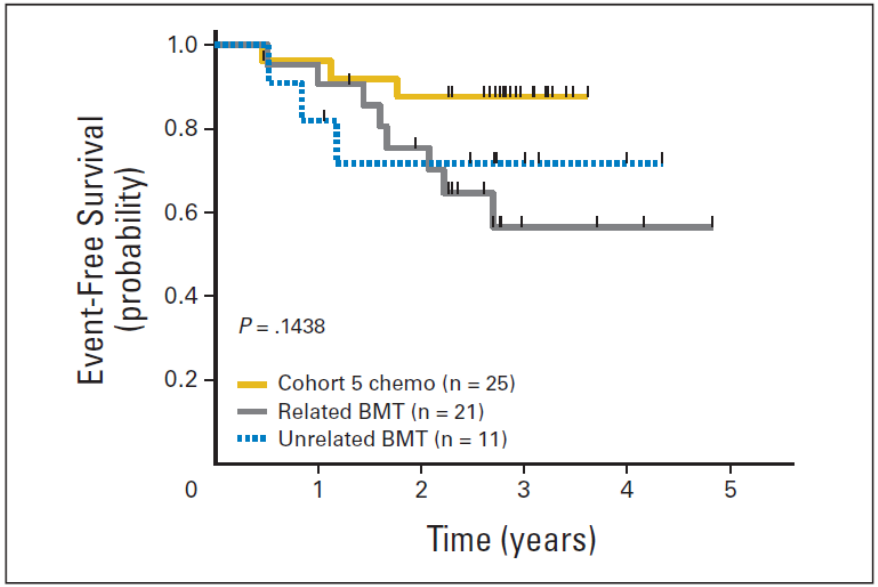
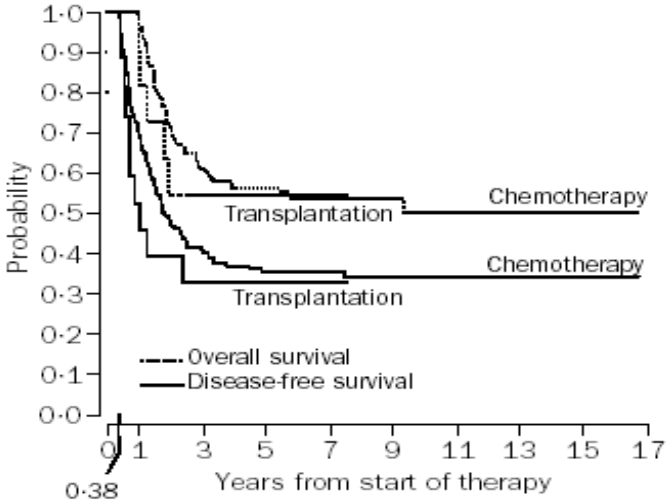


Fig 4. Comparison of event-free survival (EFS) for Cohort 5 chemotherapy only versus related-donor bone marrow transplantation (BMT) versus unrelated-donor BMT. Cohort 5 patients were compared with human leukocyte antigen (HLA) –identical sibling BMT (8 of 39 in cohorts 1-4; 13 of 44 in cohort 5) and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

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

Infant ALL: no proven benefit of allogenic BMT



Patients at risk

Overall survival							
Chemotherapy		134	80	70	44	18	11
Transplantation		11	6	3	2	0	0
Disease-free survival							
Chemotherapy	183	109	63	50	35	15	10
Transplantation	14	8	5	2	2	0	0

Figure 2: **Mantel-Byar estimates of disease-free survival with a landmark of 0·38 years, and Kaplan-Meier estimates of survival with a landmark of 1 year in patients with t(4;11)**

Pui CH, et al. *Lancet.* 2002;359(9321):1909-1915.

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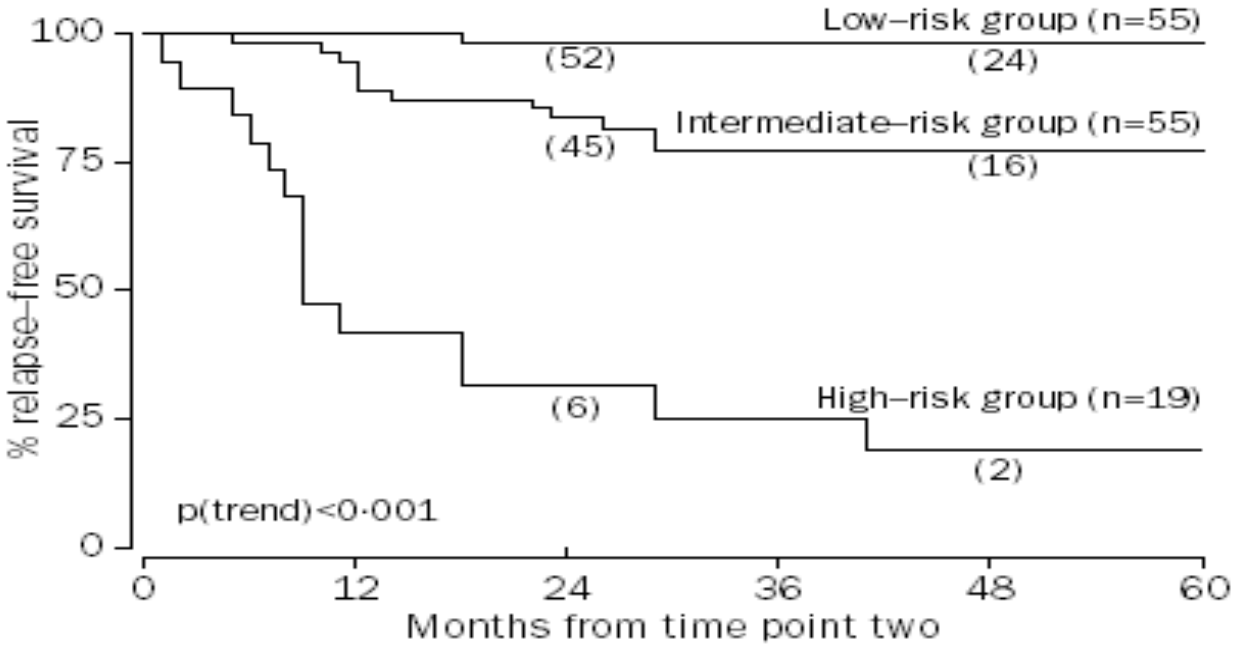
Targeting therapy in ALL

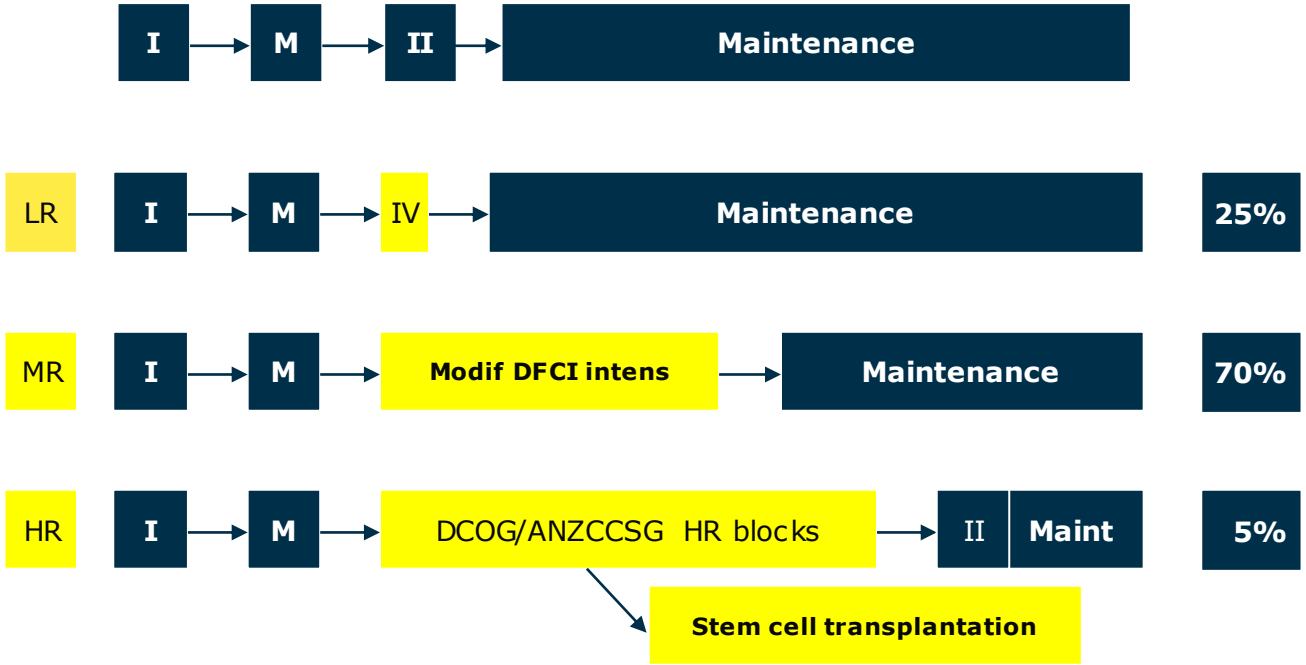
- Minimal residual disease (MRD) monitoring
- Therapeutic drug monitoring
- Genetic subclasses and pharmacology
- Specific targetable genetic lesions
- New (epi)genetic abnormalities
- Immunotherapies

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 protocol outlines



Targeting therapy in ALL

- Minimal residual disease (MRD) monitoring
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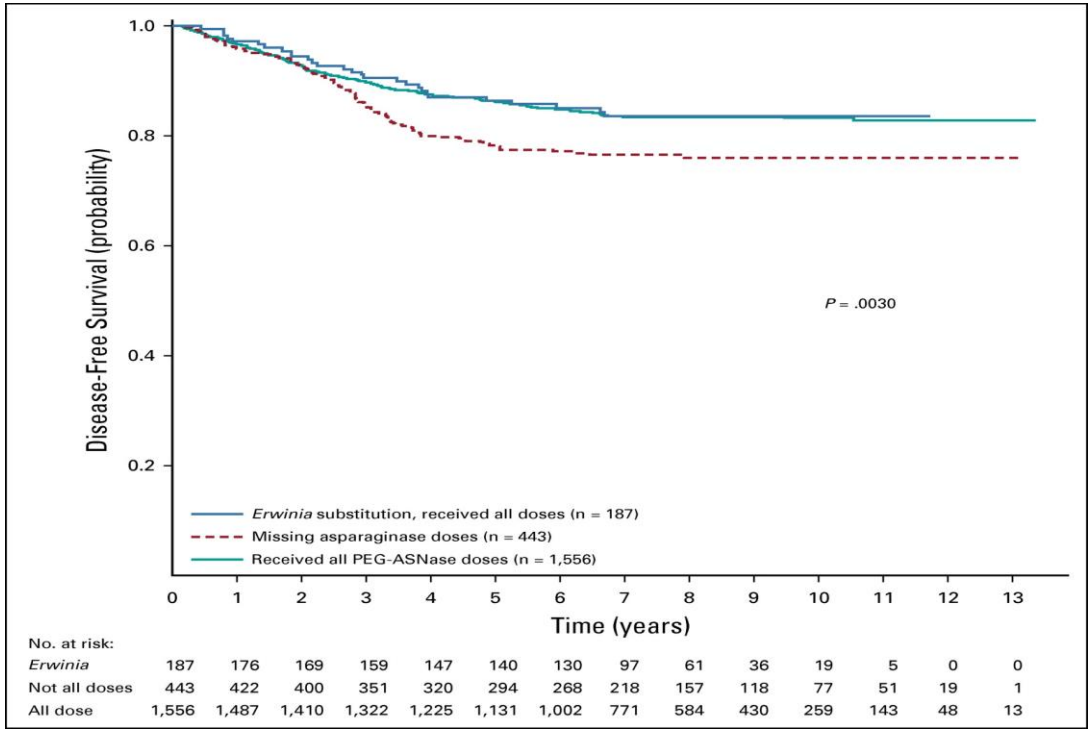
Disease-free survival of NCI high-risk patients stratified by asparaginase received



Targeting therapy in ALL

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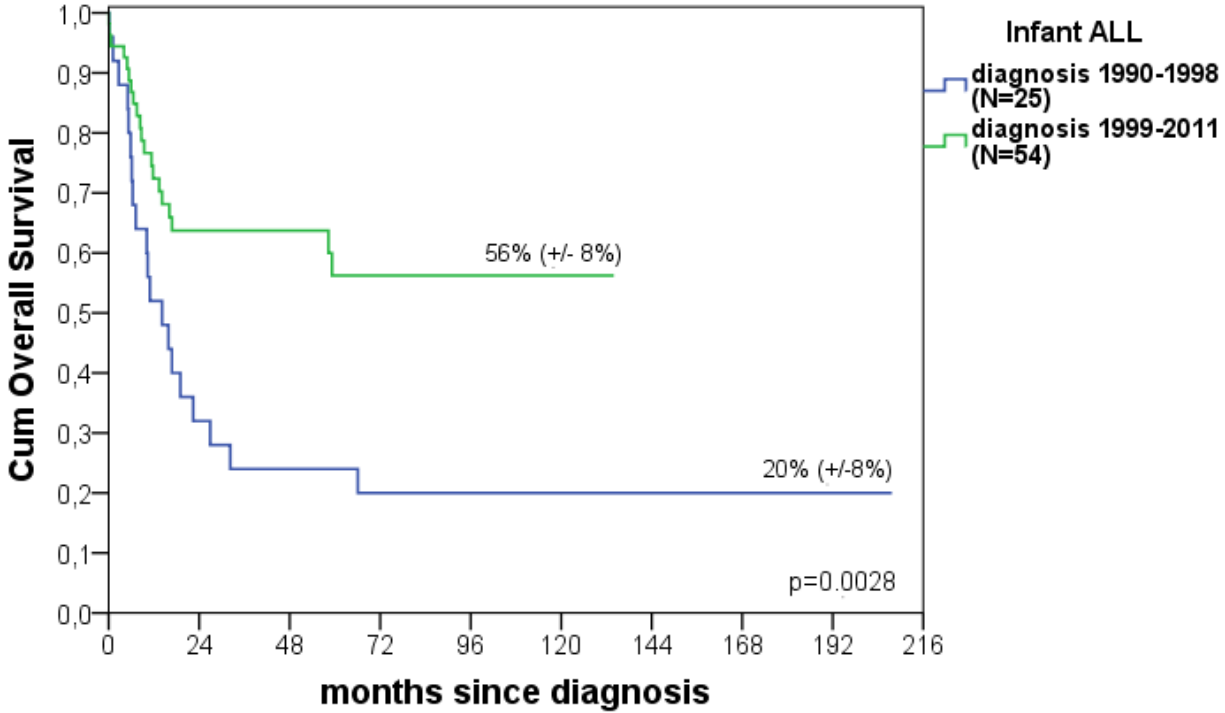
In vitro resistance/sensitivity of infant ALL

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

- Minimal residual disease (MRD) monitoring
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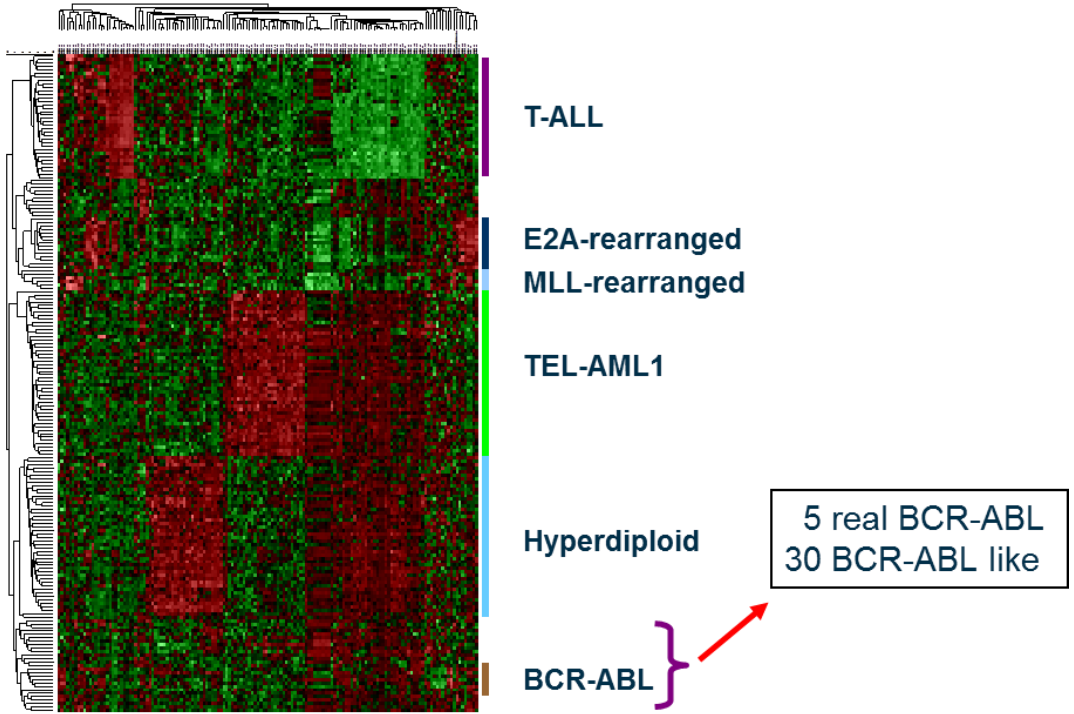
Discovery of BCR-ABL–like ALL



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

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

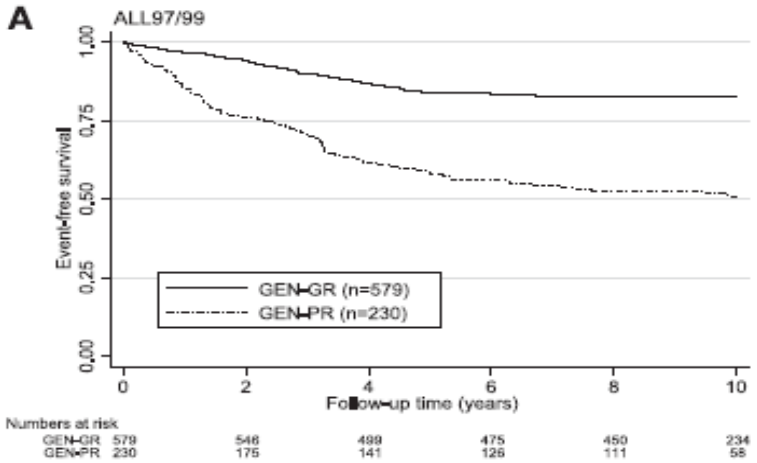
Marker	*BCR-ABL1*-like (n=77)	Remaining B-other (n=76)
***ABL1/ABL2* fusion**	**3.9%**	0%
ZMIZ1-ABL1	1	
FOXP1-ABL1	1	
RCSD1-ABL2	1	
***PDGFRB* fusion**	**5.2%**	0%
EBF1-PDGFRB	4	
***CSF1R* fusion**	**2.6%**	0%
SSBP2-CSF1R	2	
***JAK2* fusion**	**6.5%**	0%
PAX5-JAK2	3	
BCR-JAK2	1	
TERF2-JAK2	1	
CRLF2*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

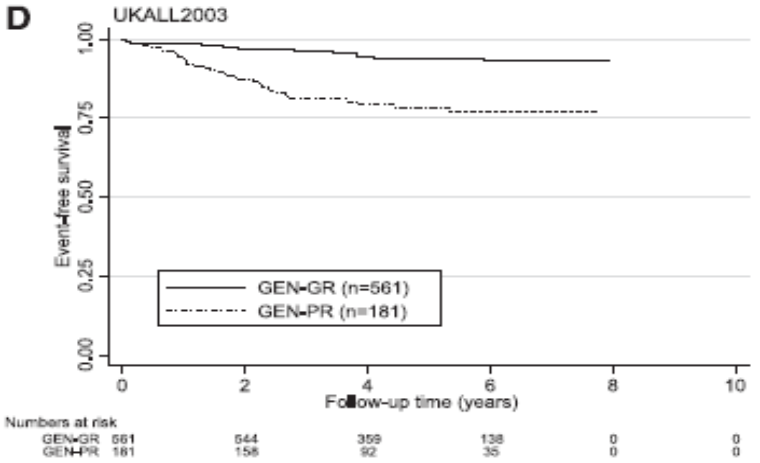
12% with ABL-1 class fusions
Targetable with imatinib/dasatinib

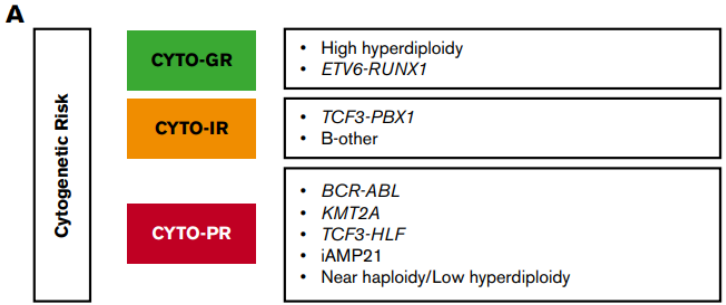
6% with JAK2 fusions
Targetable with ruxolitinib????

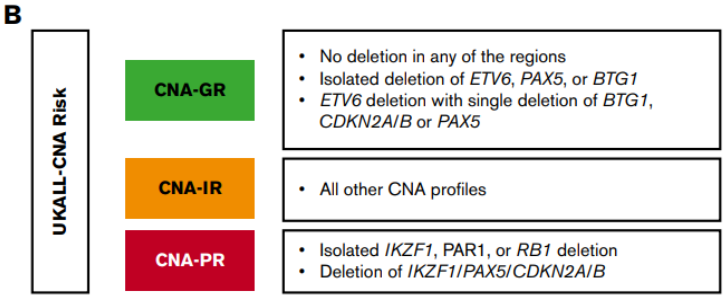
Boer JM, et al. *Oncotarget.* 2017;8(3):4618-4628.

EFS ALL97/99 and UKALL2003 by genetic risk group





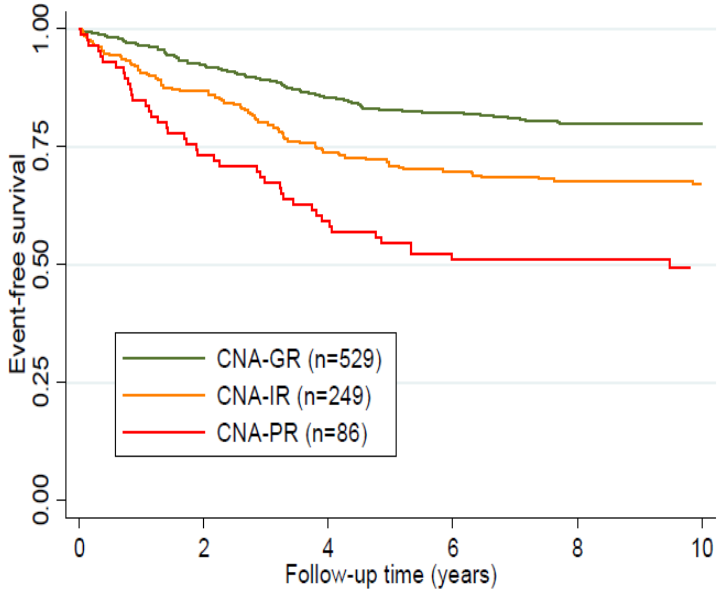




Moorman AV, et al. *Blood.* 2014;124(9):1434-1444; Hamadeh L, et al. *Blood Adv.* 2019;3(2):148-157.

UK copy number alteration (CNA) classifier in UKALL

CNA profile defines risk groups



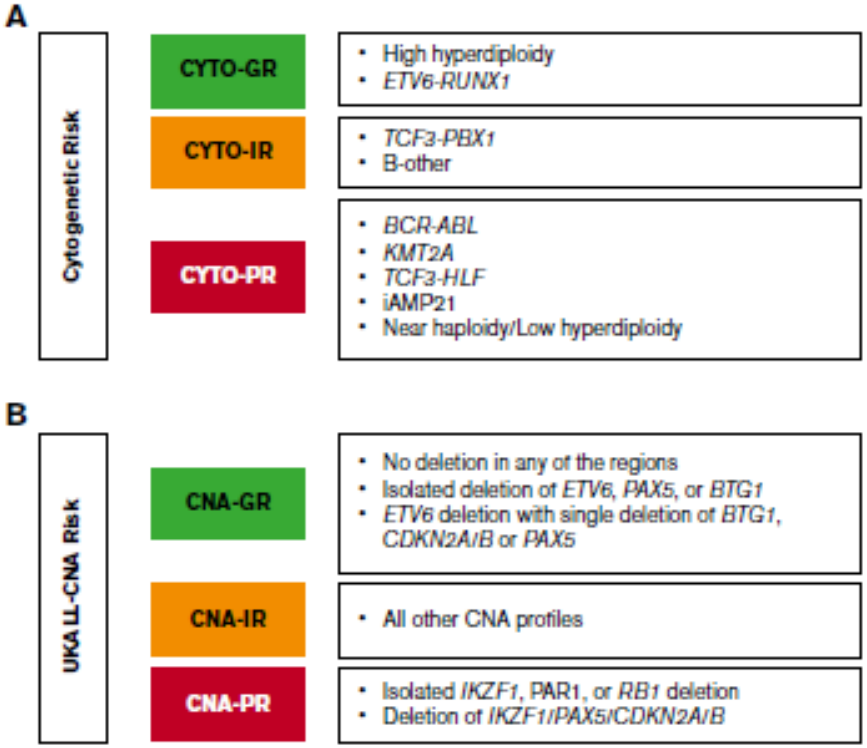
CNA profiles by MLPA

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

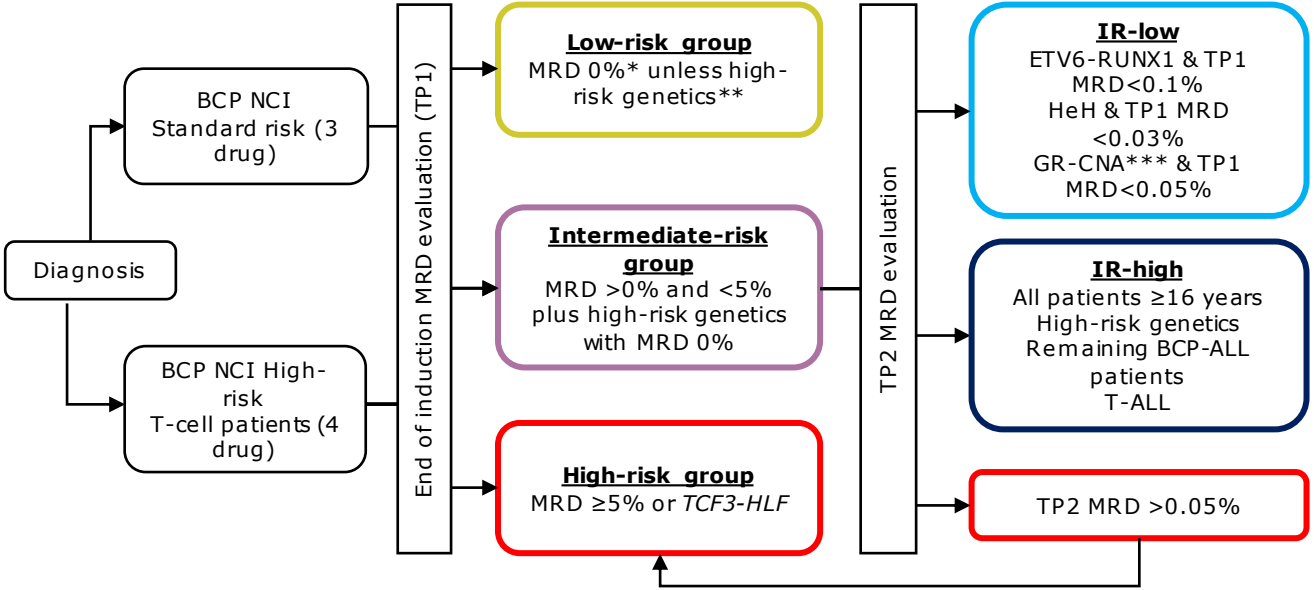
Poor risk
- Isolated *IKZF1, PAR1,* or *RB1* deletion
- Deletion of *IKZF1/PAX5/CDKN2A/B*

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 stratification by MRD and genetics for the ALLTogether trial



*0% = undetectable MRD by IG/TCR PCR; **High-risk genetics: *KMT2A/MLL* gene fusions, near haploidy, low hypodiploidy, iAMP21 and rearrangements affecting *ABL1, ABL2, PDGFRB* and *CSF1R* (except *BCR-ABL1* which are excluded from the study); ***CNA profile as per Moorman et al (2014) *Blood*;124(9):1434-1444. GR profile: no deletion of *IKZF1, CDKN2A/B, PAR1, BTG1, EBF1, PAX5, ETV6, RB1*; isolated deletions of *ETV6, PAX5, BTG1*; or *ETV6* deletions with a single additional deletion of *BTG1, PAX5, CDKN2A/B.*

Risk groups, outcome, and consequences for treatment

Risk group	% patients	EFS%	OS%	relapse %	Treatment
VLR	24%	95	99	4	Reduction: randomised +/- anthracyclines
IR-L	36%	95	98	3	Reduction: randomised +/- anthracyclines
IR-H	37%	82	89	15	Intensification: randomised +/- inotuzumab
VHR	4%	78	78	14	Experimental: CART for B, nelarabine for T

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

Answer to question 1:

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

1. **A minority of patients with Ph+ ALL benefit from receiving allogenic SCT when receiving a tyrosine kinase inhibitor such as imatinib**
2. The dose intensity of asparaginase has no impact on outcome
3. 6-thioguanine has to be preferred over 6-mercaptopurine in maintenance therapy
4. Prednisone is a more effective drug than dexamethasone

Answer to question 2:

Which assertion is correct?

1. All children with a BCR-ABL–like ALL should be treated with a tyrosine kinase inhibitor such as imatinib or dasatinib
2. Cranial irradiation is indicated in B-lineage ALL and T-lineage ALL with a WBC >50 × 10^9/L at diagnosis
3. Copy number alterations (CNA) do not predict outcome
4. End of induction MRD and/or end of consolidation MRD is the most powerful prognostic factor

Thank you!

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Global Leukemia Academy

Q&A

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Current Treatment Options for Relapsed ALL in Children Including HSCT Considerations

Hale Ören

APTITUDE HEALTH®

Overview of the talk

- Describe the importance of relapsed ALL
- Risk factors for relapsed ALL patients
- Standard therapy of relapse ALL
- HSCT indications
- New therapy approaches in relapsed ALL

Childhood ALL: Progress through collaboration

Table 1. Patient Characteristics and Treatment Results From Selected Clinical Trials

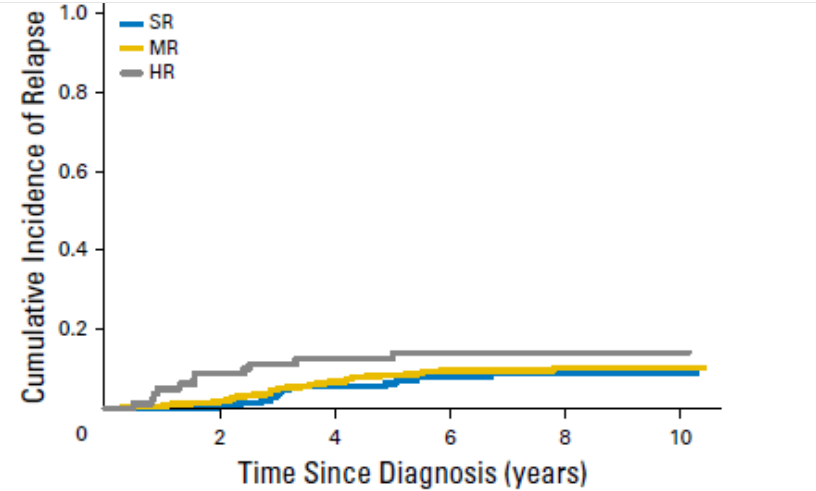
Study Group	Years of Study	No. of Patients	Age Range (years)	T-Cell ALL (%)	5-Year Cumulative Rate of Isolated CNS Relapse (% ± SE)	5-Year EFS (% ± SE)	5-Year Overall Survival (% ± SE)	Reference
AIEOP-95	1995-2000	1,743	0-18	11	1.2 ± 0.3	75.9 ± 1.0	85.5 ± 0.8	Conter et al[1]
BFM-95	1995-1999	2,169	0-18	13	1.8 ± 0.3	79.6 ± 0.9	87.0 ± 0.7	Möricke et al[2]
CoALL-97	1997-2003	667	1-18	14	4.0 ± 0.8	76.7 ± 1.7	85.4 ± 1.4	Escherich et al[3]
COG	2000-2005	7,153	0-21	7	NA	NA	90.4 ± 0.5	Hunger et al[4]
DCOG-9	1997-2004	859	1-18	11	2.6 ± 0.6	80.6 ± 1.4	86.4 ± 1.2	Veerman et al[5]
DFCI 00-01	2000-2004	492	1-18	11	NA	80.0 ± 2	91 ± 1	Vrooman et al[6]
EORTC-CLG	1998-2008	1,947	1-18	15.2	1.7 ± 0.3	82.7 ± 0.9	89.7 ± 0.7	Domenech et al[7]
IC-BFM 2002	2002-2007	5,060	1-18	13.3	1.9 ± 0.1	74 ± 1	82 ± 1	Stary et al[8]
JCCLSG ALL 2000	2000-2004	305	1-15	9.8	0.9 ± 0.1	79.7 ± 2.4	89.2 ± 1.8	Yamaji et al[9]
Ma-Spore ALL 2003	2002-2011	556	0-18	8.8	1.4	80.6 ± 3.5	89.2 ± 2.7	Yeoh et al[10]
MRC UKALL 2003	2003-2011	3,126	1-25	12	1.9 ± 0.6	87.3 ± 1.4	91.6 ± 1.2	Vora et al[11]
NOPHO-2000	2002-2007	1,023	1-15	11	2.7 ± 0.6	79.4 ± 1.5	89.1 ± 1.1	Schmiegelow et al[12]
SJCRH XV	2000-2007	498	1-18	15	2.7 ± 0.8	87.3 ± 2.9	93.5 ± 1.9	Pui et al[13]
TPOG	1999-2010	152	0-18	7.2	1.4 ± 1.0	84.2 ± 3.0	90.2 ± 2.4	Liu et al[14]

Abbreviations: AIEOP, Associazione Italiana di Ematologia Pediatrica; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Münster; CoALL, Cooperative ALL (study group); COG, Children's Oncology Group; DCOG, Dutch Children's Oncology Group; DFCI, Dana-Farber Cancer Institute (consortium); EFS, event-free survival; EORTC-CLG, European Organisation for Research and Treatment of Cancer-Children's Leukemia Group; IC-BFM, Intercontinental BFM; JCCLSG, Japanese Children's Cancer and Leukemia Study Group; Ma-Spore, Malaysia-Singapore; MRC UKALL, Medical Research Council United Kingdom Acute Lymphoblastic Leukemia; NA, not available; NOPHO, Nordic Society of Pediatric Hematology and Oncology; SJCRH, St Jude Children's Research Hospital; TPOG, Taiwan Pediatric Oncology Group.

Adapted from Pui CH, et al. *J Clin Oncol.* 2015;33(27):2938-2948.

Successful therapy reduction and intensification for childhood ALL on the basis of MRD

MRD-based medium-risk patients had a significantly higher 5-year EFS rate (88%, SE 2%) with therapy intensification (including 30 weeks of asparaginase exposure and dexamethasone/vincristine pulses) compared with historical controls (76%, SE 6%). Intensive chemotherapy and stem cell transplantation in MRD-based high-risk patients resulted in a significantly better 5-year EFS rate (78%, SE 8% vs 16%, SE 8% in controls). Overall outcomes improved significantly (5-year EFS rate 87%, 5-year survival rate 92%, and 5-year cumulative incidence of relapse rate 8%) compared with preceding Dutch Childhood Oncology Group protocols.



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

Integrated cytogenetic and genomic classification refines risk-stratification in pediatric ALL

Three-quarters of UKALL2003 patients had a GR genetic profile and significantly improved event-free survival (EFS; 94%) compared with patients with a PR genetic profile (79%). This difference was driven by a lower relapse rate (4% vs 17%), seen across all patient subgroups, and independent of other risk factors. Even genetic GR patients with minimal residual disease (>0.01%) at day 29 had an EFS in excess of 90%. In conclusion, the integration of genomic and cytogenetic data defines 2 subgroups with distinct responses to treatment and identifies a large subset of children suitable for treatment deintensification.

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

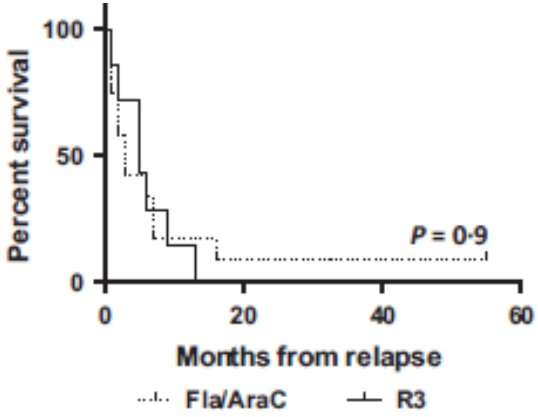
Childhood acute lymphoblastic leukemia treatment (PDQ®)

- Relapsed ALL is one of the major causes of death in children with cancer, **so reducing relapse risk is very important**
- Long-term survival rates after relapse range from about 30%–40% for early relapses, and 70%–80% for late relapses
- There is a large potential for developing different targeted treatments for children with ALL, on the basis of the abnormal findings in their individual disease (personalized medicine)

Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®): Health Professional Version. 2018; Locatelli F, et al. *Blood*. 2012;120:2807-2816; Childhood cancer by the ICCC. In: Howlader N, Noone AM, Krapcho M, et al., eds.: SEER Cancer Statistics Review, 1975-2010. Bethesda, Md: National Cancer Institute, 2013, Section 28; Ko RH, et al. *J Clin Oncol*. 2009;28:648-654.

UKALL2003 clinical outcomes teenagers and young adults

OS of relapsed patients



Comparison of R3 and fludarabine/cytarabine-based regimens

	R3	Fludarabine/Cytarabine	*P* value
	(*n* = 8*)	(*n* = 17)	
All relapsed patients			
CR after first salvage	4 (50%)	7 (41%)	
Allogeneic transplant received	3(38%)	8 (47%)	
Alive at end of study period	1 (13%)	5 (29%)	
Median OS from relapse	5·5 months	7 months	0·5
	(*n* = 7)	(*n* = 12)	
Patients relapsing on treatment only			
CR after first salvage	3 (43%)	5 (42%)	
Allogeneic transplant received	3 (43%)	5 (42%)	
Alive at end of study period	1 (14%)	1 (8%)	
Median OS from relapse	5 months	3 months	0·9

CR, complete remission; OS, overall survival; R3, protocol containing either idarubicin or mitoxantrone, as described previously (Parker *et al*, 2010).
*Excludes one patient transplanted in CR1.

Sellar RS, et al. *Br J Haematol*. 2018;181(4):515-522.

Outcome of relapse after allogeneic HSCT in children with ALL enrolled in the ALL-SCT 2003/2007 trial

- **3-year EFS 15%, OS 20%**

- The majority of children (48%) received salvage therapy without second alloSCT, 26% of the children underwent a second alloSCT, and 25% received palliative treatment only

- Combined approaches incorporating novel immunotherapeutic treatment options and second alloSCT hold promise to improve outcomes in children with post-alloSCT relapse

Kuhlen M, et al. *Br J Haematol.* 2018;180:82-89.

Prognostic risk factors in relapsed ALL

- Age
- Duration of remission
- Relapse site
- Immunophenotype
- Genetics/genomics
- Leukocyte count at diagnosis
- Response to therapy
- MRD levels

Which prognostic risk factors are important in standard therapeutic approach?

- Age
- Duration of remission
- Relapse site
- Immunophenotype
- MRD levels

UK ALL R3

A

Immunophenotype	Site of relapse	Time to relapse: Very early	Early	Late
Non-T cell	Isolated extramedullary	High risk	Intermediate risk	Standard risk
	Isolated marrow	High risk	High risk	Intermediate risk
	Combined	High risk	Intermediate risk	Intermediate risk
T cell	Isolated extramedullary	High risk	Intermediate risk	Standard risk
	Isolated marrow	High risk	High risk	High risk
	Combined	High risk	High risk	High risk

B

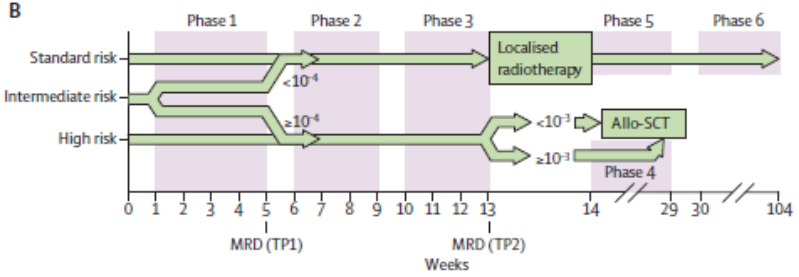


***Figure 1*: Risk stratification (A) and trial design (B)**
(A) Stratification according to immunophenotype, site of relapse, and time to relapse. Risk groups: very early refers to less than 18 months from first diagnosis; early refers to 18 months or more after first diagnosis and less than 6 months from stopping therapy; and late refers to 6 months or more after stopping therapy. (B) MRD sampling TPs are marked. At TP1, standard-risk and intermediate-risk patients with MRD lower than 10^{-4} cells were ineligible, and high-risk and intermediate-risk patients with MRD of 10^{-4} cells or more were eligible for allo-SCT. Localised radiotherapy was given to those with extramedullary disease and not proceeding to allo-SCT. When MRD assessment was not possible in intermediate-risk patients, allo-SCT was allowed provided relapse occurred within 24 months of stopping therapy. Details of the phases are provided in table 1. MRD=minimal residual disease. TP=timepoint. Allo-SCT=allogenic stem-cell transplant.

Treatment protocols for relapsed ALL mostly depends on immunophenotype, site of relapse, time to relapse, MRD…genetics/genomics

Parker C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet* 2010;376:2009-17.

HSCT in relapsed ALL

Indications to HSCT for relapsed ALL in the IntReALL 2010 protocol

Risk group	Patient subgroup	MRD[a] GR[b]	PR[b]	NA
SR	• Late isolated or combined bone marrow relapse of BCP-ALL	NO	MMD	MD
	• Early combined bone marrow relapse	MD	MMD	MMD
		Time of relapse		
	• Isolated extramedullary relapse	Early	Late	
		MD	NO	
HR	• Very early isolated extramedullary relapse of BCP or T-ALL • Early isolated or any very early bone marrow relapse of BCP-ALL • Any bone marrow relapse of T-ALL	HSCT in ALL patients (with a MD or a MMD)		

Time point of relapse: very early, < 18 months after primary diagnosis and < 6 after completion of primary therapy; early, ≥ 18 months after primary diagnosis and < 6 after completion of primary; late, ≥ months after completion of primary. MD permitted donor: HLA-matched sibling or non-sibling donor, MMD permitted donor: HLA-matched or HLA-mismatched donor

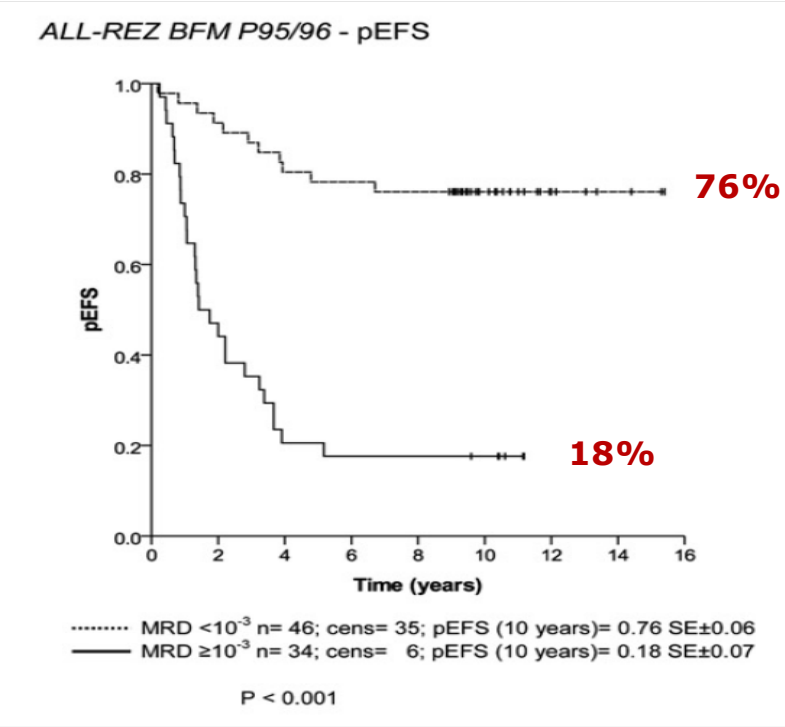
GR good response, *HR* high risk, *HSCT* hematopoietic stem cell transplantation, *MRD* minimal residual disease, *NA* not available, *NO* HSCT not indicated, *PR* poor response, *SR* standard risk

[a] MRD response after induction

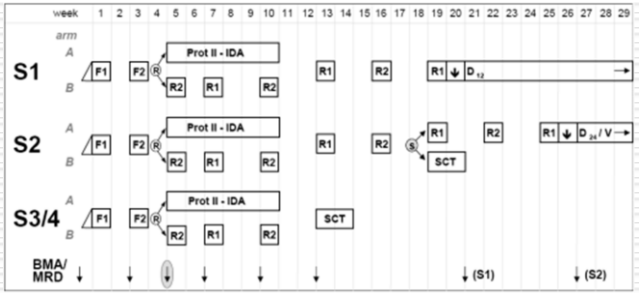
[b] MRD cutoff is defined by the specific treatment arm

Merli P, et al. *Curr Hematol Malig Rep.* 2019;14(2):94-105.

Minimal residual disease after induction is the strongest predictor of prognosis in intermediate-risk relapsed acute lymphoblastic leukemia: Long-term results of trial *ALL-REZ BFM P95/96*



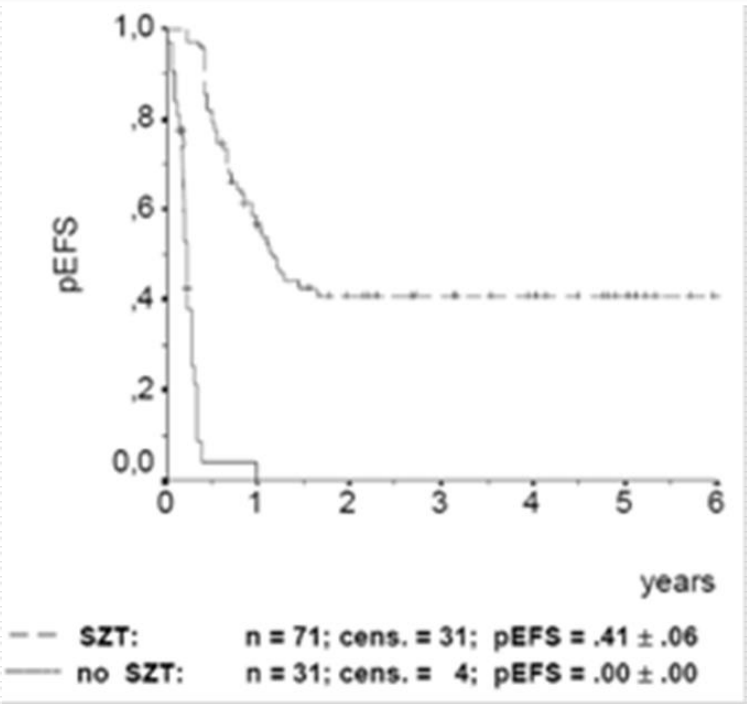
ALL REZ-BFM 2002



Merli P, et al. *Curr Hematol Malig Rep.* 2019;14(2):94-105.

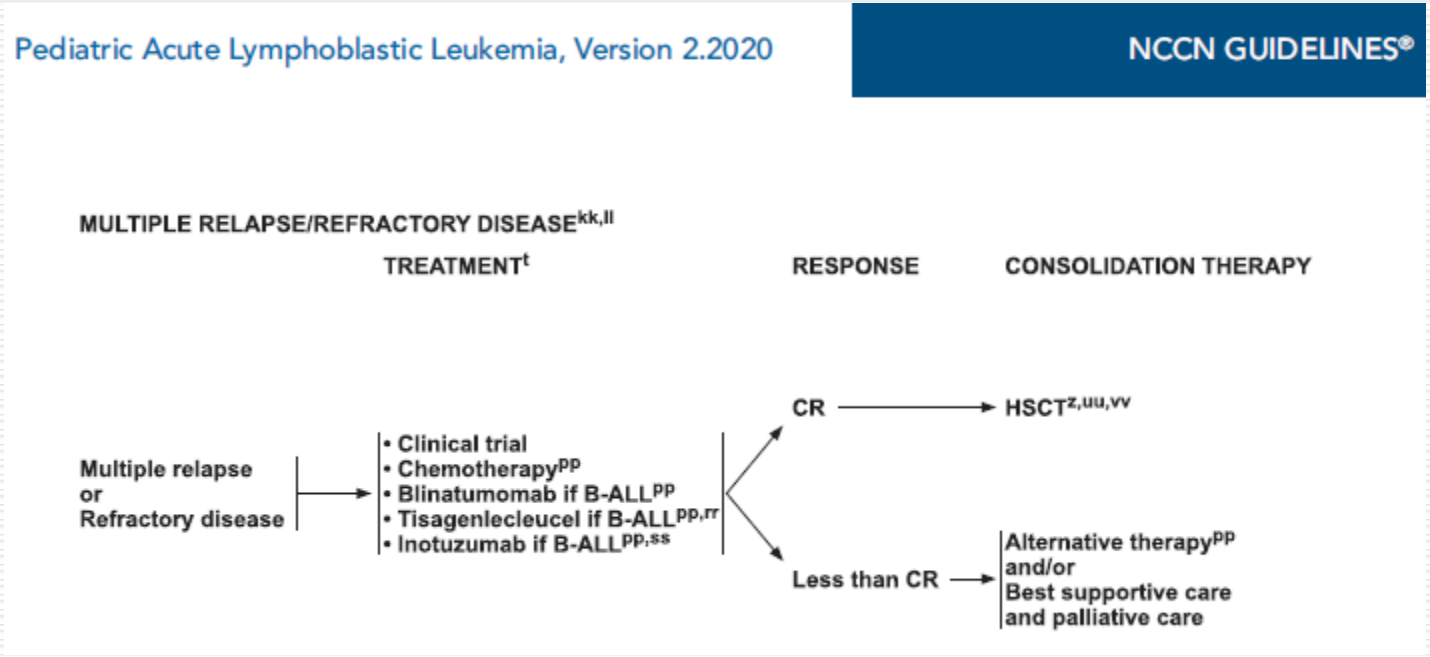
ALL-REZ BFM **S3/S4** EFS

(HRG)



Eckert C, et al. *J Clin Oncol.* 2013;31(21):2736-2742.

NCCN Guidelines pediatric ALL



NCCN Guidelines Pediatric ALL version 2.2020: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf

New targeted therapy for ALL

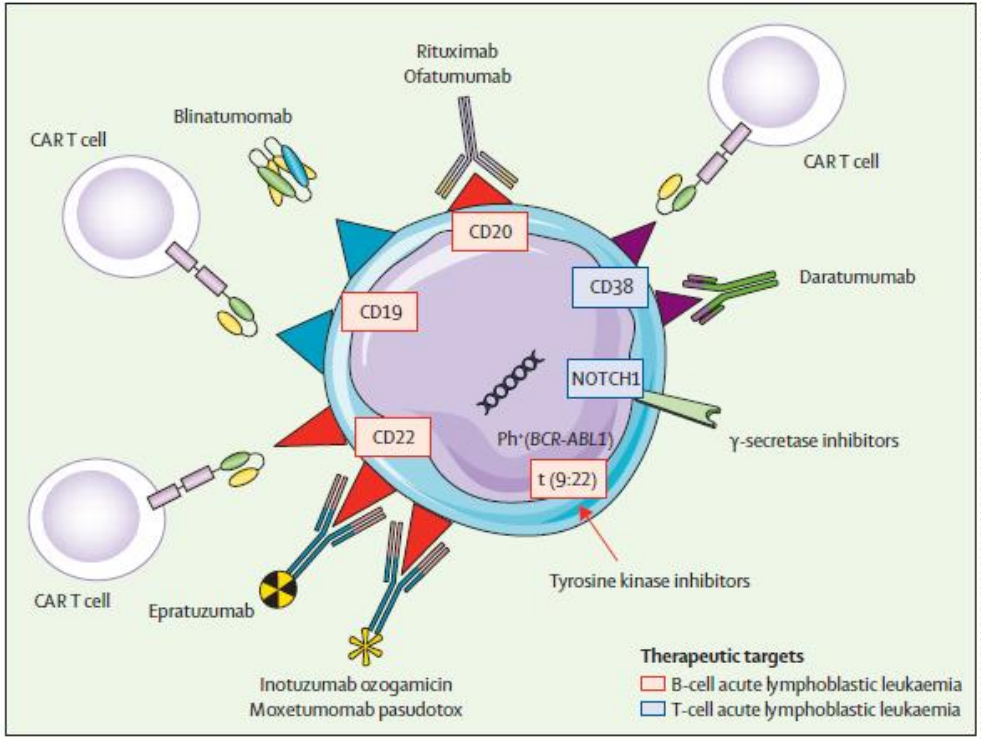


Figure 2: **New targeted therapy for acute lymphoblastic leukaemia**
Ph+=Philadelphia chromosome-positive.

Malard F, Mohty M. *Lancet.* 2020;395:1146.

Leukemia
https://doi.org/10.1038/s41375-020-0770-8

LETTER

Acute lymphoblastic leukemia

Blinatumomab versus historical standard therapy in pediatric patients with relapsed/refractory Ph-negative B-cell precursor acute lymphoblastic leukemia

Franco Locatelli[1] · James A. Whitlock[2] · Christina Peters[3] · Christiane Chen-Santel[4] · Victoria Chia[5] · Robyn M. Dennis[6] · Kenneth M. Heym[7] · Aaron J. Katz[5] · Michael A. Kelsh[5,8] · Richard Sposto[9] · Huakang Tu[5] · Catherine A. Tuglus[5] · Anupam Verma[10] · Luciana Vinti[1] · Jennifer J. Wilkes[11,12] · Nathalya Zubarovskaja[3] · Gerhard Zugmaier[13] · Arend von Stackelberg[4] · Weili Sun[14,15]

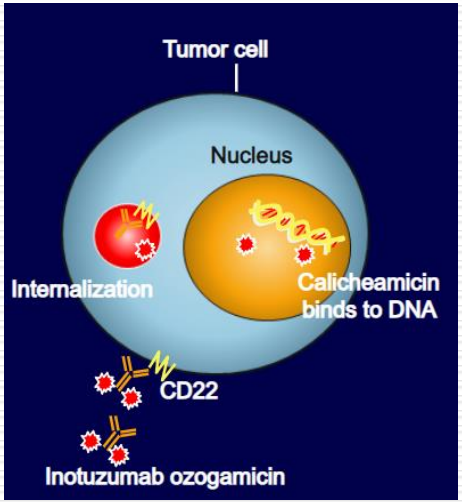
Received: 6 September 2019 / Revised: 16 January 2020 / Accepted: 12 February 2020

In standardized IPTW, patients in the blinatumomab group were almost twice as likely to achieve a CR-full rate as the combined historical control group (OR, 1.82; 95% CI, 0.74–4.51). The HR for death with blinatumomab group versus historical controls was 0.65 (95% CI, 0.44–0.94)

"Effective bridge to transplantation"

Locatelli F, et al. *Leukemia.* 2020 Feb 24. doi: 10.1038/s41375-020-0770-8. Online ahead of print.

Inotuzumab ozogamicin



3 Inotuzumab ozogamicin

3.1 Mechanisms of action

CD22 is expressed on more than 90% of B-ALL cells and mature B lymphocytes, but not on normal hematopoietic B cell precursors, non-B lymphoid cells, myeloid cells, hematopoietic stem cells, or non-hematopoietic lineage cells [34, 35]. Therefore, CD22 is another attractive target for immunotherapy. Inotuzumab ozogamicin is a humanized CD22 monoclonal antibody conjugated to calicheamicin [36]. After inotuzumab binds to CD22, the complex is rapidly internalized to lysosomal vesicles. Similar to the treatment with gemtuzumab ozogamycin [37], which targets CD33-positive myeloid cells, the acidic pH environment in the lysozyme liberates calicheamicin. As a potent cytotoxic antitumor antibiotic, calicheamicin binds to DNA in the minor groove and causes double-strand DNA breaks and apoptotic cell death [38].

Jabbour E, et al. ASH 2014. Abstract 794.

A phase 2 trial of inotuzumab ozogamicin (InO) in children and young adults with relapsed or refractory (R/R) CD22+ B-acute lymphoblastic leukemia (B-ALL): Results from Children's Oncology Group protocol AALL1621

- 48 patients received InO; 1.8 mg/m^2
- Median age was 9 years (range 1–21)
- 67% were in >2nd relapse, 21% were in 1st relapse but refractory to reinduction, 23% had prior HSCT, 23% had prior CD19 CAR T, and 29% had prior blinatumomab
- CR/CRi rate 58.3%
- In responders, 65.4% achieved MRD <0.01%
- Minimal hepatic toxicity was observed during InO therapy. SOS occurred in 30.7% of pts who underwent subsequent HSCT (8.3% of pts overall)

O'Brien MM, et al. *Blood.* 2019;134(suppl 1):741.

CAR T-cell studies and their results

Patients	Phase	*N*	Response	Survival	Adverse effects
Pediatric and young adults, relapsed/refractory B-ALL[58] (19-BBz)	I/II	30	CR*, 90% (MRD negative**, 88%)	6-month overall survival, 78%	CRS, 100% (mild/moderate), 27% (severe) Neurologic, 43%
Pediatric and young adults, relapsed/refractory B-ALL[59] (19-BBz)	II	75	CR*, 81% (MRD negative, 100%)	6-month overall survival, 90%	CRS, 77% (any), 46% (grade ≥ 3) Neurologic, 40% (any), 13% (grade 3)
Pediatric and young adults, relapsed/refractory B-ALL/NHL[60] (19-28z)	I	21	CR*, 67% (MRD negative**, 86%)	10-month overall survival, 51.6%	CRS, 76% (any), 29% (grade ≥ 3)
Adults, relapsed/refractory B-ALL[61] (19-28z)	I	53	CR*, 83% (MRD negative**, 73%)	Median survival, 12.9 months	CRS, 85% (any), 26% (grade ≥ 3) Neurologic, 43% (grade ≥ 2), 42% (grade ≥ 3)
Pediatric and young adults, relapsed/refractory B-ALL[81] (19-BBz)	I	43	MRD negative CR*, 93%	12-month overall survival, 69.5%	CRS, 93% (any), 23% (severe) Neurologic, 49% (any), 21% (severe)
Pediatric and young adults, relapsed/refractory B-ALL[101] (22-BBz)	I	21	CR*, 57% (MRD negative**, 75%) CR*, 73% ($\geq 1 \times 10^6$ CAR T)	Median remission duration, 6 months	CRS, 76% (any), 0% (grade ≥ 3) No severe neurotoxicity
Pediatric and young adults, relapsed/refractory B-ALL[80] (19 [low affinity]-BBz)	I	14	MRD-negative CR*, 86%	12-month overall survival, 63%	CRS, 93% (any), 0% (grade ≥ 3) Neurologic, 43% (any), 0% (grade ≥ 3)
Pediatric and adults, relapsed/refractory B-ALL/NHL[103] (19–28/BBz and 22–28/BBz cocktail)	II	89	MRD-negative CR*#, 96%	12-month overall survival#, 62.8%	CRS, 95.5% (any), 21.3% (grade ≥ 3) Neurologic, 13.5% (any), 1.1% (grade ≥ 3)

Early intervention for CRS with tocilizumab and/or corticosteroids reduced the incidence of transition from mild to severe CRS and had no detrimental effect on the MRD– complete remission rates or functional CAR T-cell persistence

ALL, acute lymphoblastic leukemia; CR, complete remission; MRD, minimal residual disease; CRS, cytokine release syndrome; NHL, non-Hodgkin lymphoma; BBz, intracellular signaling domains of 4-1BB with CD3z; 28z, intracellular signaling domains of CD28 with CD3z.
*CR includes that with incomplete counts recovery; **Percentage of MRD-negative patients among those with CR; #ALL only (51 patients).
Inaba H, Pui CH. *Cancer Metast Rev.* 2019;38:595-610.

CAR T cells

- The use of HSCT after CAR T-cell therapy is controversial
- CAR T cells migrate to extramedullary sites, thus can be used to treat extramedullary relapses
- Loss of CAR T-cell function may occur
- Prior blinatumomab CT may affect CAR T-cell efficacy
- Harvesting problems in some children
- CD19– relapses
- Cytoreduce prior to infusion to reduce CRS

Inaba H, Pui CH. *Cancer Metast Rev.* 2019;38:595-610.

How about current treatment options in pediatric patients with relapsed T-cell ALL?

- No new drugs
- Bortezomid
- γ secretase inhibitors
- Daratumumab
- CAR T-cells

Treatment in relapsed T-cell ALL

- Nelarabine (55% response rate in first remission)
- Bortezomib-based CTs
- γ-Secretase inhibitors for NOTCH1 signaling
- Daratumumab antiCD38
- CAR T cells targeting CD5 or CD7

Malard F, et al. *Lancet.* 2020;395:1146; Charrot S, et al. *HemaSphere.* 2019;3:2.

British Journal of Haematology, 2019, **186,** 274–285

bjh research paper

Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group

Terzah M. Horton,[1] James A. Whitlock,[2] Xiaomin Lu,[3] Maureen M. O'Brien,[4] Michael J. Borowitz,[5] Meenakshi Devidas,[3] Elizabeth A. Raetz,[6] Patrick A. Brown,[5] William L. Carroll[7] and Stephen P. Hunger[8,9]

Table II. Demographics n = 146 eligible patients.

	Number (%)
Characteristics	
Male	84 (58%)
Female	62 (42%)
Age, years (median, range)*	8 (0–25)
Presenting WBC, average ($\times 10^9$/l)	40·4 ± 14
Race¶	

Table I. Treatment plan.

Study phase	Dosing
Block 1 (VPLD) 28 days; response at Day 28–36	
CNS 1 or 2: IT- AraC/IT- MTX*	Day 1/Day 15 and 29
CNS3: IT-AraC/IT-MTX + HC + AraC (ITT)*	Day 1/Days 8, 15, 22 and 29
Vincristine 1·5 mg/m^2 (max 2 mg) IV	Days 1, 8, 15, and 22
Doxorubicin (60 mg/m^2) IV	Day 1
Prednisone (40 mg/m^2/day PO divided BID)†	Days 1–28
Bortezomib (1·3 mg/m^2) IV	Days 1, 4, 8, and 11
PEG-asparaginase (2500 units/m^2) IM	Days 2, 8, 15, and 22
Block 2: 28 days; response at Day 28–36	
CNS: IT MTX/CNS3 ITT	Days 1 and 22
Etoposide (100 mg/m^2) IV	Days 1–5
Cyclophosphamide (440 mg/m^2) IV	Days 1–5
Bortezomib (1·3 mg/m^2) IV	Days 1, 4, and 8
Methotrexate (5000 mg/m^2) IV	Day 22
Block 3: 28 days; response assessed at Day 28	
Cytarabine (3000 mg/m^2/dose) IV BID	Days 1, 2, 8 and 9
E-coli asparaginase (6000 units/m^2) IM‡	Days 2 and 9

‡Early relapse = 18–36 months from diagnosis.
§With or without central nervous system or extramedullary.
¶Percentages total <100% due to rounding.

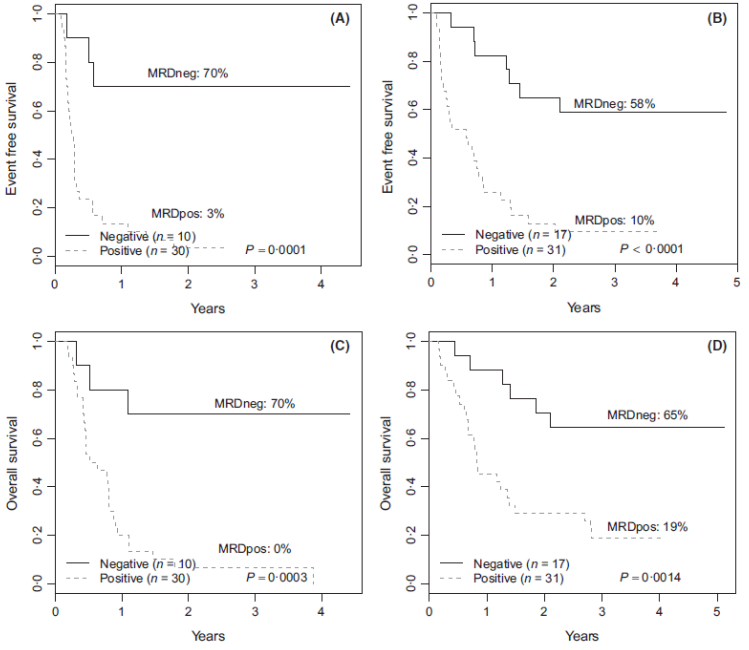


Fig 3. Survival as a function of MRD in pre-B ALL patients less than 21 years of age in early relapse. (A) Three-year EFS for patients relapsing <18 months from diagnosis (very early relapse) stratified by MRD status at the end of the first cycle of therapy (reinduction). (B) 3-year EFS for patients relapsing 18–36 months from diagnosis (early relapse) stratified by MRD status. (C) Three-year overall survival for very early relapse patients stratified by MRD status. (D) 3-year EFS for early relapse patients stratified by MRD status. EFS, event-free survival; MRD, minimal residual disease; MRDneg, minimal residual disease negative; MRDpos, minimal residual disease positive.

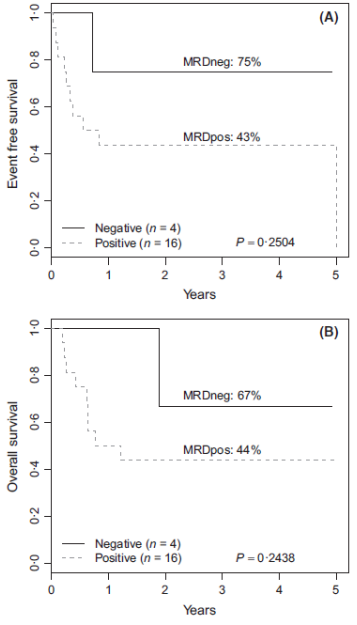


Fig 4. Outcome by MRD status (cut-off 0·01%) in patients with T-ALL. (A) Event free survival in MRD negative patients (EFS 75%) and in MRD positive patients (43% until censored). (B) Overall survival in MRD negative patients (EFS 67%) *versus* MRD positive patients (EFS 43%). ALL, acute lymphoblastic leukaemia; EFS, event-free survival; MRD, minimal residual disease; MRDneg, minimal residual disease negative; MRDpos, minimal residual disease positive.

Conclusions

- The treatment approach for relapsed ALL is changing rapidly
- CT induction followed by blinatumomab may be a new standard in the relapsed ALL
- InO may be used in these patients since the MRD– cure rates are promising
- Further CAR T-cell development may improve some of the current challenges experienced with tisagenlecleucel
- The potential to replace HSCT with CAR T-cell therapy and CAR T-cell administration to treat extramedullary relapses in relapsed ALL patients is still in investigation
- Clinicians need to be aware of the adverse effects and toxicities of new drugs

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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

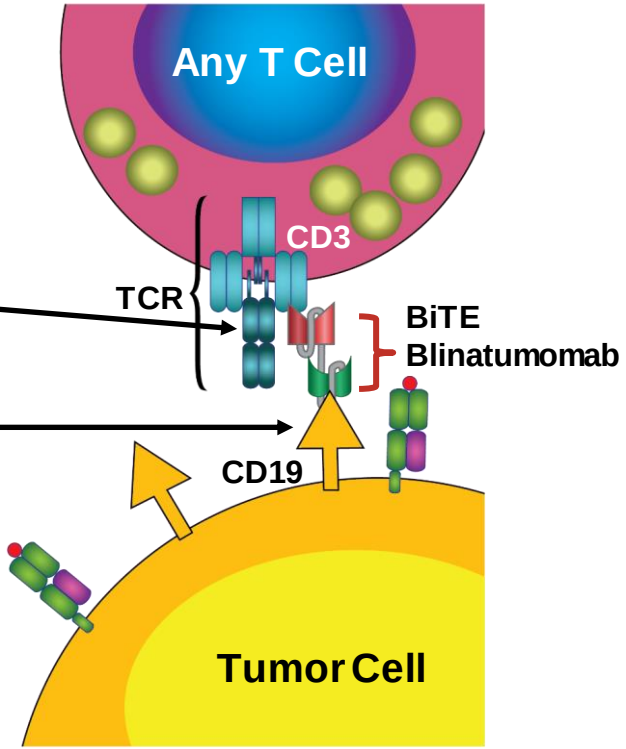
Bispecific anti-CD19/CD3 BiTE antibody blinatumomab designed to kill autologous tumor cells

Relies on *functional endogenous cytotoxic T-cell response*

Act independently of specificity of T-cell receptor (TCR)

Allow T-cell recognition of tumor-associated surface antigen (TAA)

Do not require MHC Class I and/or peptide antigen

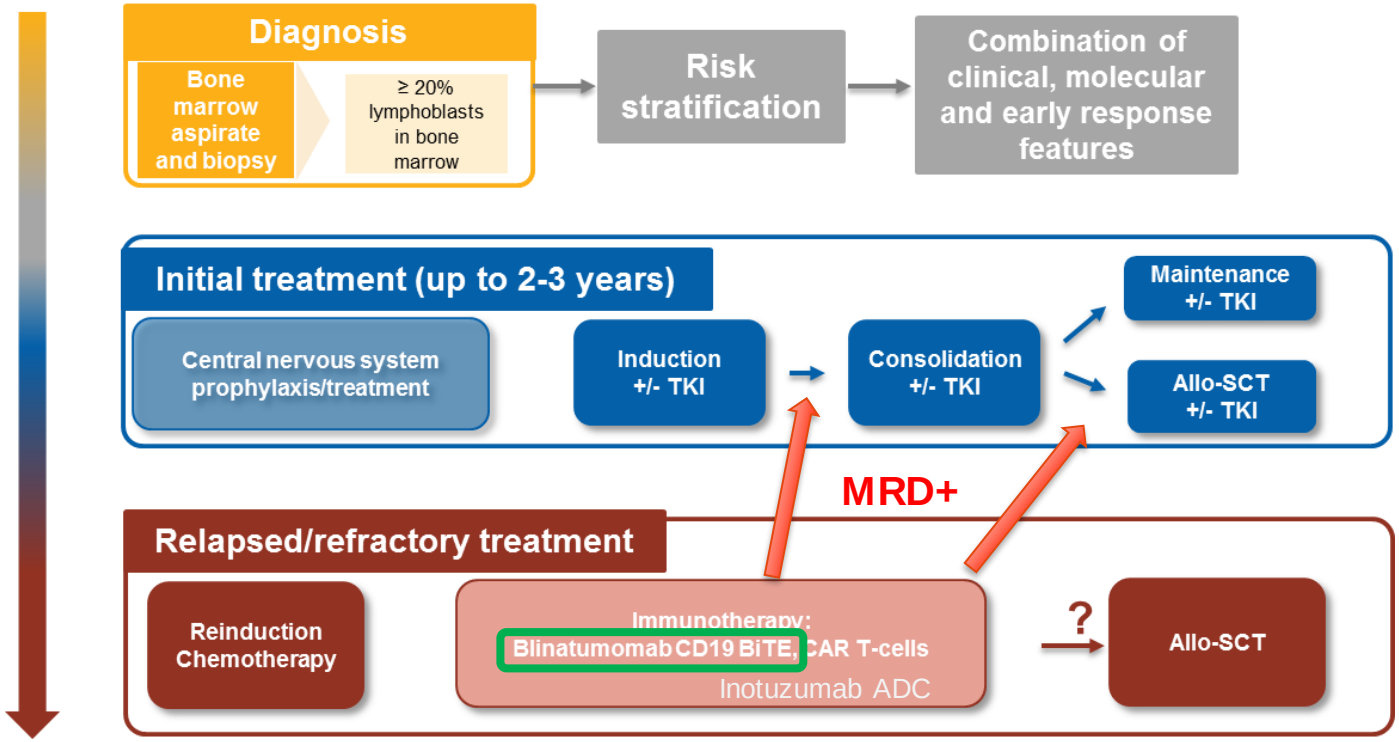


Given as 28-day continuous infusion IV; bag changes q 4-7 days

BiTE, Bispecific T-Cell Engager

Adapted from/courtesy of Amgen.

Diagnosis and Treatment of ALL



Allo-SCT, allogeneic stem cell transplant; FISH, fluorescence in situ hybridization; TKI, tyrosine kinase inhibitor (for BCR-ABL–positive disease)

NCCN Guidelines® for Acute Lymphoblastic Leukemia (Version 2.2015) © 2015 National Comprehensive Cancer Network, Inc. Available at: NCCN.org; 2. Hahn T et al. *Biol Blood Marrow Transplant*. 2006;12(1):1-30. 3. Raetz EA et al. *Hematol Am Soc Hematol Educ Program*. 2012;2012:129-136. 4. National Cancer Institute. Childhood acute lymphoblastic leukemia treatment (PDQ®). http://www.cancer.gov/cancertopics/pdq/treatment/childALL/HealthProfessional. Accessed July 10, 2017.

Response Rates and Survival in Relapsed/Refractory B-ALL

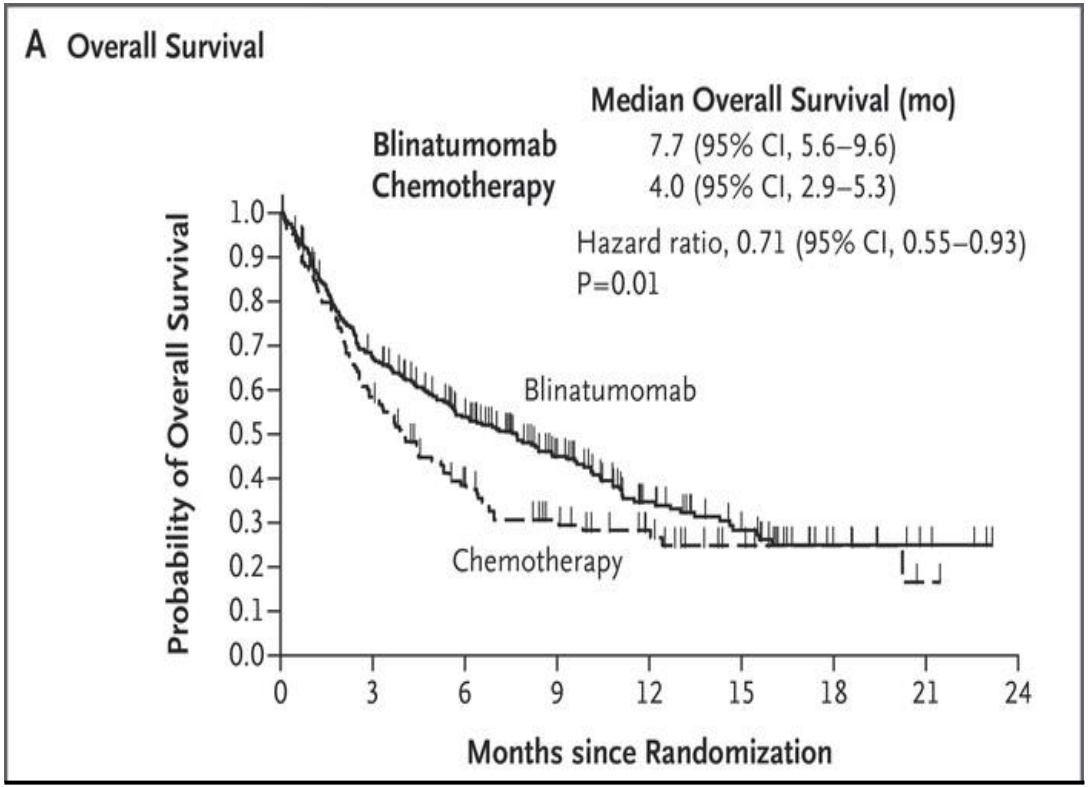
Agent	Type	Target	Responses (CR / MRD–)	Toxicities	FDA indication	Cost
Blinatumomab[1]	BiTE	CD19	44% / 33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	$180K
Inotuzumab[2]	Immuno-conjugate	CD22	81% / 63%	Hepatotoxicity	Adult R/R B-ALL	$168K
Tisagenlecleucel[3]	CAR T cell	CD19	81% / 81%	CRS, 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. Kantarjian, H. et al. N Engl J Med 2016;375:740-753; 3. Maude SL, et al N Engl J Med 2018;378:439-448

Survival in R/R ALL (adult)

Blinatumomab

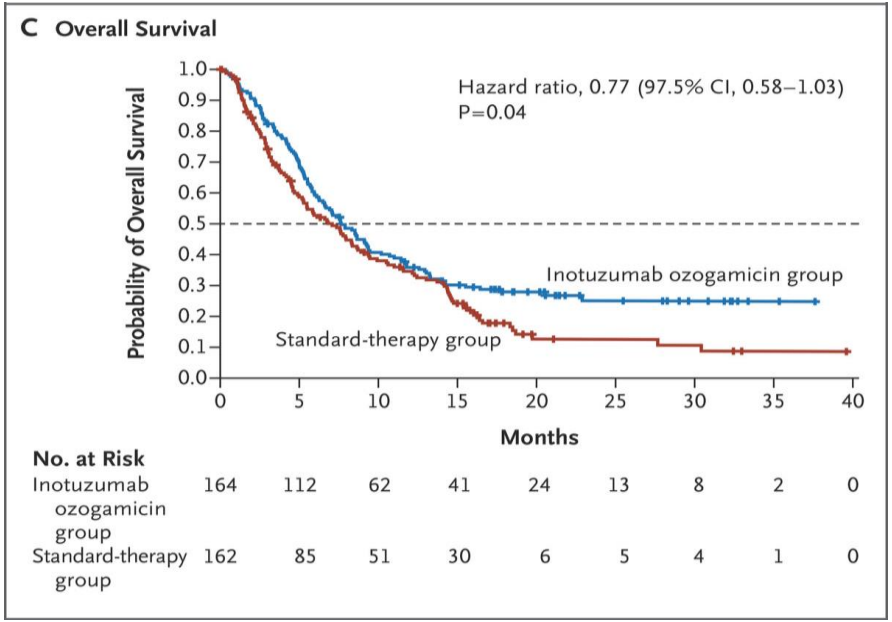


Blina: Improved survival initially, but not durable

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

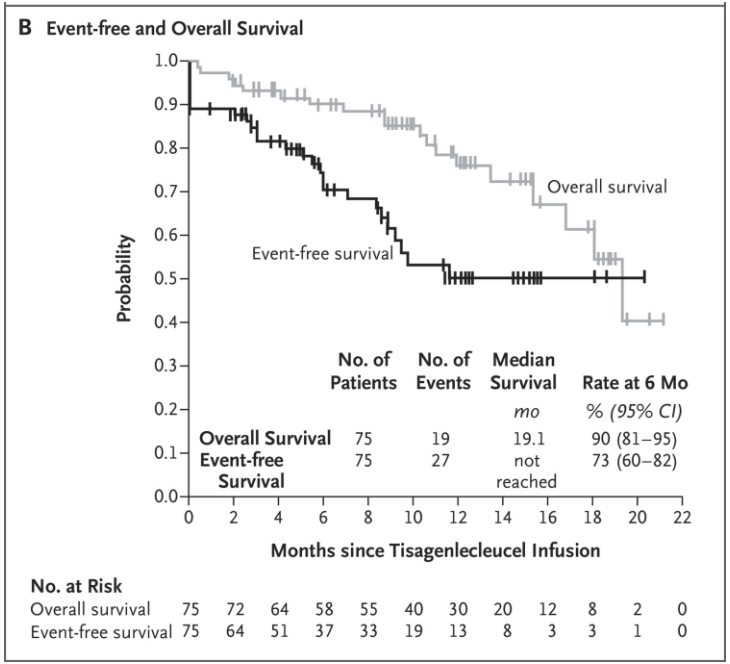
Survival in R/R ALL

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

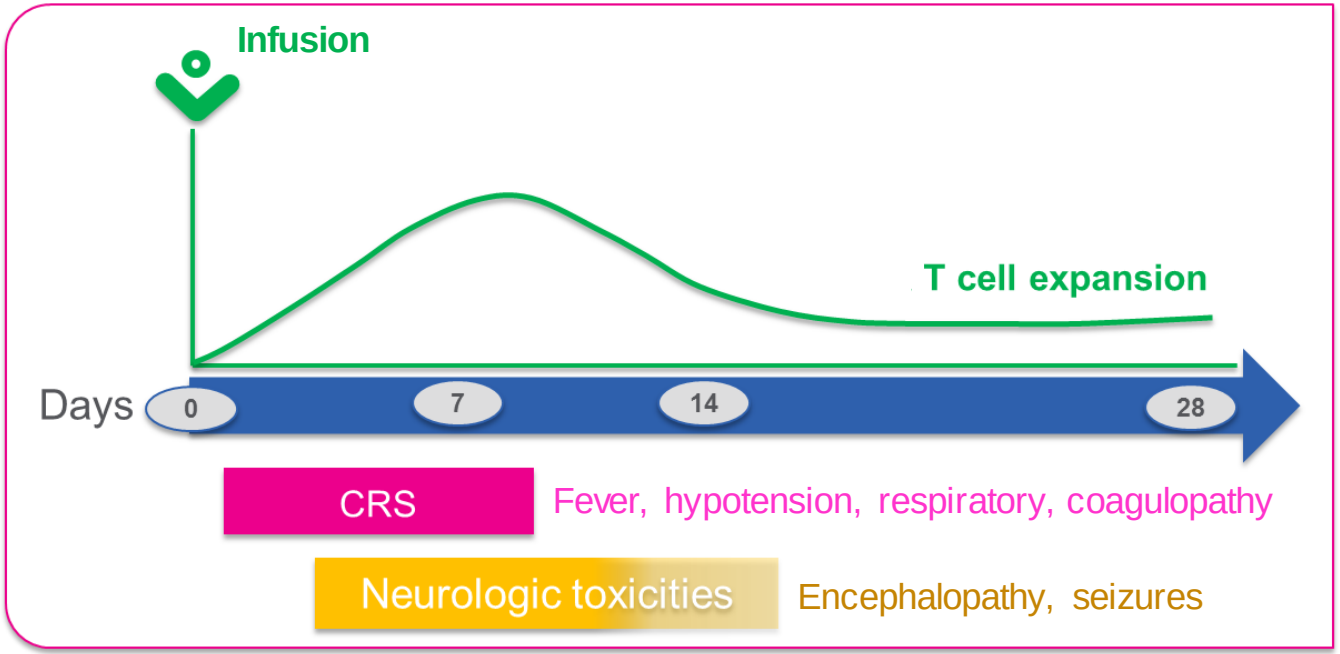
1. Kantarjian, H. et al. N Engl J Med 2016;375:740-753; 2. Maude SL, et al N Engl J Med 2018;378:439-448

Adverse Events in Relapsed/Refractory B-ALL

Agent	Type	Target	Responses (CR / MRD–)	Toxicities	FDA indication	Cost
Blinatumomab[1]	BiTE	CD19	44% / 33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	$180K
Tisagenlecleucel[2]	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 2016;375:740-753; 2. Maude SL, et al N Engl J Med 2018;378:439-448

AEs After Blinatumomab and CAR T Cells



- CRS 40-80% (20-40% Gr3+), Neuro 10-30% (5-10% Gr3+)
- CRS and neuro may **not** correlate
- CRS -> IVF, tocilizumab (anti-IL6R), steroids
- Neuro -> self-limiting, reversible; steroids (toci not effective)

MRD+

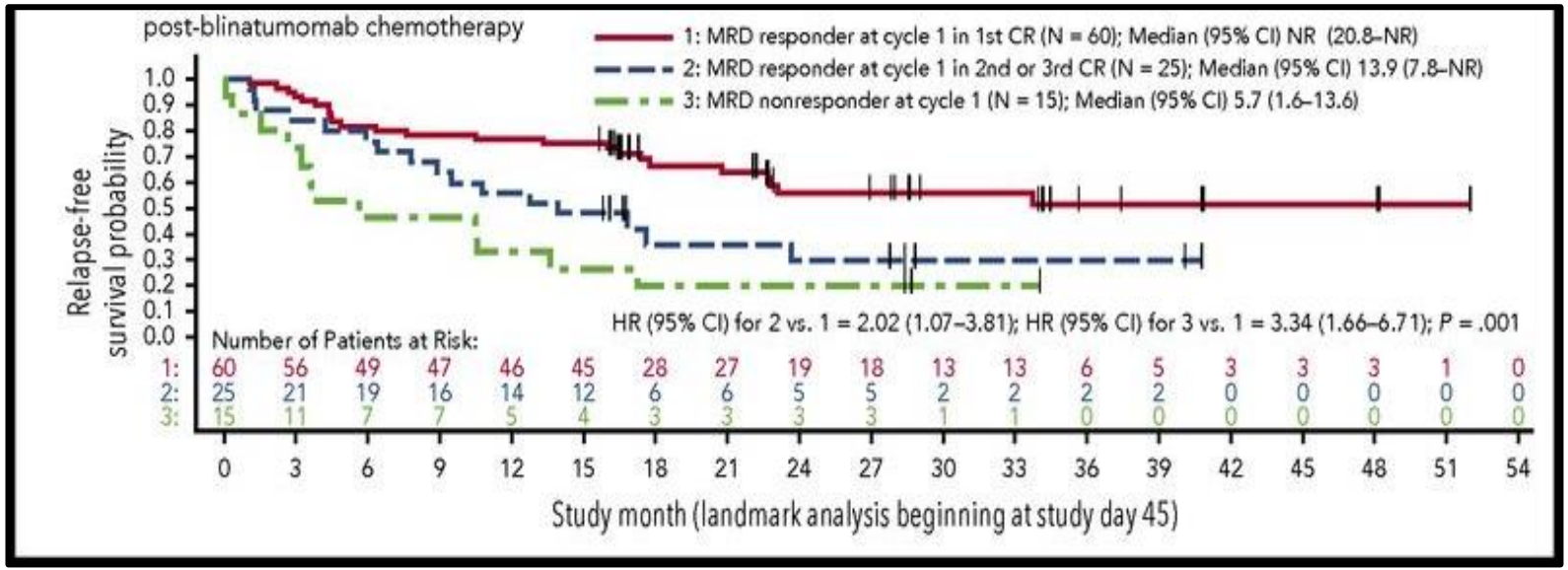
*Incidence of CRS strikingly lower in MRD+ setting; neurotox is similar

Adapted from/courtesy of Novartis.

Response Rates and Survival in MRD+ B-ALL

- N=116 adults, international multicenter single-arm Ph 2
- MRD+ (>10^{-3})
- 35% MRD+ in 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

Stratifications

- Risk group (HR vs IR)
- For HR
  - Site (BM vs iEM)
  - For BM: CR1 duration (<18 vs 18-36 mo)

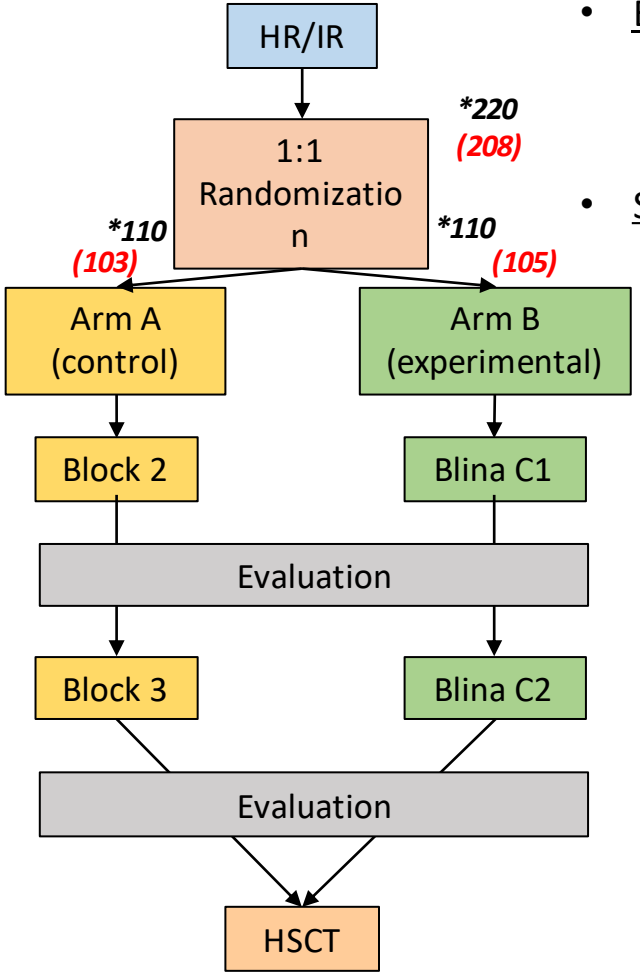
UKALLR3, Block 2*

- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

UKALLR3, Block 3*

- VCR, DEX week 1
- HD ARAC, *Erwinia* weeks 1-2
- ID MTX, *Erwinia* week 4
- IT MTX or ITT

*UKALLR3 reference: *Parker, et al. Lancet. 2010; 376: 2009-17*



- Endpoints
  - Primary: DFS
  - Other: OS, MRD response, ability to proceed to HSCT
- Sample size n=220 (110 per arm)
  - Power 85% to detect HR 0.58 with 1-sided α=0.025
  - Increase 2-yr DFS from 45% to 63%

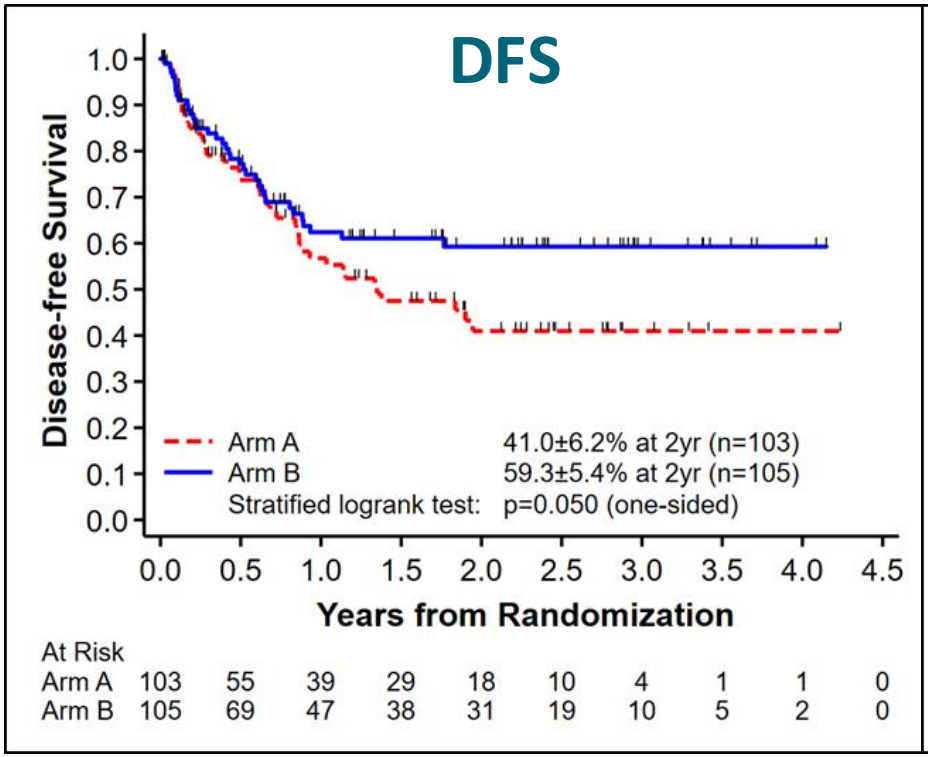
Blina C1 and Blina C2

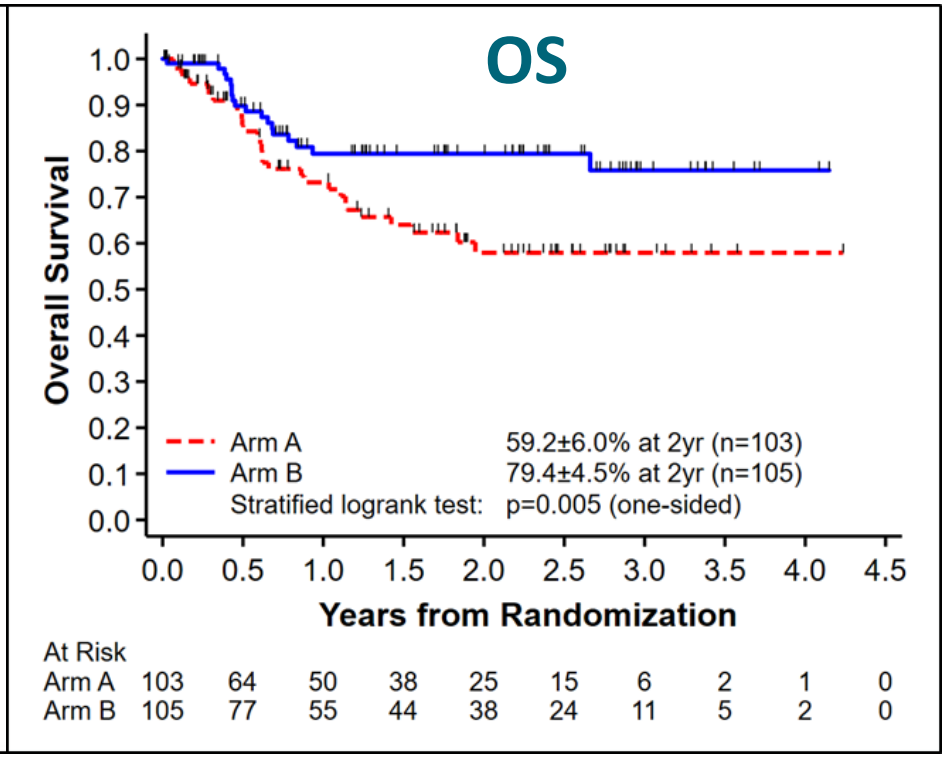
- Blinatumomab 15 µg/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed (C1 only)

- ***First patient randomized Jan 2015***
- ***Randomization halted Sep 2019 (95% projected accrual)***

Brown et al. *Blood* 2019; 134 (Supplement_2): LBA-1.

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



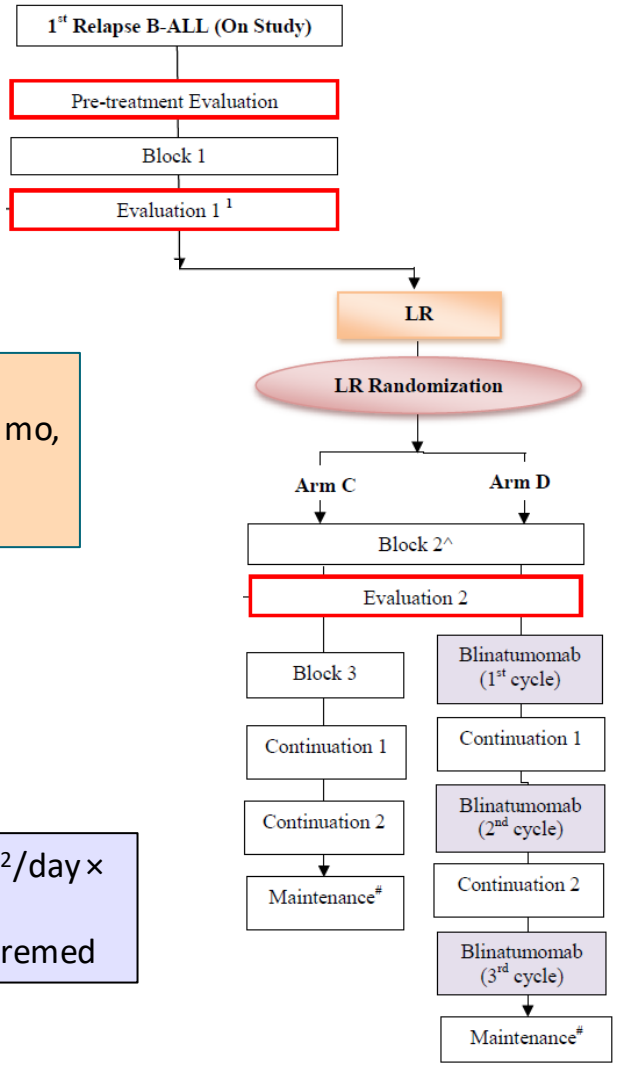


CHILDREN'S ONCOLOGY GROUP

Median follow-up 1.4 years

Brown et al. *Blood* 2019; 134 (Supplement_2): LBA-1.

LR Randomization



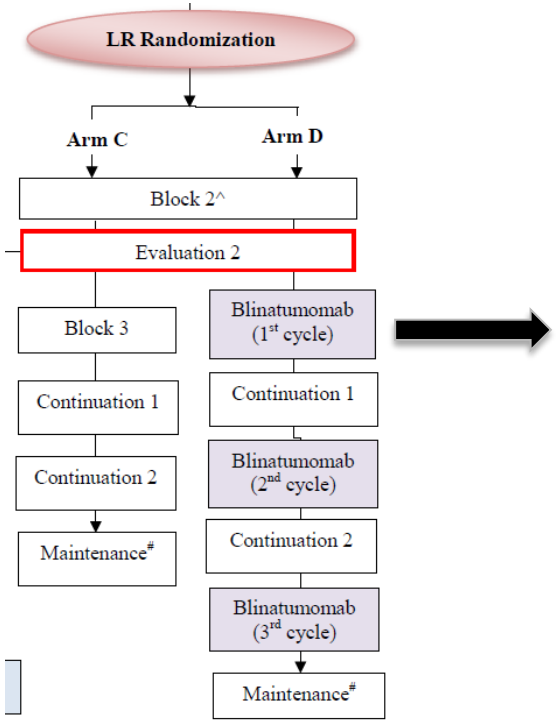
LR

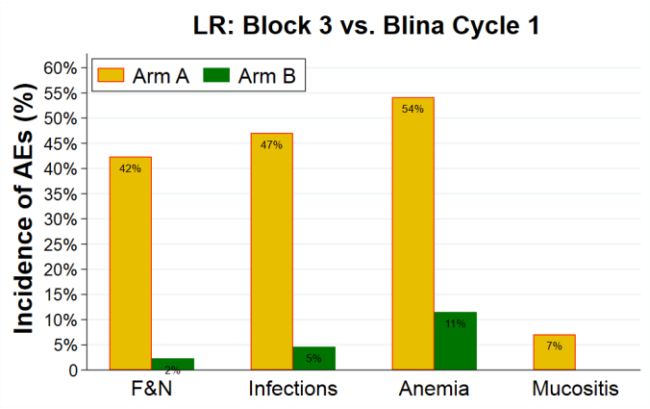
- BM or combined ≥36 mo, MRD <0.01% EOI
- IEM ≥18 mo

- Blinatumomab 15 µg/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed

Unpublished data.

Adverse Events: LR (grade 3+)



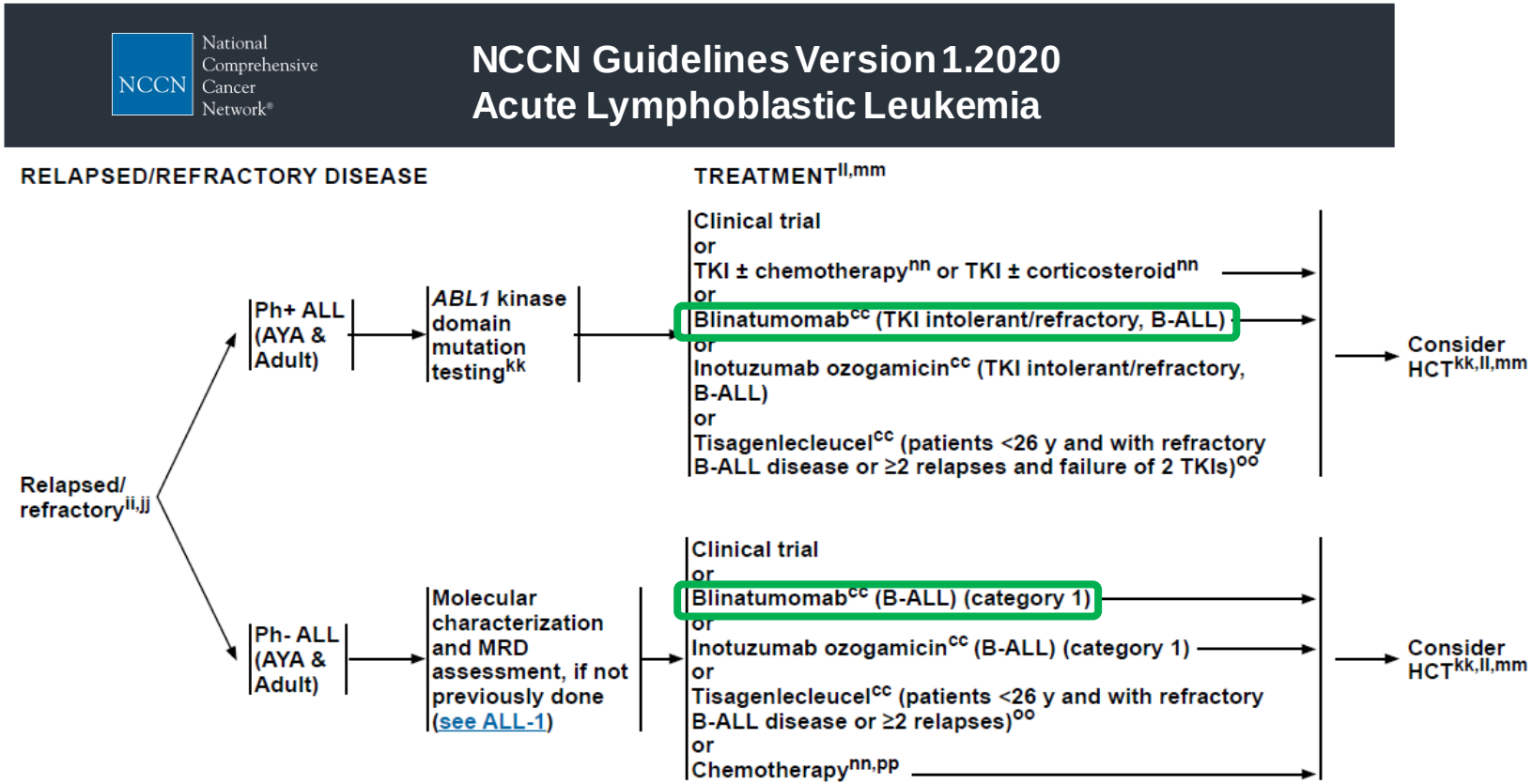


Data cutoff
3/4/19

CHILDREN'S ONCOLOGY GROUP

Unpublished data.

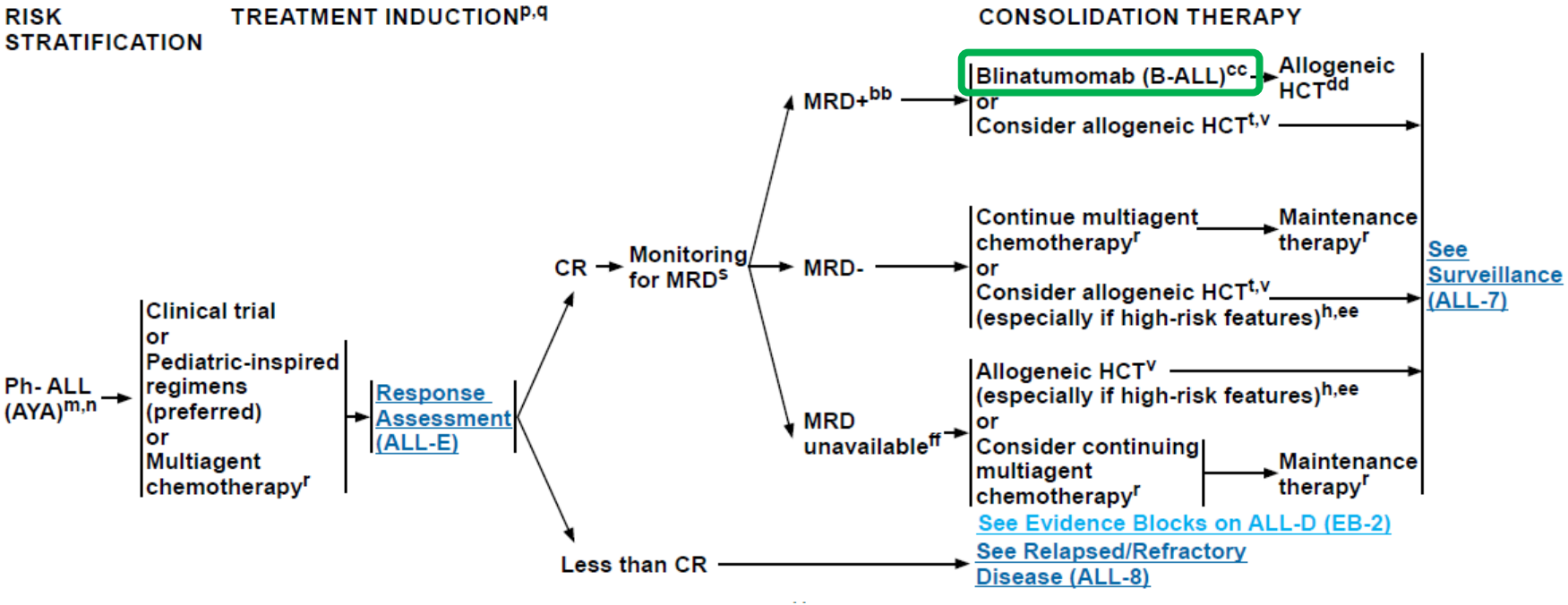
Where Is Blinatumomab in NCCN Adult ALL Guidelines?



Where Is Blinatumomab in NCCN Adult ALL Guidelines?

National Comprehensive Cancer Network®

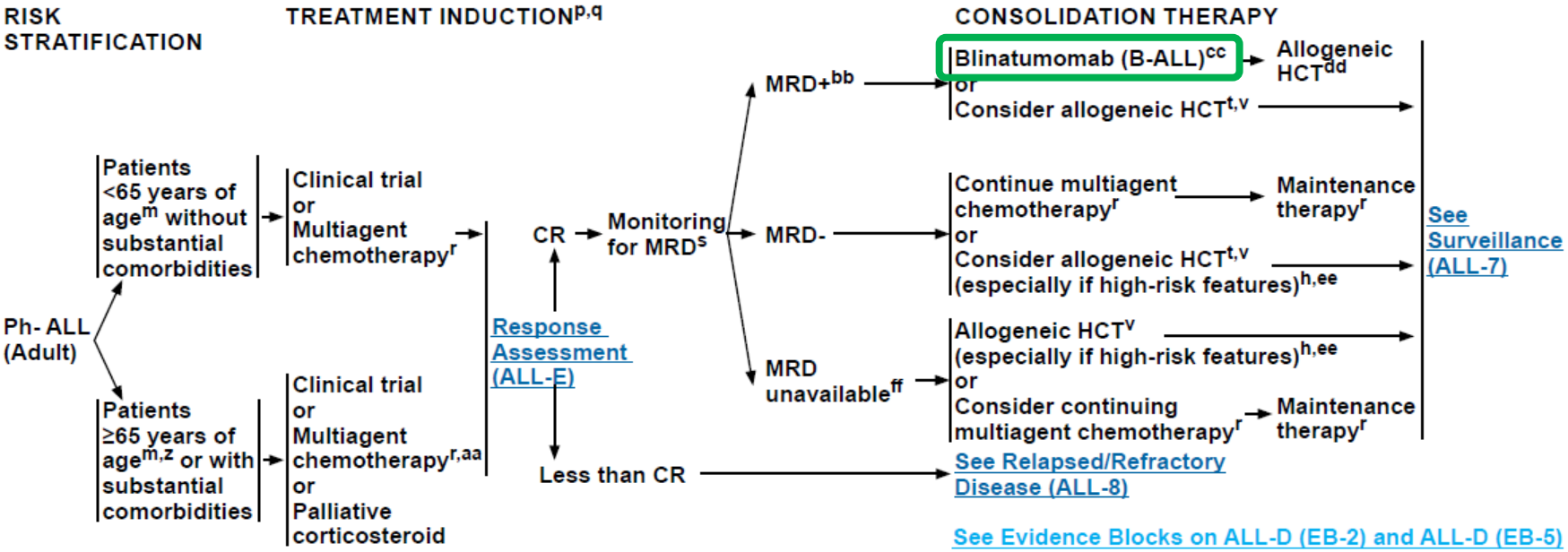
NCCN Guidelines Version 1.2020
Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Adult ALL Guidelines?

National Comprehensive Cancer Network®

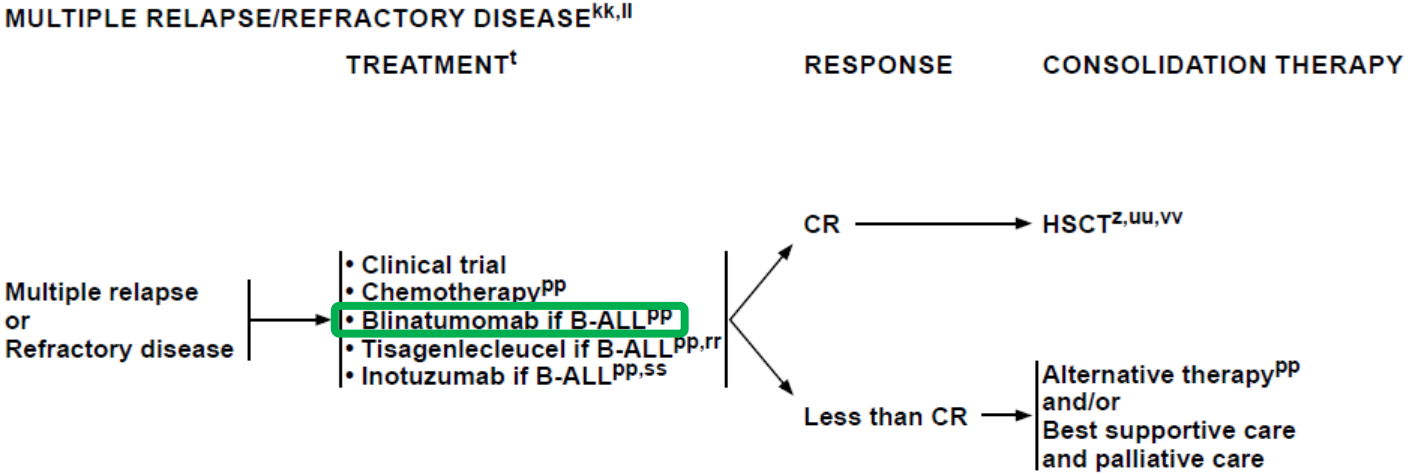
NCCN Guidelines Version 1.2020
Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

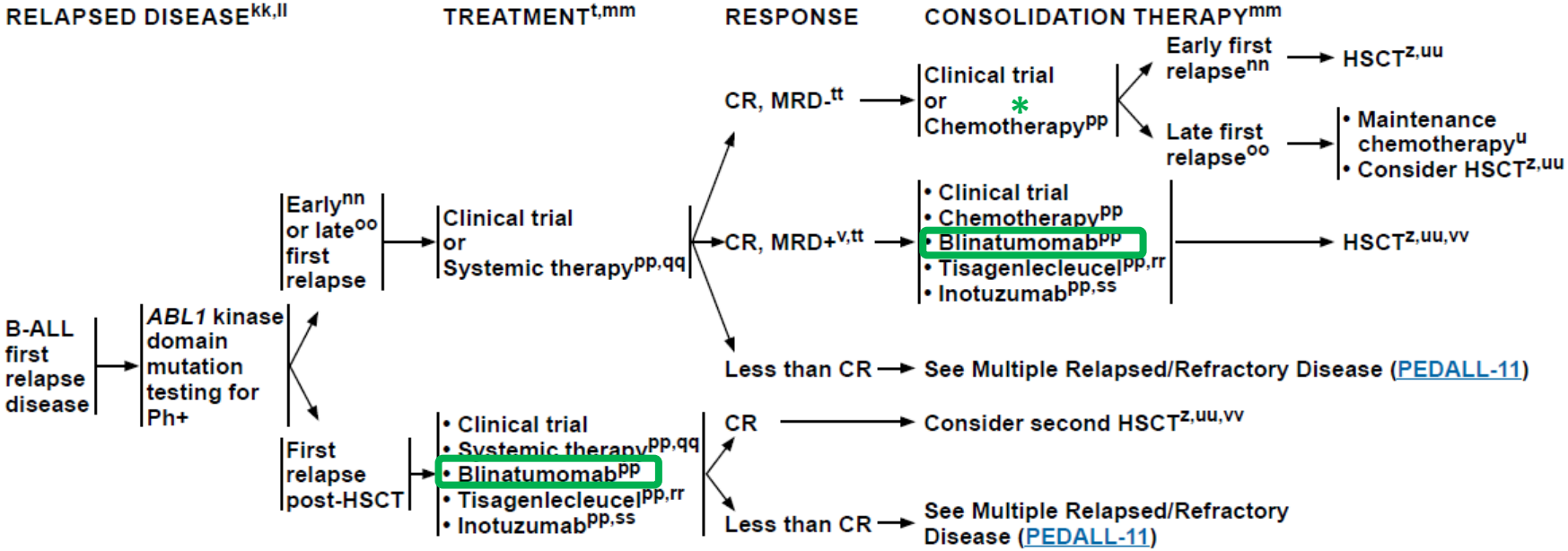
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

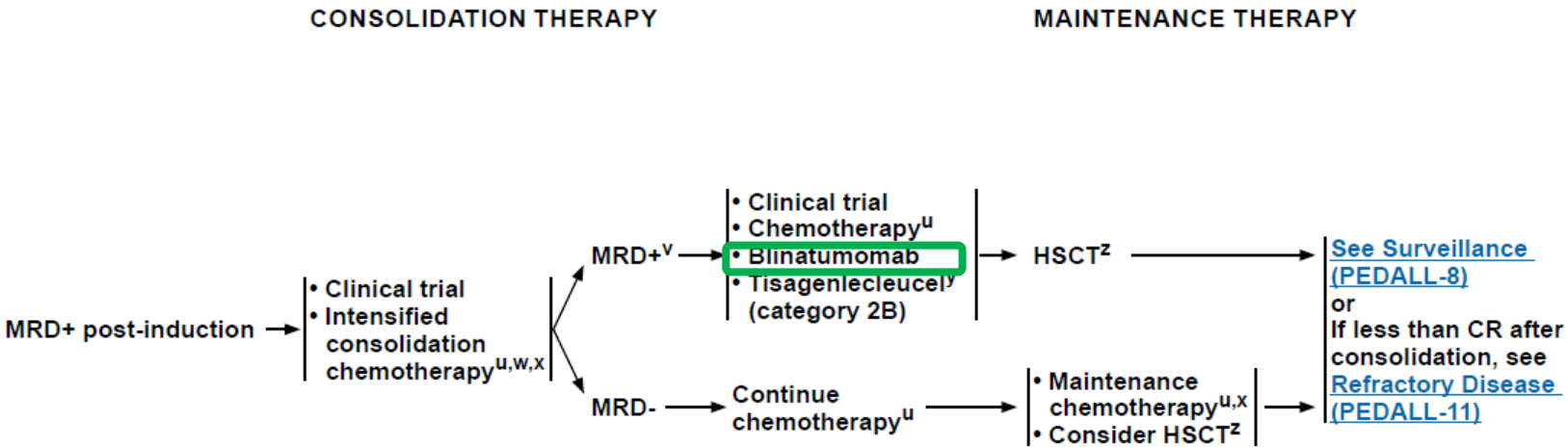
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

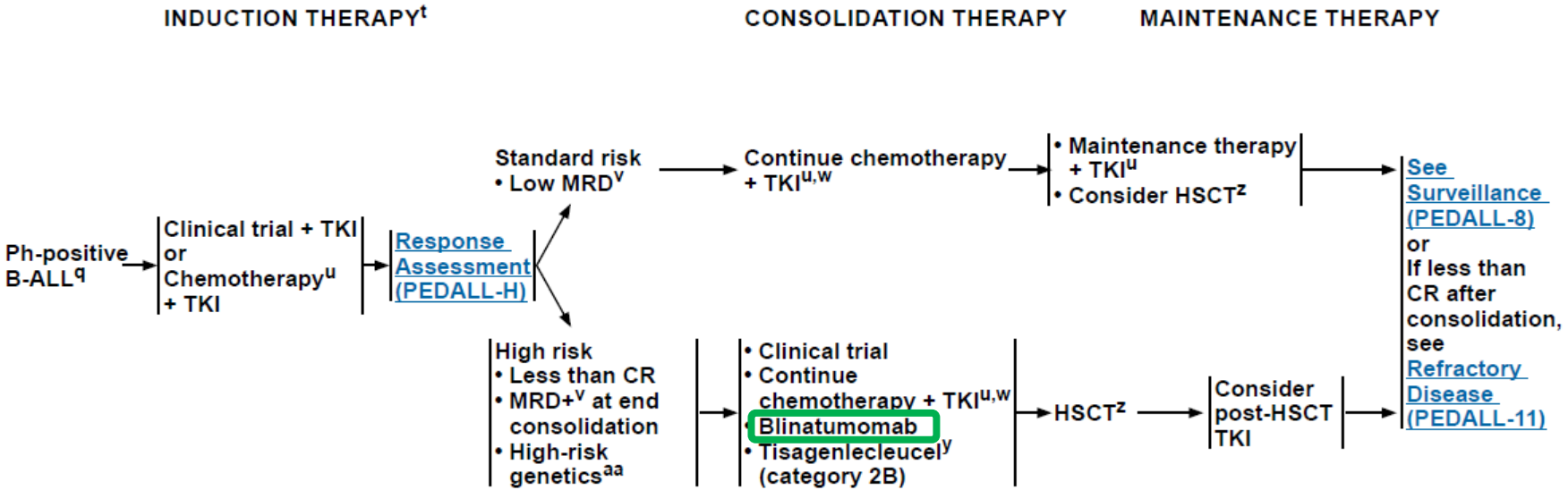
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

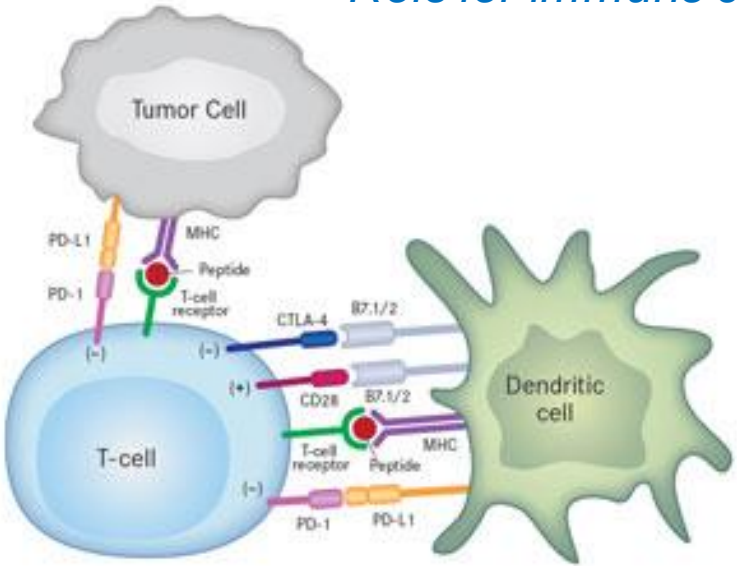
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



What Happens When Blinatumomab Doesn't Work?

- EARLY: Endogenous T-cell "exhaustion"

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

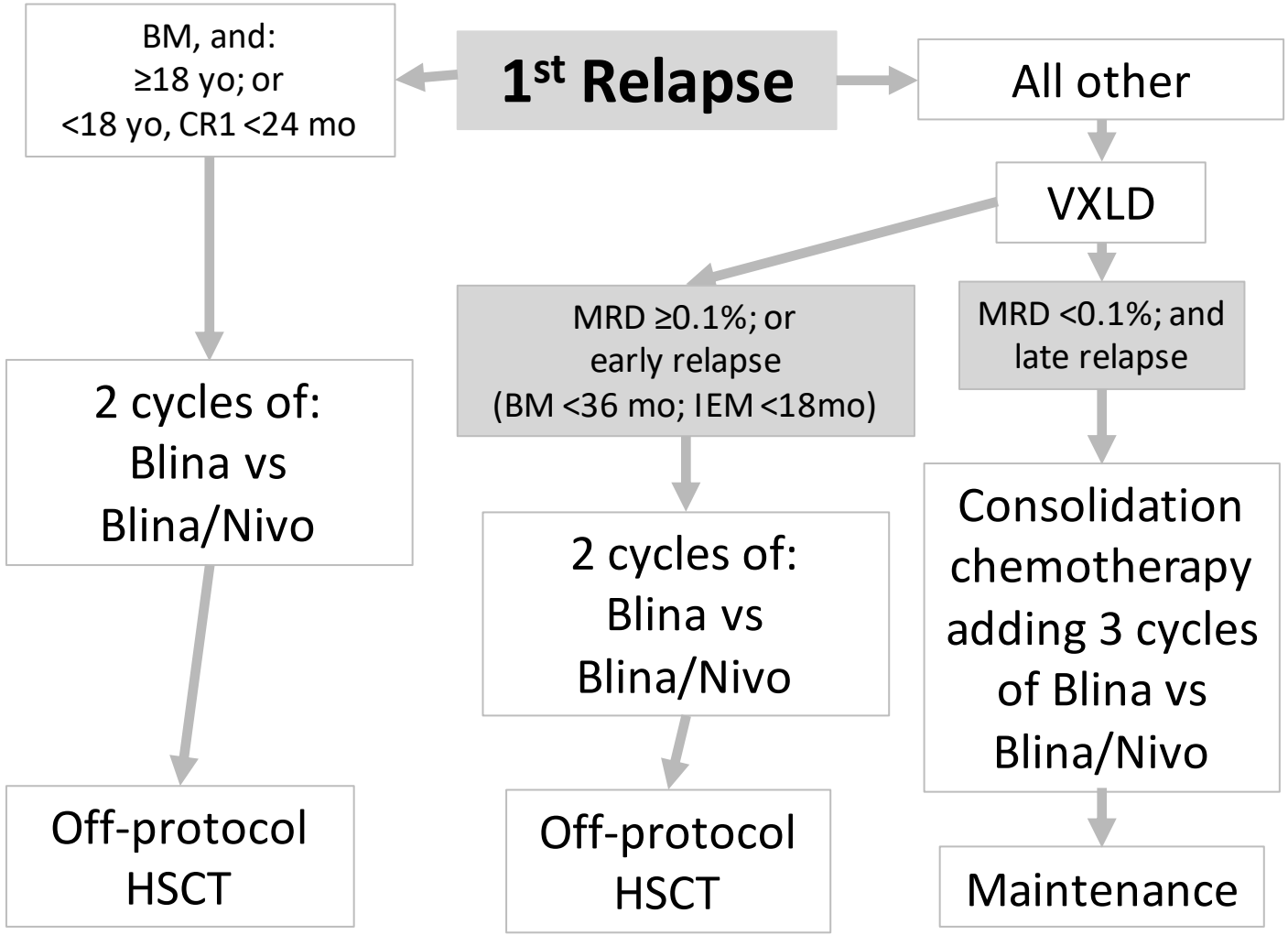


PD-1	PD-L1	CTLA-4
Nivolumab	Atezolizumab	Ipilimumab
Pembrolizumab*	Avelumab	
	Durvalumab	

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

- *Feucht, et al. Oncotarget 2016 Nov 22;7(47):76902-19*

Adapted from Zaravinos A. Oncotarget. 2014 Jun 30;5(12):3956-69.

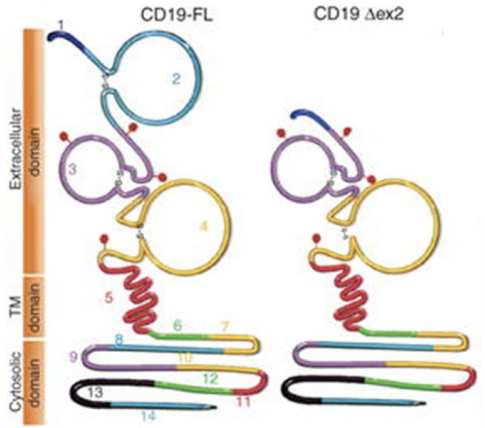


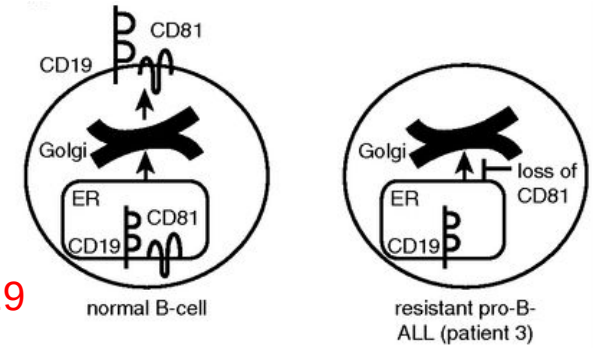
Unpublished data.

Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

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

Multi-antigen 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 Discovery. 2015; 5(12):1282-95; 2. Braig, et al. Blood. 2017 Jan 5;129(1):100-104; 3. Gardner, et al. Blood. 2016; 127(20):2406-100-104

Can We Predict When Blinatumomab Won't Work?

bjh BRITISH JOURNAL OF HAEMATOLOGY

Correspondence | Free Access

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

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

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

Brown PA, et al. Br J Haematol. 2020;188(4):e36-e39.

Efficacy Outcomes in Patients Enrolled in Phase I/II Study

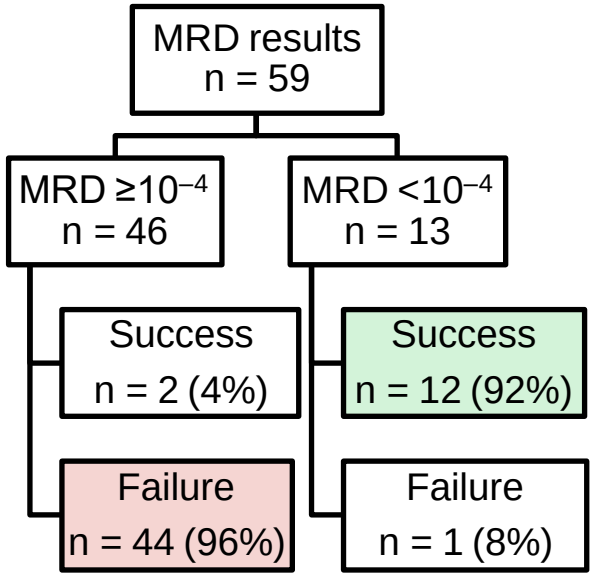
Response	Patients at Recommended Dose Who Had Response Assessment (N = 64)[a]	
	n/N (%)	95% CI
CR within the first 2 cycles	27/64 (42)	30, 55
Non-responders (did not achieve CR)	37/64 (58)	45, 70
Partial remission	4	
Blast-free or aplastic bone marrow	2	
Progressive disease	10	
No response	21	
MRD response in patients who achieved CR within the first 2 cycles		
Complete MRD response	14/27 (52)	32, 71
No MRD response	12/27 (44)	26, 64
No data available	1/27 (4)	

- Study definitions
  - "**Success**" was defined as complete MRD response in CR (n = 14)
  - "**Failure**" was defined as anything other than success (n = 50)

Adapted from von Stackelberg, et al. *J Clin Oncol.* 2016;34:4381-4389.

Biomarkers to Predict Blinatumomab Success/Failure

- Overall, day 15 MRD results predicted best response after 2 cycles with 95% accuracy (correctly in 56 of 59 patients)



Parameter	Accuracy (n/N)	Accuracy (%)
Day 8 PB morphology (clearance of blasts)	19/40	49
Day 15 BM morphology (M1)	54/60	90
Day 29 BM morphology (M1)	42/51	84
Day 15 BM MRD (< 10^{-4})	***56/59***	***95***
Day 29 BM MRD (< 10^{-4})	42/49	86

NOTE: Day 8 PB is an especially poor predictor of subsequent response

- Study definitions
  - "**Success**" was defined as complete MRD response in CR (n = 14)
  - "**Failure**" was defined as anything other than success (n = 50)

As patients with MRD ≥10^{-4} at day 15 could potentially pursue alternative therapies, such as dose escalation or combination therapies, ***day 15 MRD results may allow personalized treatment and improve outcomes in pediatric patients with relapsed/refractory B-ALL***

CR, complete remission; MRD, minimal residual disease.
Brown PA, et al. Br J Haematol. 2020;188(4):e36-e39.

Blinatumomab: Questions and Discussion

- HSCT after MRD clearance with blinatumomab?
- Ability of checkpoint inhibition to safely enhance blinatumomab response?
- Predictive biomarkers of blinatumomab response?
- Risk of prior blinatumomab exposure and CD19 escape after subsequent CD19 CAR T therapy?

A 21-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)

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

A. True

B. False

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Q&A

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Case-Based Panel Discussion: Management of Long- and Short-Term Toxicities

Rob Pieters

Hale Ören

APTITUDE HEALTH®

Global Leukemia Academy

Case-Based Panel Discussion: 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?

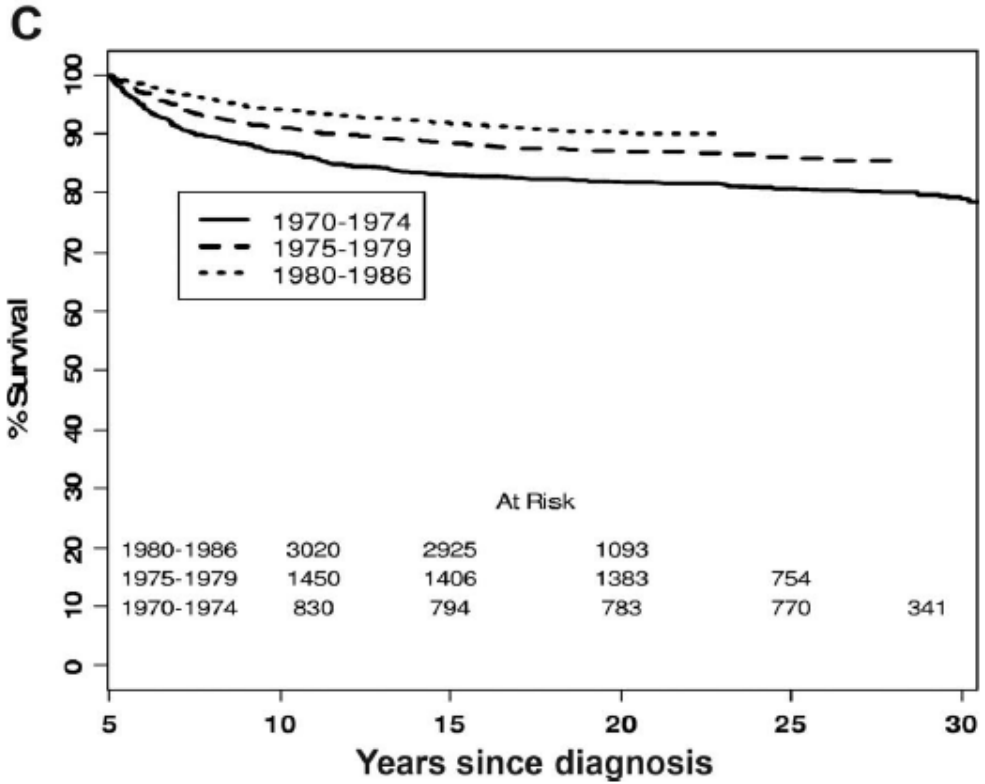
1. The anthracyclines daunorubicin and/or doxorubicin in a cumulative dose of >30 mg/m^2 in a child aged 5 years at diagnosis
2. Methotrexate in a cumulative dose of 20.000 mg/m2 in a child aged 8 years at diagnosis
3. Cranial radiotherapy in a child aged 2 years at diagnosis
4. Dexamethasone in a female child aged 14 years at diagnosis

Question 2:

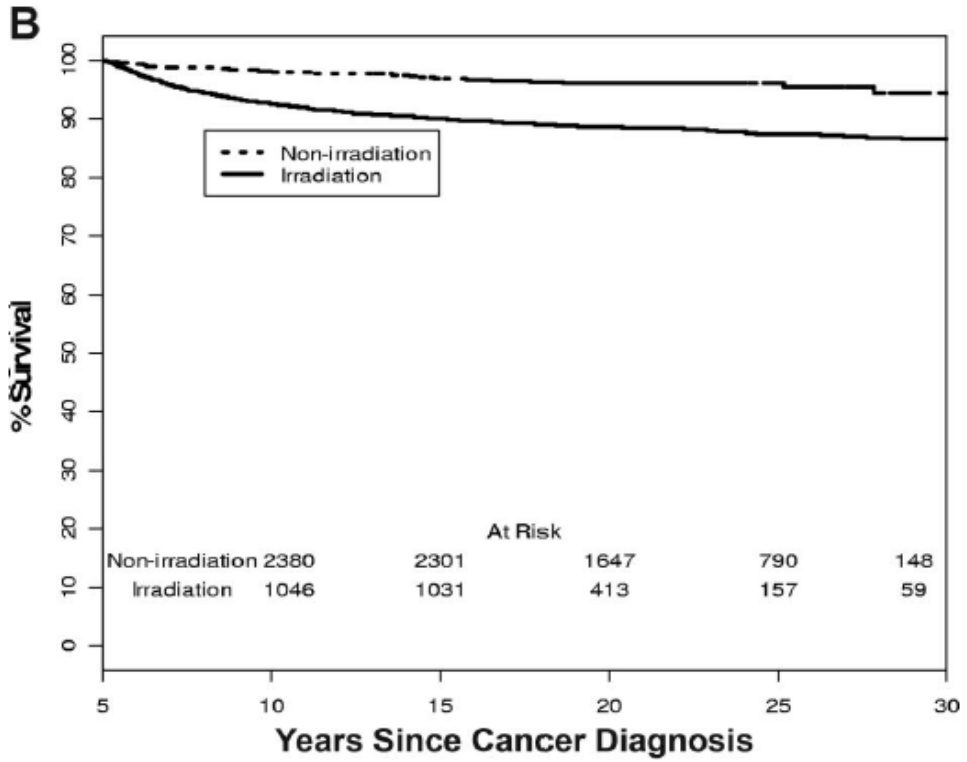
Which assertion is NOT correct?

1. Dexamethasone can cause osteonecrosis
2. The risk of osteonecrosis is lowest in children <10 years of age
3. The risk of osteonecrosis is highest in adults with ALL
4. The risk of osteonecrosis is higher with a continuous schedule of glucocorticoids than with a discontinuous schedule in the same cumulative dose

Survival of 5-year ALL survivors



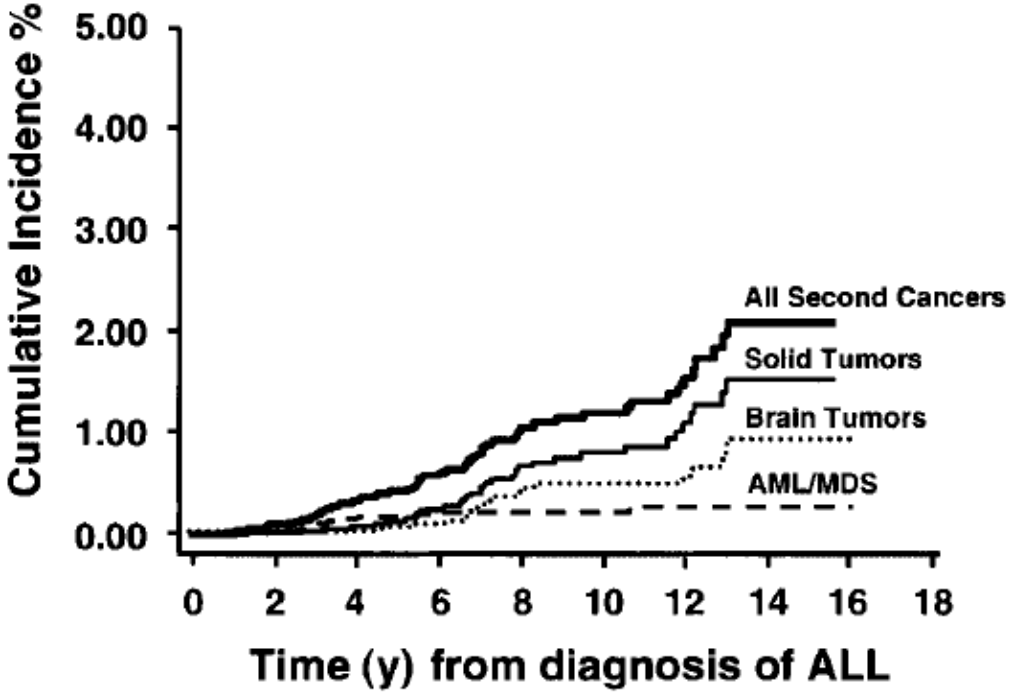
Survival of 5-year ALL survivors: irradiated vs nonirradiated



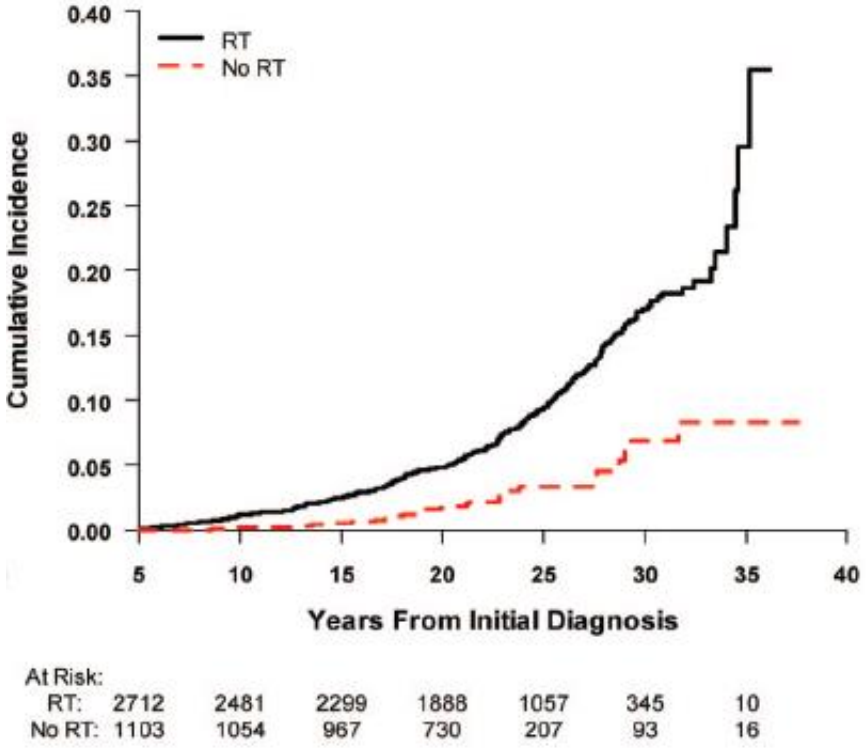
Late effects of treatment in ALL

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

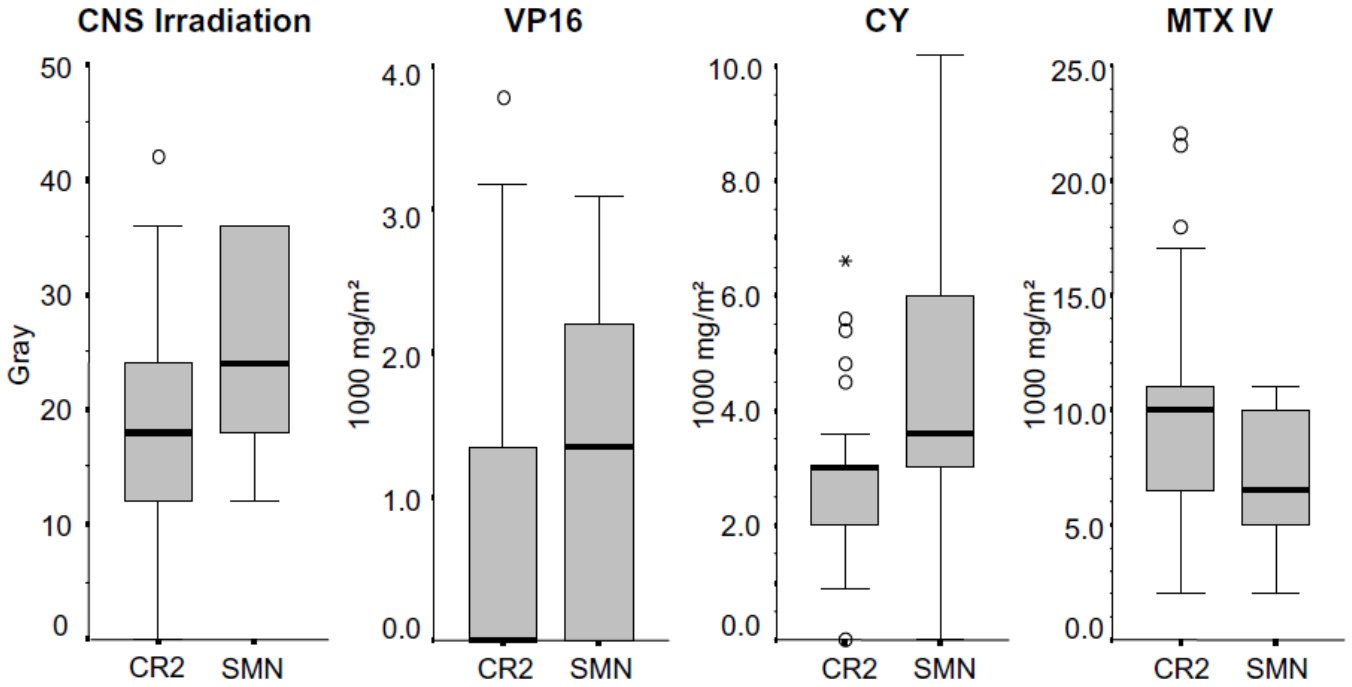
Cumulative incidence of second neoplasms in 8831 children with ALL



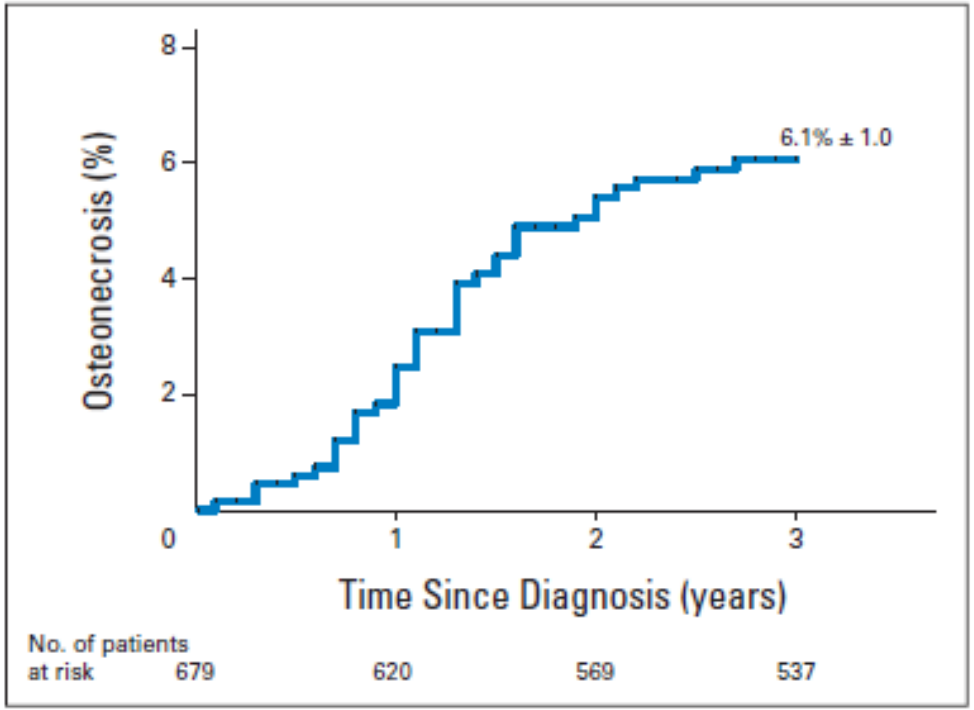
Second neoplasms among 5-year survivors of childhood ALL in the CCSS cohort: role of radiotherapy



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

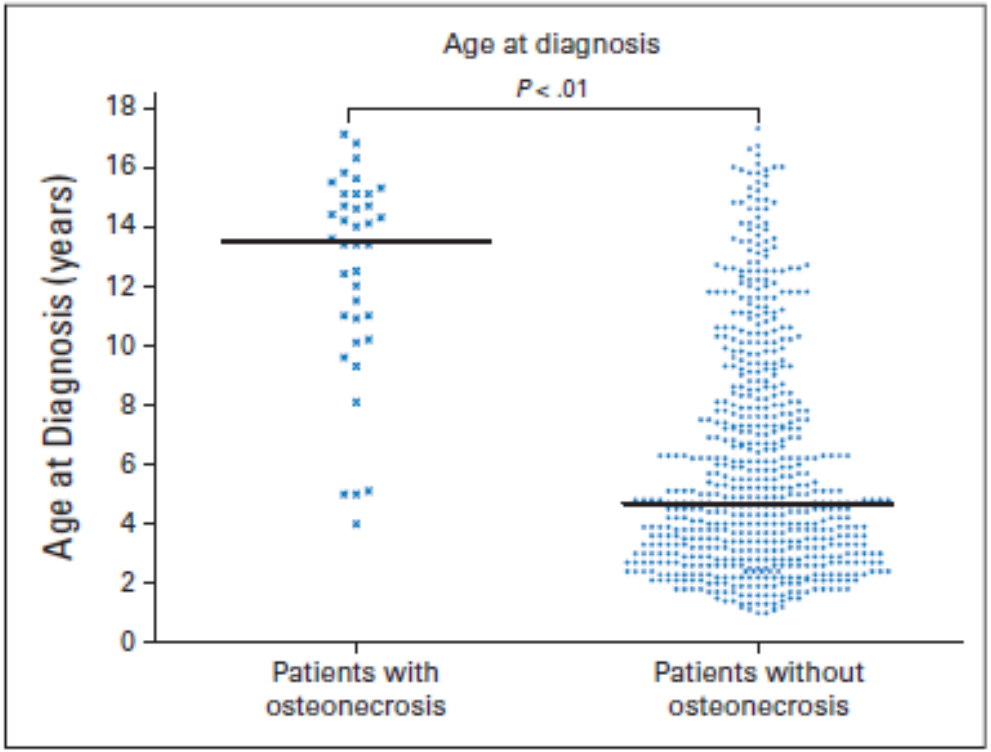


Cumulative incidence of symptomatic osteonecrosis in pediatric ALL



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

Age at diagnosis in patients with and without symptomatic osteonecrosis



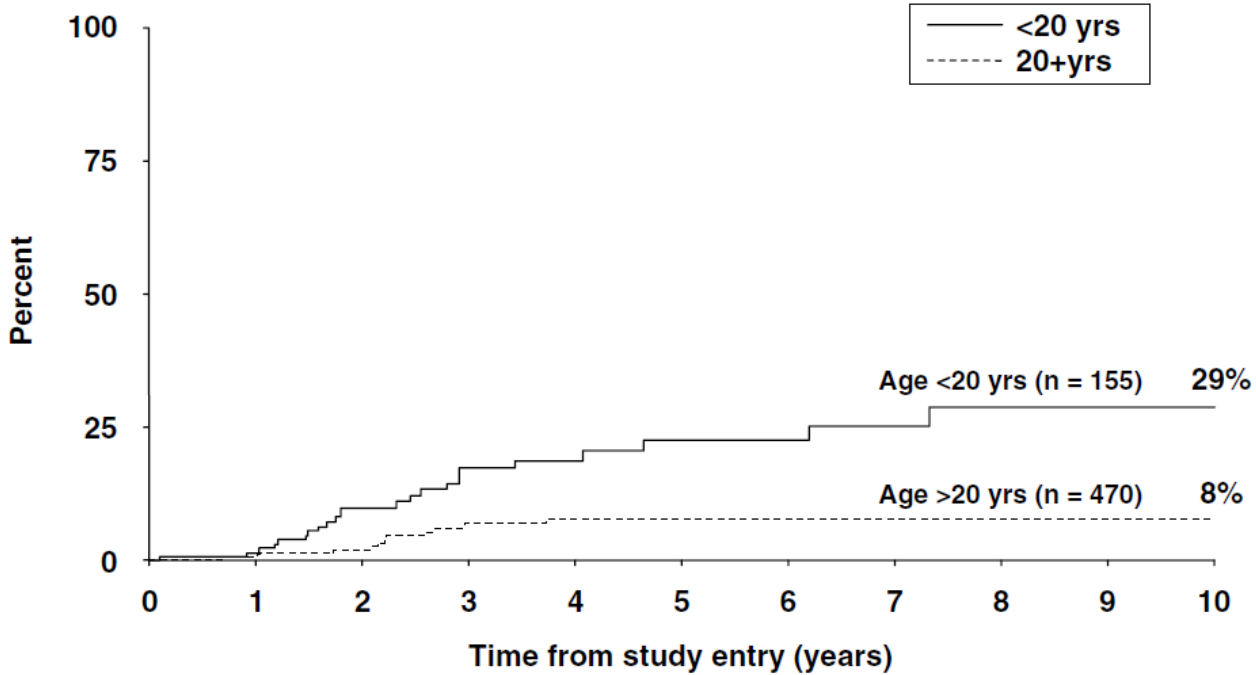
Te Winkel ML, et al. *J Clin Oncol.* 2011;29(31):4143-4150.

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

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

Osteonecrosis by age in ALL: UKALL XII study

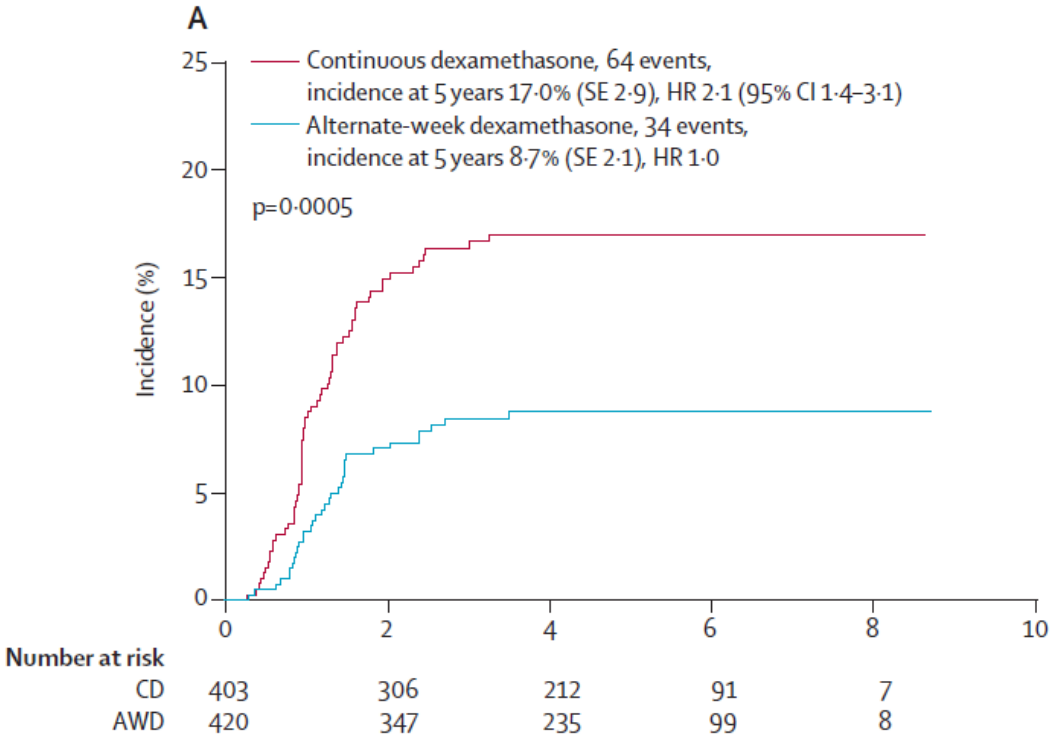


At risk:

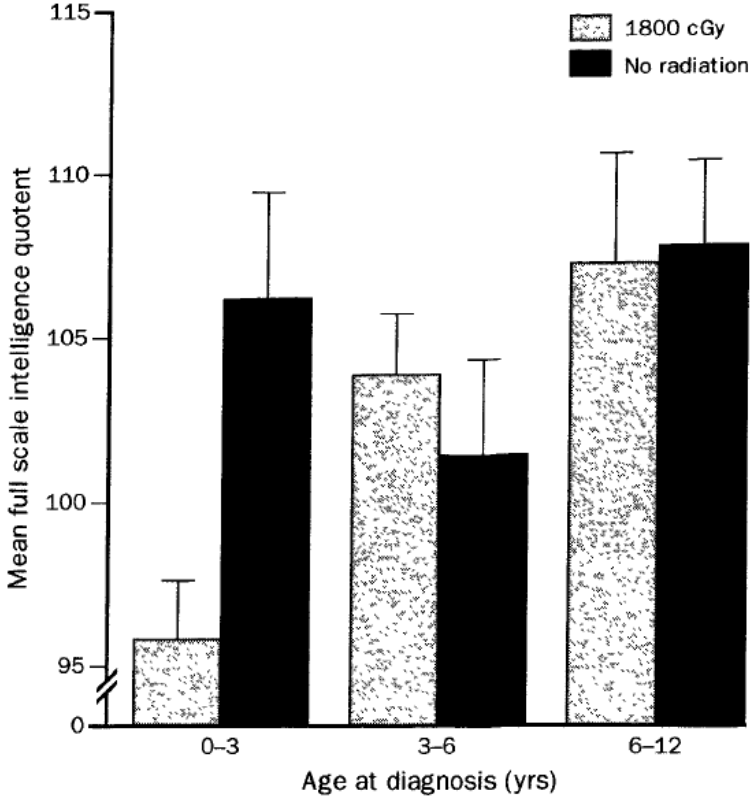
<20 yrs	155	126	93	61	46	34	28	23	18	16	9
20+ yrs	470	264	161	109	86	66	54	43	30	23	21

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

Osteonecrosis: continuous vs alternate-week dexamethasone

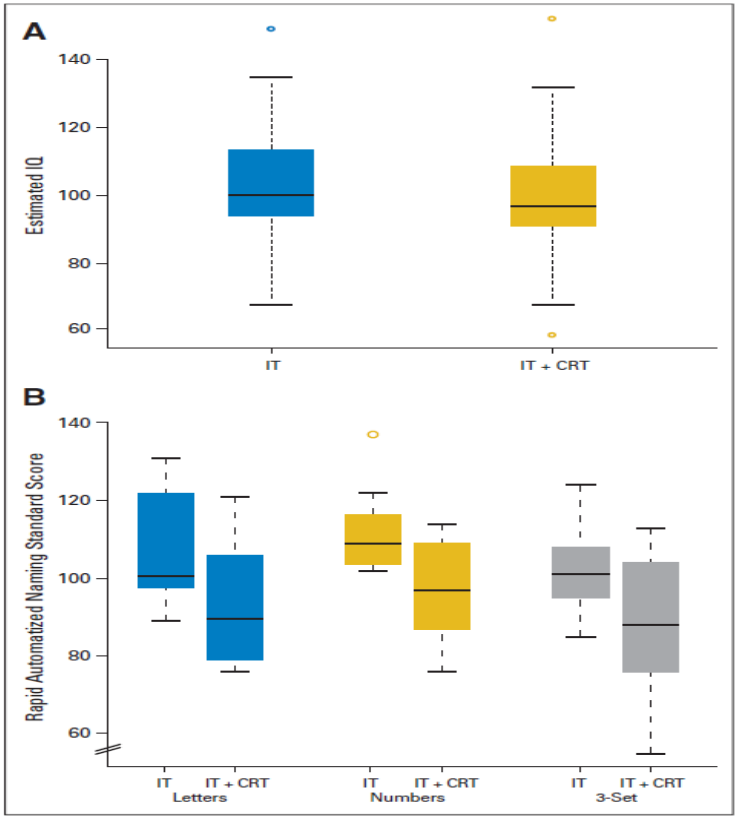


Effects of 1800 cGy cranial radiation on intellectual performance as a function of age at diagnosis

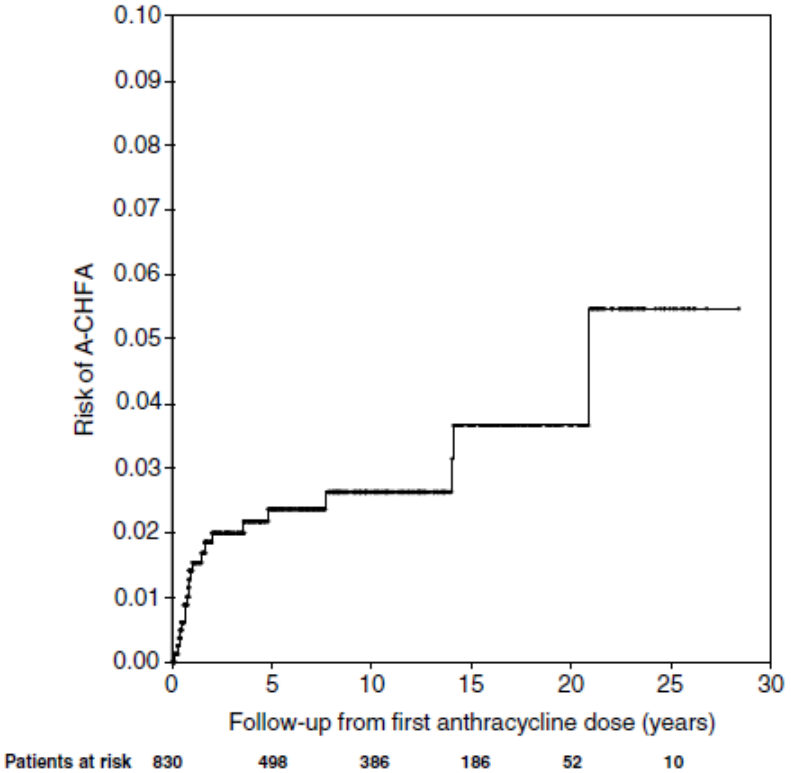


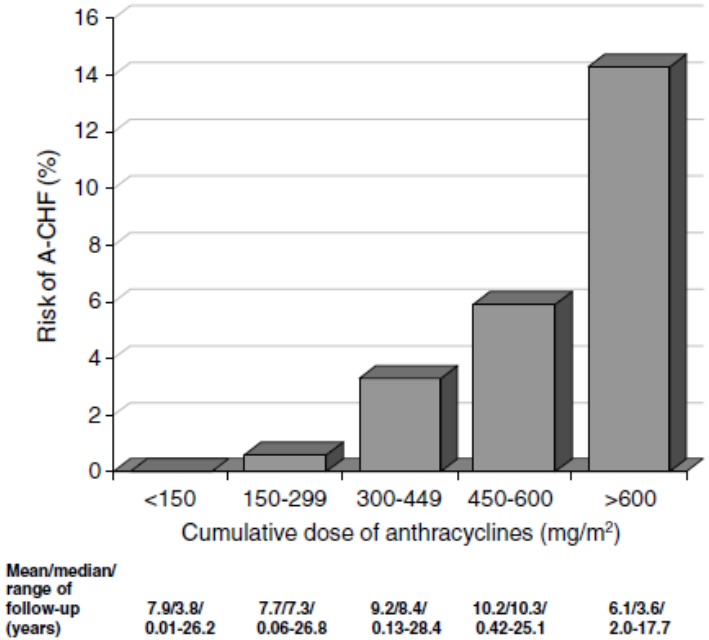
Jankovic M, et al. *Lancet.* 1994;344(8917):224-227.

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

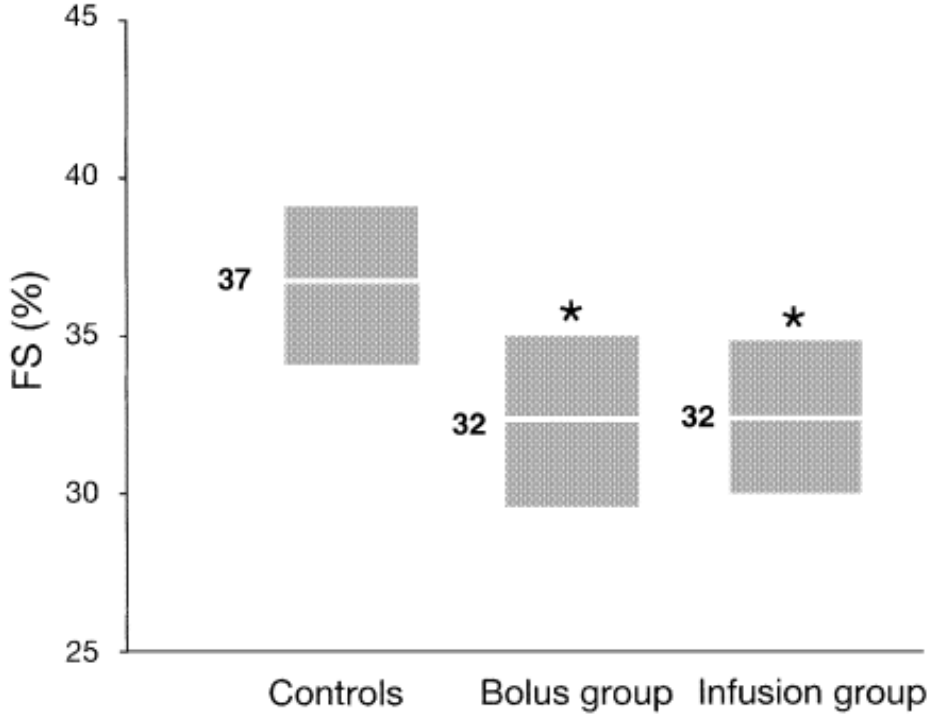


Risk of anthracycline-induced clinical heart failure in childhood cancer

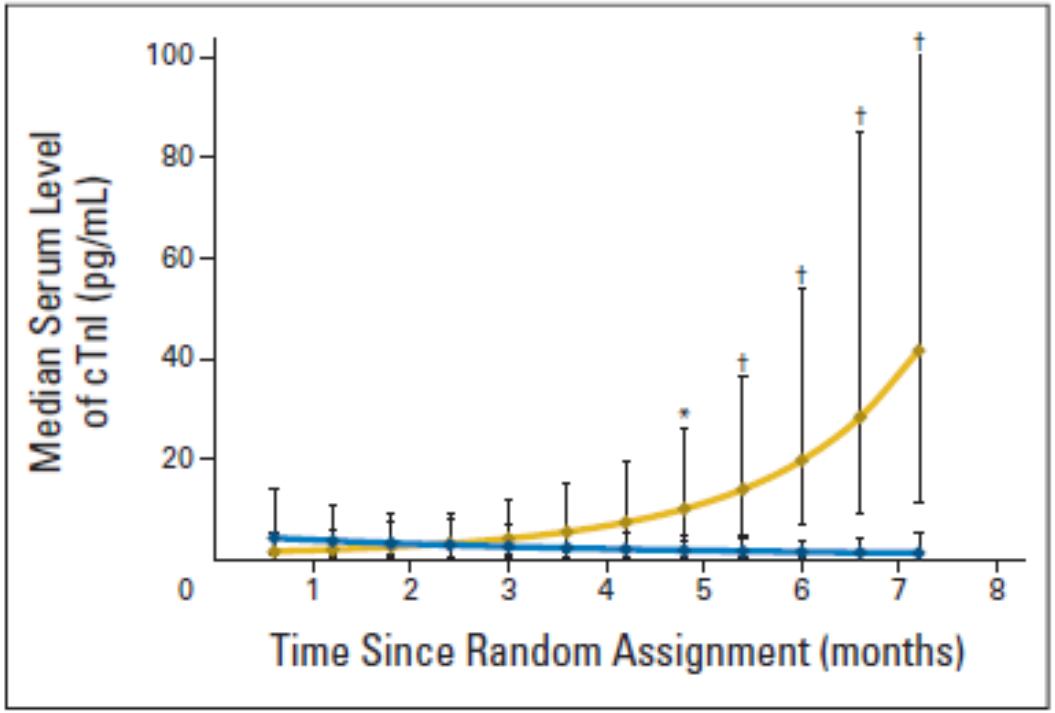




Shortening fraction by bolus or 6-hour infusion of daunorubicin



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

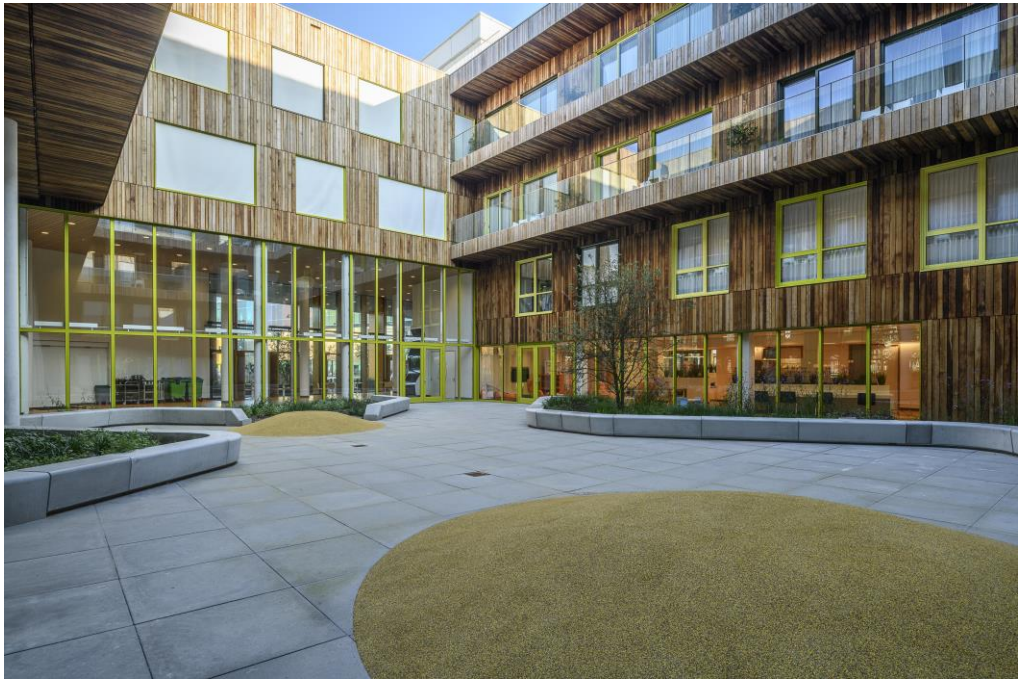


Late effects of treatment in ALL

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

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

Late effects outpatient clinic



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 >30 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 female child aged 14 years at diagnosis

Answer to question 2:

Which assertion is NOT correct?

1. Dexamethasone can cause osteonecrosis
2. The risk of osteonecrosis is lowest in children <10 years of age
3. **The risk of osteonecrosis is highest in adults with ALL**
4. The risk of osteonecrosis is higher with a continuous schedule of glucocorticoids than with a discontinuous schedule in the same cumulative dose

Thank you!

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Q&A

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Case-Based Panel Discussion: Patient Case Presentation

Hale Ören

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Short-term toxicities associated with treatment of childhood ALL

- Hypersensitivity to asparaginase
- Hyperlipidemia
- Osteonecrosis
- Asparaginase-associated pancreatitis
- Arterial hypertension
- Posterior reversible encephalopathy syndrome
- Seizures
- Depressed levels of consciousness
- MTX-related stroke-like syndrome
- Peripheral neuropathy
- High-dose MTX-related severe nephropathy
- Sinusoidal obstruction syndrome
- Thromboembolism
- *Pneumocystis jirovecii* pneumonia

Schmiegelow K, et al. *Lancet Oncol.* 2016;17(6):e231-e239.

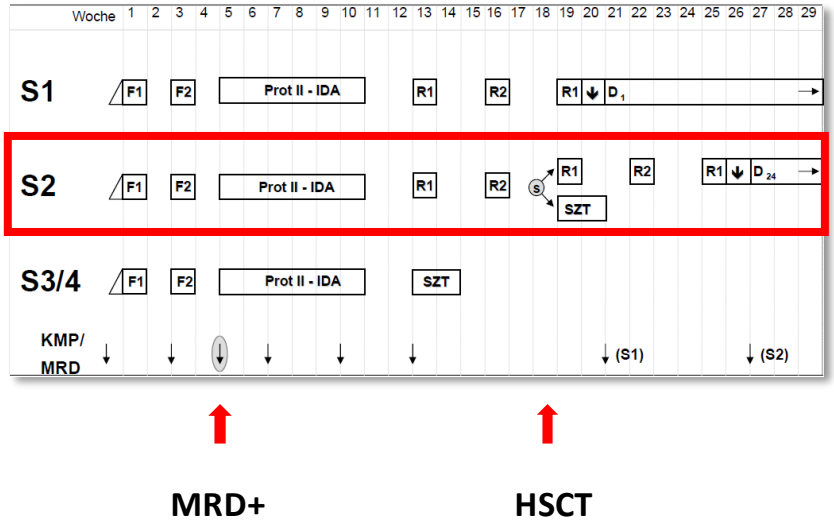
Clinical case: Initial diagnosis (May 2012)

- 10-year-old male
- Pre–B-cell ALL, CNS negative
- Treatment started according to ALL-BFM 2000 protocol
- MLL (-), t(9;22) (-), t(12;21) (-)
- No abnormalities in cytogenetic analysis
- PGR on day 8
- 15th day and 33rd day BM in remission
- MRD-PCR: TP 1 – 10^{-2}; TP 2 – 10^{-3}; TP 3 – (-)/10^{-5} (intermediate-risk group)
- Treatment completed: May 2014

Clinical case: First relapse (Feb 2016)

56 months after diagnosis

- Isolated bone marrow relapse
- Treatment according to ALL-REZ BFM 2012-S2
- MRD still positive before protocol II-IDA
  - HSCT decision
- AlloHSCT after R2 (29.11.2016)
  - 9/10 MUD



Clinical case: Second relapse (May 2018)

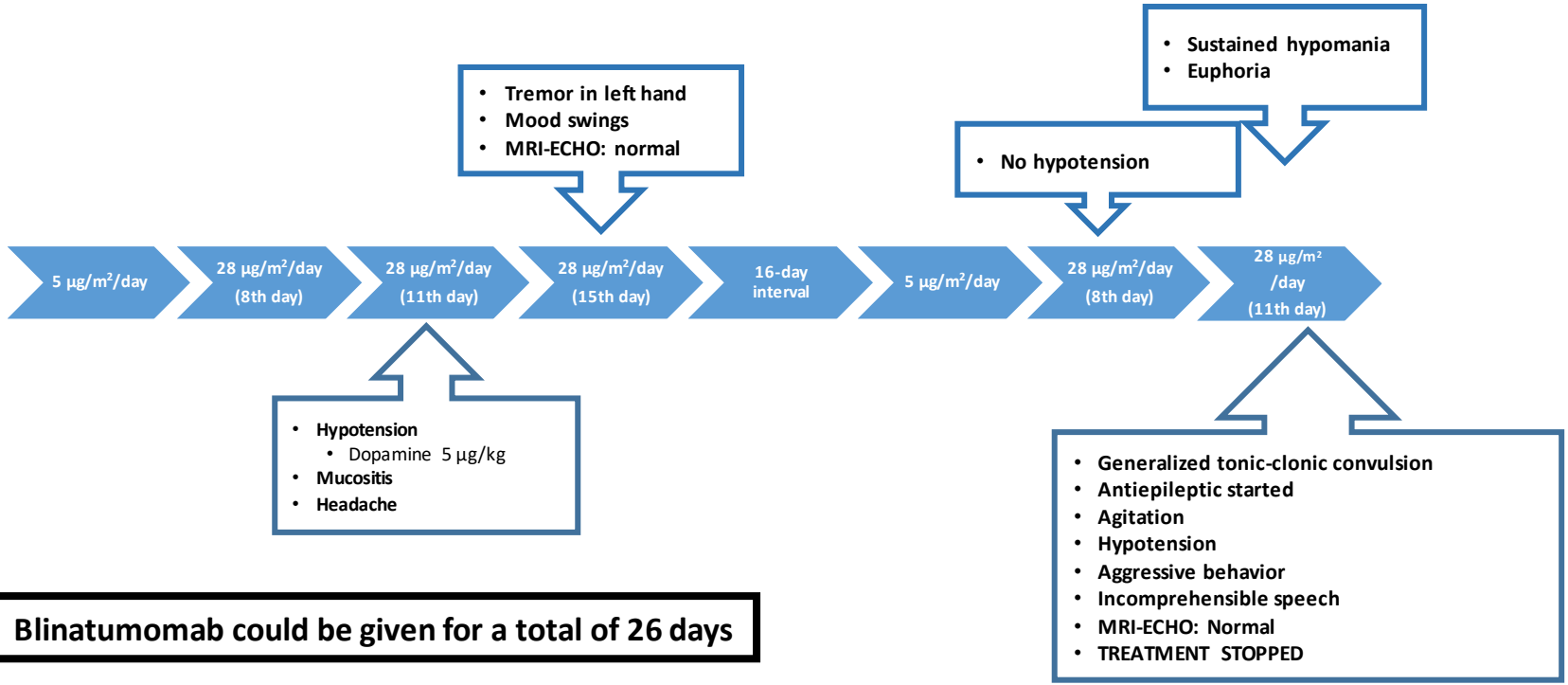
19 months after HSCT (30.05.2018)

- Isolated bone marrow relapse
  - Trisomy 8+, 23%
- FLAG
  - M3 bone marrow
- FLAG + mitoxantrone
  - M2 bone marrow, MRD+

What would you do next?

1. AlloHSCT
2. Start CAR T-cell therapy
3. Start blinatumomab therapy
4. Palliative care

Clinical case: Blinatumomab treatment (14.08.2018)



Blinatumomab could be given for a total of 26 days

Which dose of blinatumomab would you prefer to give?

1. Start and continue with 5 µg/m^2/day
2. Start and continue with 30 µg/m^2/day
3. Start with 5 µg/m^2/day, then give 15 µg/m^2/day after day 8
4. Start and continue with 15 µg/m^2/day

Recommended dose confirmed in phase 1 was applied to phase 2

On the basis of the phase 1 dose-escalation study, the recommended blinatumomab dose for children with R/R B-cell precursor ALL is:

5 µg/m^2/day
for the first 7 days

followed by

15 µg/m^2/day
starting at day 8

ALL, acute lymphoblastic leukemia; R/R, relapsed/refractory.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Clinical case, continued

- Remission status after blinatumomab
  - M1 BM
  - MRD–
- Second alloHSCT (MUD) (01.11.2018)
- Antiepileptic therapy stopped, normal EEG (20.11.2019)
- MRD still negative
- BM is still in CR (March 2020)

MT103-205

Some patients treated with blinatumomab experienced neurologic/psychiatric events

	All Patients n = 70[a]
Patients with neurologic/psychiatric events of any grade regardless of relation to treatment, n (%)	17 (24)
Tremor	4 (6)
Dizziness	3 (4)
Somnolence	3 (4)
Convulsion	2 (3)
Paresthesia	2 (3)
Encephalopathy	1 (1)
Neuralgia	1 (1)
Ataxia	1 (1)
Atonic seizure	1 (1)
Cerebrospinal fluid leakage	1 (1)
Depressed level of consciousness	1 (1)
Dysgeusia	1 (1)
Hypoesthesia	1 (1)
Nystagmus	1 (1)
Syncope	1 (1)
Confusional state	1 (1)
Mental disorder	1 (1)

13% of patients had neurologic events, primarily tremor and dizziness, that were considered treatment related; these events were of grade 2 and resolved upon treatment discontinuation

[a]All patients who received the recommended dose in phase 1 or 2.

von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389; supplementary material (online).

MT103-205

Some patients treated with blinatumomab developed cytokine release syndrome

	All Patients n = 70[a]
Patients with CRS, n (%)	
Any grade	8 (11)
Worst grade 3	3 (4)
Worst grade 4	1 (1)
Worst grade 5	0
Temporarily interrupted treatment because of CRS	2 (3)[b]
Discontinued treatment because of CRS	2 (3)[c]
Patients with CRS by age group, n (%)	
<2 years (n = 10)	2 (3)
Worst grade 3 or 4	0
2–6 years (n = 20)	2 (3)
Worst grade 3 or 4	2 (3)
7–17 years (n = 40)	4 (6)
Worst grade 3 or 4	2 (3)
Duration of grade ≥3 CRS, n (%)	
>3 to ≤7 days	2 (3)
>7 to ≤14 days	1 (1)
>14 days	1 (1)
Median (95% CI) days	6.5 (5.0–16.0)

[a]All patients who received the recommended dose in phase 1 or 2. [b]All grade 3. [c]One grade 3 and one grade 4 event.
CRS, cytokine release syndrome.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Conclusions

- To prevent CRS, dexamethasone or hydroxyurea were recommended during the first week of therapy for 4 days, and were required if bone marrow blasts were >50% at baseline
- Patients received prophylactic dexamethasone 10 mg/m^2 6–12 hours before and 5 mg/m^2 within 30 minutes of the start of infusion
- IL-6 inhibitors (tocilizumab/siltuximab), dexamethasone/methylprednisolone in CRS if necessary
- Regarding neurotoxicity, withholding blinatumomab is recommended for grade 3 toxicity until improvement to grade <1 is noted for 3 consecutive days. Restart with lower dose. For grade 4 toxicity, discontinue
- Daily fundus examination, EEG, MRI, LP
- Intensive care
- Antiepileptics

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Q&A

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Case-Based Panel Discussion: Management of Long- and Short-Term Toxicities

Patrick Brown
Rob Pieters
Hale Ören
Sema Anak
Gulyuz Öztürk
Akif Yesilipek

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Educational ARS Questions

Rob Pieters

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Educational questions Pediatric ALL
Question 1: which assertion is correct for children with ALL?

1. All patients with MLL rearranged ALL should be transplanted
2. All patients with BCR-ABL positive ALL should be transplanted
3. No patient with BCR-ABL positive ALL should be transplanted
4. AlloSCT is part of treatment for children with early relapsed ALL

Educational questions Pediatric ALL
Question 2: which assertion is correct for children with ALL?

1. Blinatumomab and inotuzumab are part of first-line treatment
2. Blinatumomab and inotuzumab can not be administered sequentially
3. Therapeutic drug monitoring of asparaginase improves outcome
4. Dexamethasone and vincristine are standard components of maintenance therapy

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Closing remarks

Rob Pieters

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Thank You!

- Please complete the **evaluation page** that will appear on your screen momentarily
- Your notes on the slides will be emailed to you by July 17
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website by July 17
- You will also receive a certificate of attendance by email by July 17

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THANK YOU FOR YOUR PARTICIPATION!

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