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Global Leukemia Academy

A Worldwide Collaboration to Define and Refine the Most Effective Treatments in Leukemias

6 December 2022

Virtual Breakout: Pediatric Leukemia Patients

Global Leukemia Academy

Session Open

Elizabeth Raetz

APTITUDE HEALTH

Meet the Faculty

CHAIR

Elizabeth Raetz, MD
NYU Grossman School of Medicine, New York, NY, USA

FACULTY

Marcos de Lima, MD
Ohio State University, Columbus, OH, USA

Stephanie Dixon, MD, MPH
St. Jude Children's Research Hospital, Memphis, TN, USA

Shaun Fleming, MBBS(Hons), FRACP, FRCPA
Alfred Hospital, Melbourne, VIC, Australia

Stephen P. Hunger, MD
Children's Hospital of Philadelphia, PA, USA

Hagop Kantarjian, MD
MD Anderson Cancer Center, Houston, TX, USA

Michael Osborn, MBBS, FRACP, FRCPA
SA Pathology, Adelaide, SA, Australia

Jae Park, MD
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Co-chair (Adult Session)
Elias Jabbour, MD
MD Anderson Cancer Center, Houston, TX, USA

Objectives of the Program

- Examine current treatment patterns and technological developments in ALL
- Learn how MRD is being used in ALL management and monitoring
- Discuss the latest developments in bispecific antibodies used for ALL
- Understand how stem cell transplantation is being utilized as a consolidation choice in first remission
- Learn current genomic testing practices and how these results inform treatment choices
- Learn how current antibody-drug conjugate treatments are being used in ALL
- Gain insights into promising novel and emerging therapies in ALL
- Learn about the regional challenges and differences in ALL treatment patterns in the Asia Pacific region

Virtual Breakout – Pediatric ALL Sessions (Day 2)

Tuesday, December 6 | 9.00 AM – 11.45 AM (GMT+8) Shanghai

ARS voting system will be used throughout the meeting

Time	Title	Speaker
9.00 – 9.10	**Session Open** • ARS questions	Elizabeth Raetz
9.10 – 9.40	**Optimizing First-Line Therapy in Pediatric ALL: How to Balance Cure and Long-term Risks?** • Optimal use of treatment choices in frontline pediatric ALL, including HSCT	Michael Osborn
9.40 – 10.00	**Optimal Management and Treatment Coordination of Long-term Toxicities in Pediatric ALL** • Long-term follow-up care for pediatric ALL survivors	Stephanie Dixon
10.00 – 10.40	**ALL Case-Based Panel Discussion** • Local case 1: Frontline setting (10 min) • Local case 2: Management of long-term toxicities (10 min) • Discussion and Q&A (20 min)	Moderators: Michael Osborn and Elizabeth Raetz Savenaca Seduadua Claudia Toro All faculty
10.40 – 10.50	***Break***	
10.50 – 11.15	**Current Treatment Options for Relapsed ALL in Children** • Optimal use of treatment choices in relapsed/refractory ALL, including HSCT	Elizabeth Raetz
11.15 – 11.35	**ALL Case-Based Panel Discussion** • Local case 3: Relapsed/refractory setting (10 min) • Discussion and Q&A (10 min)	Moderators: Michael Osborn and Elizabeth Raetz Miri Tukana All faculty
11.35 – 11.45	**Session Close** • ARS questions	Elizabeth Raetz

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Introduction to the Voting System

Elizabeth Raetz

APTITUDE HEALTH

Question 1

In which country do you currently practice?

A. Australia
B. China
C. Hong Kong
D. Japan
E. Malaysia
F. Singapore
G. South Korea
H. Taiwan
I. Other country in Asia Pacific
J. Other country outside Asia Pacific

Question 2

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

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

Question 3

Which assertion is correct for children with B-ALL?

A. Inotuzumab is approved for induction treatment of relapsed B-ALL in childhood

B. Inotuzumab dosage is 3 mg/m^2

C. Blinatumomab is approved for consolidation treatment before HSCT in children with B-ALL

D. None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

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

Michael Osborn

APTITUDE HEALTH

1950s

SHOULD WE TREAT LEUCHÆMIA IN CHILDHOOD?[1]

By JOHN H. COLEBATCH[2] and A. L. WILLIAMS,[2]
From the Children's Hospital, Melbourne.

LEUCHÆMIA at any age is a disease invariably fatal and in its terminal stages often distressing. In children it almost always occurs in the acute form, with consequences that are particularly tragic. There was until recently but one blessing—that the illness at least was generally very brief.

In the past two decades, however, the prognosis for children with acute leuchæmia has been altered by the use of blood transfusions, sulphonamides and penicillin. In 1948 Diamond observed that partial or complete remissions occurred in 10% of 300 cases, the average duration of the remissions being slightly less than ten weeks. Since then other antibiotics have been added to our armamentarium, but even so it has rarely been possible to delay the fatal outcome for more than a few weeks or months. Most doctors, including ourselves, when confronted with a child suffering from acute leuchæmia, still felt that the treatment was worse than the disease and that the alleviation of distress was all that should be attempted.

This was the position in June, 1948, when Sydney Farber, of Boston Children's Hospital, published the results of a year's experience with the use of folic acid antagonists in acute leuchæmia (Farber *et alii*, 1948). Improvement

Colebatch JH, Williams AL. *Med J Aust*. 1950;2(25):892-895.

1960s
<10% cured

1960s
<10% cured

1970s
40% cured

1960s
<10% cured

1970s
40% cured

1980s
75% cured

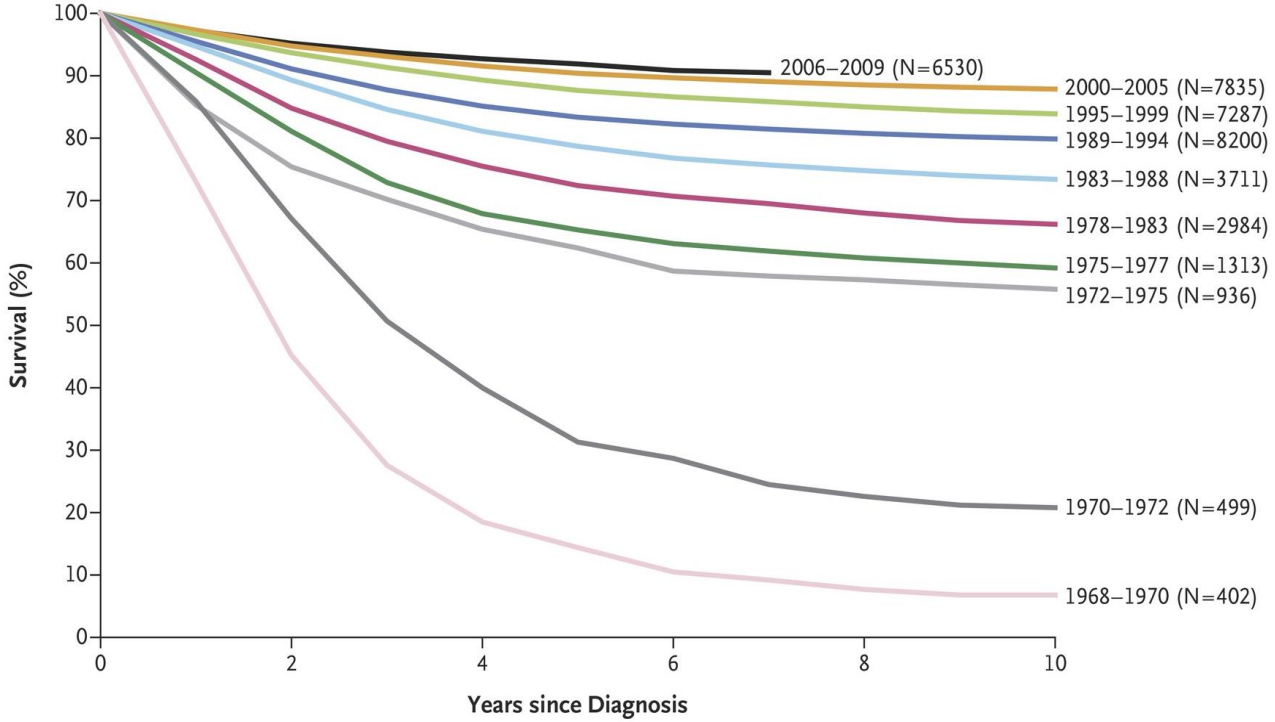
1960s
<10% cured

1970s
40% cured

1980s
75% cured

2022
>85% cured

Improvements in Survival Are Now Plateauing



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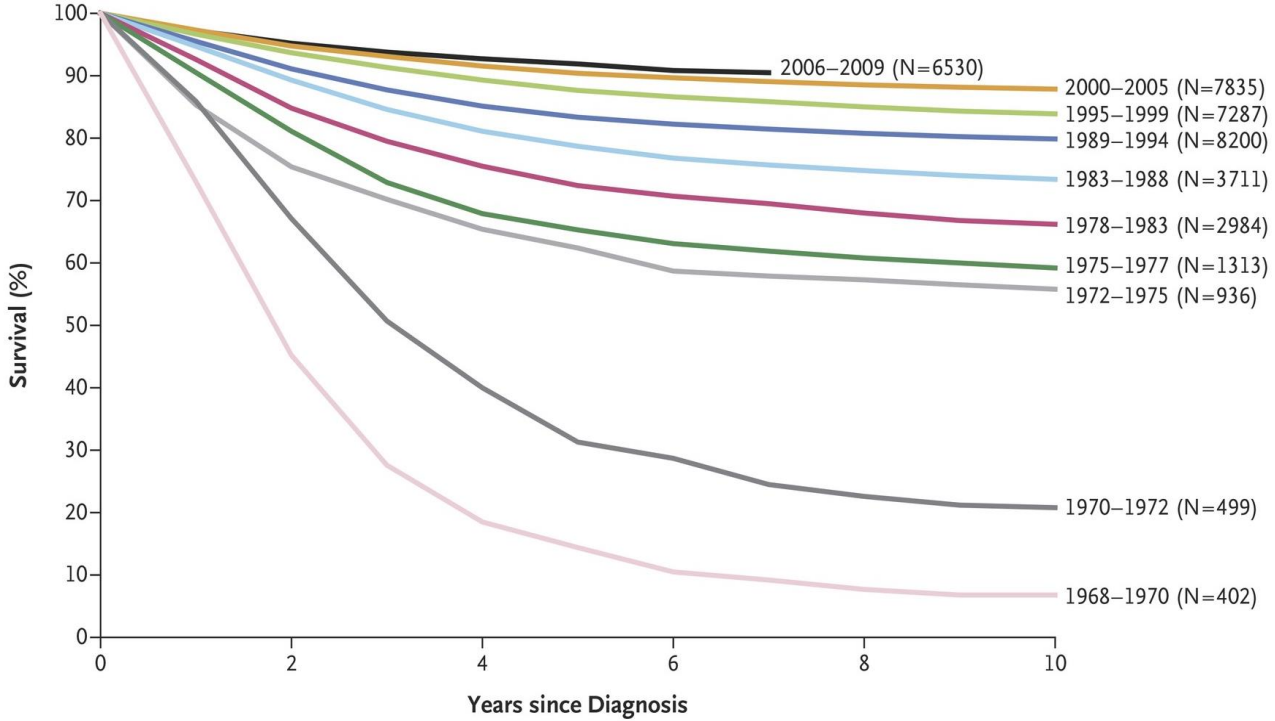
Hunger SP, Mullighan CG. N *Engl J Med*. 2015;373(16):1541-1552.

Improvements in Survival Are Now Plateauing



Relapse

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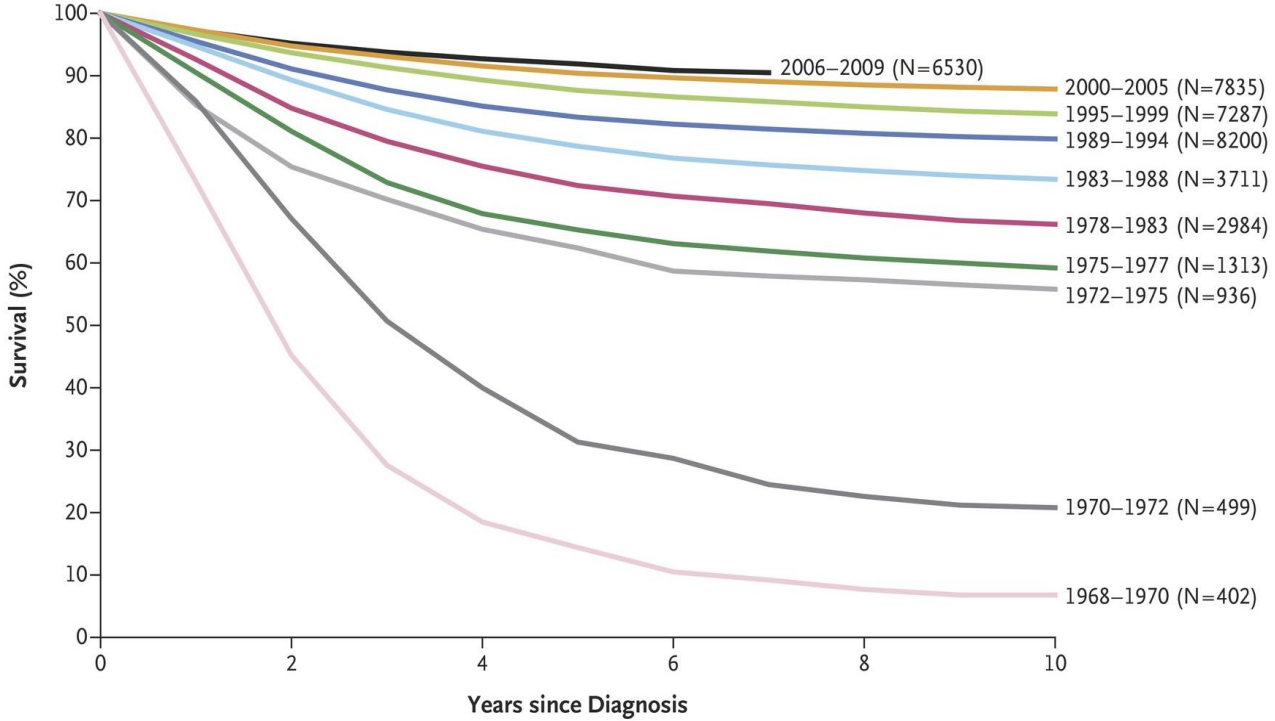
Hunger SP, Mullighan CG. N *Engl J Med.* 2015;373(16):1541-1552.

Improvements in Survival Are Now Plateauing



Relapse

Cost of cure

Acute toxicity
Late effects
Psychosocial

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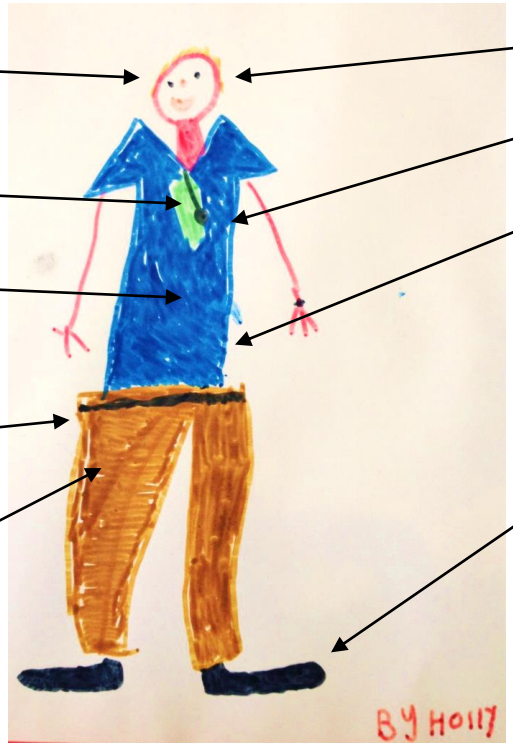
Hunger SP, Mullighan CG. N *Engl J Med*. 2015;373(16):1541-1552.

Improvements in Survival Are Now Plateauing

- Cognitive impairment
- Cardiac failure
- Pancreatitis complications
- Avascular necrosis
- Subfertility*
- Second malignancy



- Psychosocial
- ↓ Fitness
- Obesity and metabolic syndrome
- Endocrine*
- Peripheral neuropathy
- Iron overload

Relapse

Cost of cure

Acute toxicity
Late effects
Psychosocial

*Mainly post-HSCT

Improvements in Survival Are Now Plateauing

DOI: 10.1002/pbc.28835

Pediatric Blood & Cancer | SIOP | aspho The American Society of Pediatric Hematology/Oncology | WILEY

SURVIVORSHIP: RESEARCH ARTICLE

Late mortality from other diseases following childhood cancer in Australia and the impact of intensity of treatment

Danny R. Youlden[1,2] | Thomas S. Walwyn[3,4] | Richard J. Cohn[5,6] | Hazel E. Harden[7] | Jason D. Pole[8,9,10] | Joanne F. Aitken[1,2,11,12]

- Childhood leukemia 5-year survivors (treated between 1983–2011)
  - Standardized mortality ratio (noncancer disease-related deaths) = **3.55**
- All childhood cancers
  - Relative risk of noncancer disease-related mortality 2× higher in patients treated with “most-intensive” vs “least-intensive” therapy: SMR 5.94 vs 2.98
  - Cumulative 30-year risk of noncancer disease-related death: **1.4%**

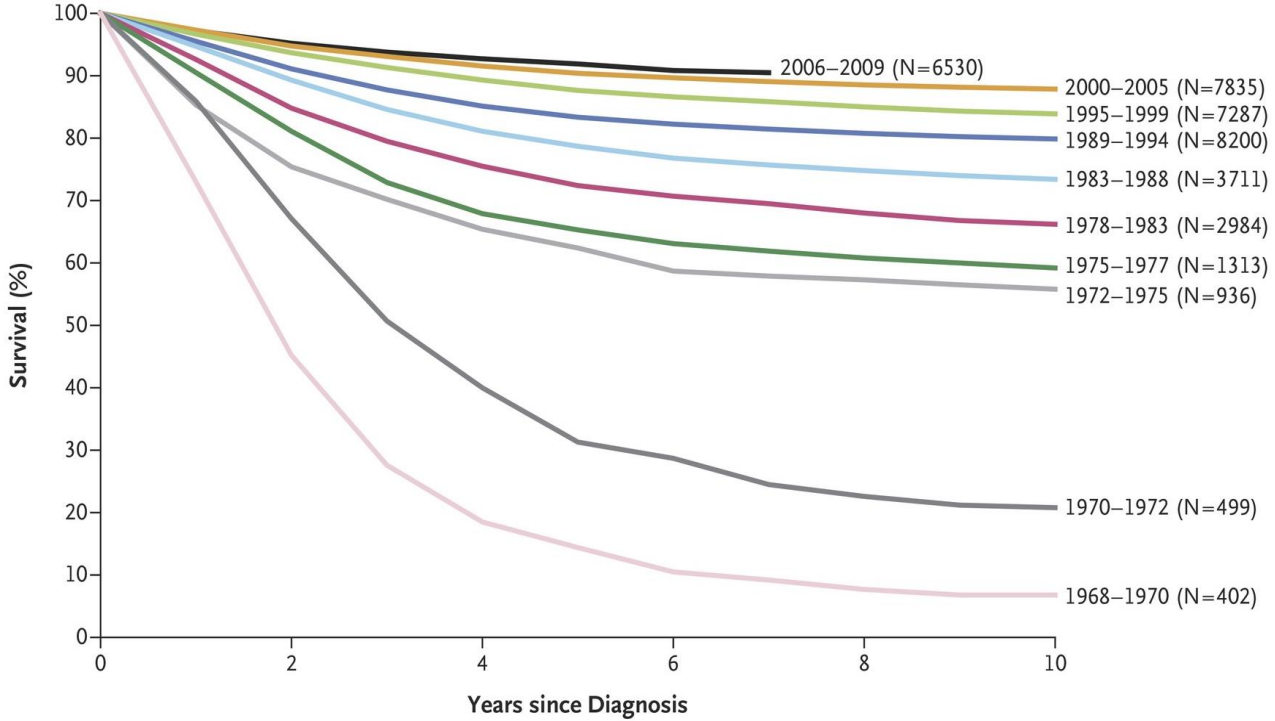
Relapse

Cost of cure

Acute toxicity
Late effects
Psychosocial

Improvements in Survival Are Now Plateauing

So We Need More-Effective, Less-Toxic Therapies



Relapse

Cost of cure

Acute toxicity
Late effects
Psychosocial

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Hunger SP, Mullighan CG. N *Engl J Med*. 2015;373(16):1541-1552.

Improvements in Survival Are Now Plateauing

So We Need More-Effective, Less-Toxic Therapies . . .

. . . With Strategies to Improve Outcomes for LMICs

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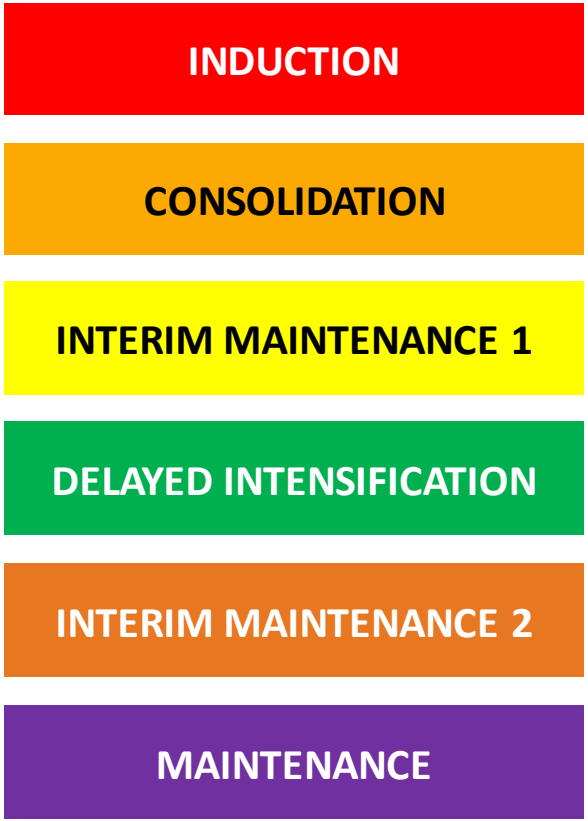
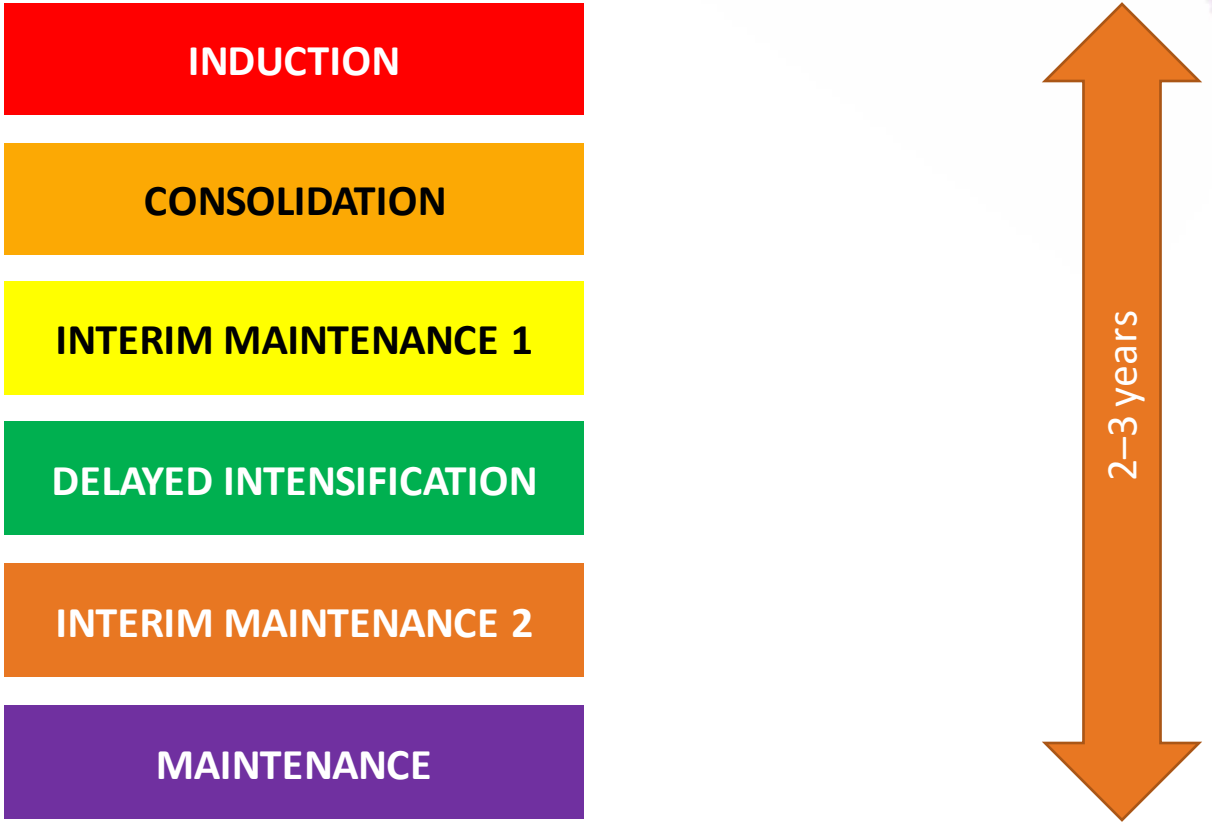
Overview of ALL Therapy in Children



Overview of ALL Therapy in Children



Overview of ALL Therapy in Children

RISK STRATIFICATION		
NCI Rome Criteria		
Standard:	Age 1–9.99	WCC <50
High:	Age <1 or ≥10	WCC ≥50
CNS involvement		
Immunophenotype (B, T, MPAL)		
Cytogenetics *ETV6-RUNX1*, double trisomies: +4, +10 Ph+, hypodiploid, iAMP21, KMT2A-R, t(17;19)		
Molecular subtype "Ph-like" (COG); Ikaros^{plus} (BFM)		
Response to treatment Induction failure Minimal residual disease		

INDUCTION

CONSOLIDATION

INTERIM MAINTENANCE 1

DELAYED INTENSIFICATION

INTERIM MAINTENANCE 2

MAINTENANCE

2–3 years

Overview of ALL Therapy in Children

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NCI Rome Criteria		
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INTERIM MAINTENANCE 1

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MAINTENANCE

Cranial Irradiation

Overview of ALL Therapy in Children

RISK STRATIFICATION		
NCI Rome Criteria		
Standard:	Age 1–9.99	WCC <50
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Response to treatment Induction failure Minimal residual disease		

INDUCTION

CONSOLIDATION

INTERIM MAINTENANCE 1

DELAYED INTENSIFICATION

INTERIM MAINTENANCE 2

MAINTENANCE

Targeted Therapies

Cranial Irradiation

2–3 years

Overview of ALL Therapy in Children

RISK STRATIFICATION		
NCI Rome Criteria		
Standard:	Age 1–9.99	WCC <50
High:	Age <1 or ≥10	WCC ≥50
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Molecular subtype "Ph-like" (COG); Ikaros^{plus} (BFM)		
Response to treatment Induction failure Minimal residual disease		

INDUCTION

CONSOLIDATION

INTERIM MAINTENANCE 1

DELAYED INTENSIFICATION

INTERIM MAINTENANCE 2

MAINTENANCE

Targeted Therapies

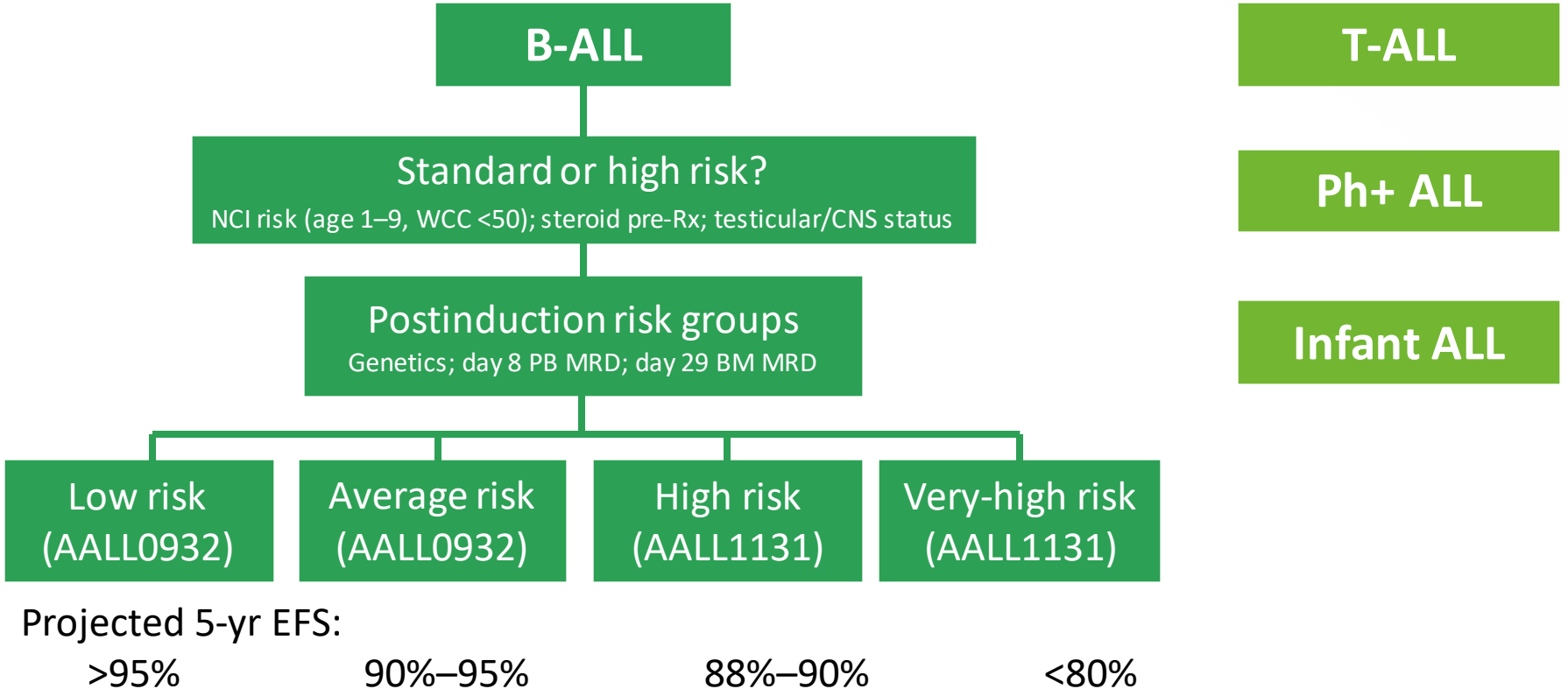
Stem Cell Transplant

Cranial Irradiation

2–3 years

What Have We Learned in the Last 10 Years?

Children's Oncology Group Approach



What Have We Learned in the Last 10 Years?
Children's Oncology Group: Standard-Risk B-ALL

Study	Question	Conclusions
AALL0331	• Does **intensified PEG-Asp** benefit **SR-low**? • Does **intensified consolidation** benefit **SR-Av**?	• **No**: 5-yr CCR Standard Asp 94% vs Intens Asp 96% • **No**: 5-yr CCR SC: 88.5% vs IC: 89.7% • Subgroup of SR-Av with d29 MRD 0.01%–0.1% who received less-intensive Rx had EFS of only 77%, so **all MRD ≥0.01% should get intensified Rx**
AALL0932	• Is P9904-based regimen (with 6× Int dose MTX, no alkylating agents, and no anthracyclines) as good as the outpatient-based SR-Av approach for **SR-Low?** • Does **higher maintenance MTX dose** of 40 mg/m^2 vs 20 mg/m^2 benefit **SR-Av**? • Are 12-weekly VCR-DEX pulses in maintenance as good as 4-weekly in **SR-Av**?	• **Yes**: 5-yr DFS: 98.5% vs 98.7% • **No**: 5-yr DFS 94% vs 95% • **Yes**: 5-yr DFS 95% vs 94%

Maloney KW, et al. *J Clin Oncol.* 2020;38(6):602-612; Angiolillo AL, et al. *J Clin Oncol.* 2021;39(13):1437-1447.

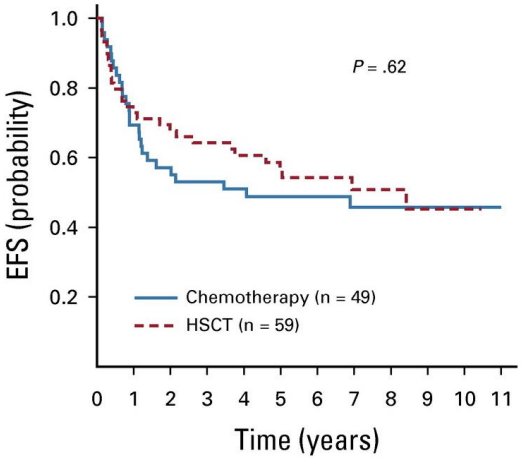
What Have We Learned in the Last 10 Years?
Children's Oncology Group: High-Risk and VHR B-ALL

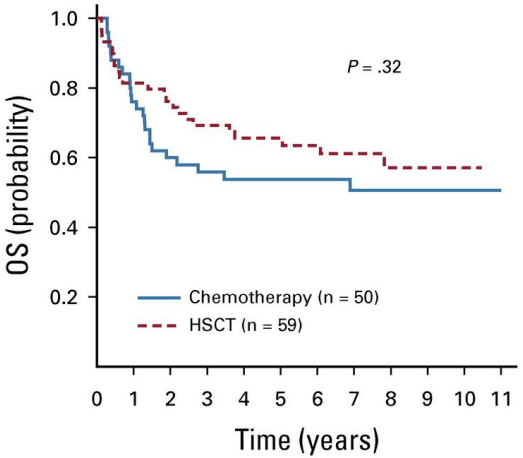
Study	Question	Conclusions
AALL0232	• Is **HDMTX** superior to escalating **Capizzi MTX**? • Is **dexamethasone** (14 days) as safe and efficacious as **prednisolone** in induction?	• **Yes**: 5-yr EFS 80% vs 75% (*P* = .007) • Excessive **osteonecrosis** in **≥10 yr old** and no better • **Better in <10 yr old**, but interaction with MTX randomization • 5-yr EFS DH 91%, DC 84%, PH 80%, PC 82%
AALL1131	• Are **triple intrathecals** superior to **IT MTX** in HR? • Is **clofarabine**, **cyclophosphamide,** and **etoposide** consolidation (or **cyclo** and **etop**) superior to conventional consolidation in VHR?	• **No** • **No** – randomization closed because of **unacceptable toxicity** with clofarabine, and cyclo-etop no better than conventional consolidation

Larsen EC, et al. *J Clin Oncol.* 2016;34(20):2380-2388; Salzer WL, et al. *J Clin Oncol.* 2020;38(23):2628-2638; Burke MJ, et al. *Haematologica.* 2019;104(5):986-992; Salzer WL, et al. *Cancer.* 2018;124(6):1150-1159.

What Have We Learned in the Last 10 Years?
Children's Oncology Group: Hypodiploid B-ALL

Study	Question	Conclusions
AALL03B1 (Hypodiploid subset)	• Does CR1 **HSCT** improve survival in **hypodiploid** B-ALL?	• **No**: 5-yr EFS 57% vs 47% (*P* = .49) • Confirmed by Ponte di Legno group • 5-yr OS 59% vs 52% • **New treatment strategies urgently needed**





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McNeer JL, et al. *J Clin Oncol*. 2019;37(10):780-789; Pui CH, et al. *J Clin Oncol*. 2019;37(10):770-779.

What Have We Learned in the Last 10 Years?
Children's Oncology Group: **T-ALL**

Study	Question	Conclusions
AALL0434	• Does **nelarabine** improve outcomes for intermediate- (IR) and high-risk (HR) children?* • Is **HDMTX** superior to escalating **Capizzi MTX**?	• **Yes**: 4-yr DFS 88% vs 83% (*P* = .03), but not T-ALL Less CNS relapses **"New standard of care in T-ALL"** • **Capizzi superior**: 92% vs 86% (*P* = .005)

*Not approved for ALL in Australia outside clinical trials.

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Dunsmore KP, et al. *J Clin Oncol.* 2020;38(28):3282-3293; Winter SS, et al. *J Clin Oncol.* 2018;36(29):2926-2934; Teachey DT, et al. ASH 2020. Abstract 266.

What Have We Learned in the Last 10 Years?
Children's Oncology Group: **T-ALL**

Study	Question	Conclusions
AALL0434	• Does **nelarabine** improve outcomes for intermediate- (IR) and high-risk (HR) children?* • Is **HDMTX** superior to escalating **Capizzi MTX**?	• **Yes**: 4-yr DFS 88% vs 83% (*P* = .03), but not T-ALL Less CNS relapses **"New standard of care in T-ALL"** • **Capizzi superior**: 92% vs 86% (*P* = .005)
AALL1231 (Closed early because of 0434 results)	• Does **bortezomib** (added to an augmented BFM backbone during induction and DI) improve outcomes?* • Can **CNS irradiation be omitted** in standard- (SR) and intermediate-risk (IR) children if chemo is intensified (dexamethasone as sole steroid; extra PEG-Asp)?	• **No**: 4-yr EFS 83% vs 82%, 4y OS 88% vs 88% (Benefit seen in T-ALL: 4-yr EFS 86% vs 76%) • **Yes**: Relapse rate identical to 0434: 8.4% vs 9.3% *and* only 9.5% irradiated (cf 91% in AALL0434) • More toxicity than AALL0434 and more toxic deaths (4% vs 2%)

*Not approved for ALL in Australia outside clinical trials.

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Dunsmore KP, et al. *J Clin Oncol.* 2020;38(28):3282-3293; Winter SS, et al. *J Clin Oncol.* 2018;36(29):2926-2934; Teachey DT, et al. ASH 2020. Abstract 266.

What Have We Learned in the Last 10 Years?
AIEOP-BFM

Study	Question	Conclusions
AIEOP-BFM ALL 2000	• **Dexamethasone** vs **prednisolone** (21 days + taper) in induction? • Can we decrease the intensity of delayed intensification? (30% less DEX and 50% less VCR, DOX, CPM)	• Dexamethasone had **lower relapse rate:** 10% vs 15% (esp **extramedullary**), but worse **toxicity** and TRM (2.5% vs 0.9%) • Survival benefit only for **T-ALL** with pred good response • **Not for everyone**: 8-yr DFS 89% vs 92% (*P* = .04) • ETV6-RUNX1 and ages 1–6 performed equally well
AIEOP-BFM ALL 2009	• R1 randomization: **2 vs 4 DAUN** in induction for pre-B non-HR • R2 randomization: **20 weeks** of **PEG-Asp** in protocol II for pre-B MR • R_{HR} randomization: **4 × PEG-Asp** in protocol 1B for pre-B HR • Is PEG-Asp safe? • Is a day 10 dose of CPM for T-ALL with pred poor response safe?	• ***Data awaited*** • ***To be presented at ASH 2022*** • **Yes**: acceptable toxicities and less allergies • **Yes**: no increase in life-threatening/fatal AEs

Academy

Moricke A, et al. *Blood*. 2016;127(17):2101-2112; Schrappe M, et al. *J Clin Oncol*. 2018;36(3):244-253.

Oral 6MP Adherence <90% → 3.9× Relapse Risk

6MP adherence in a multiracial cohort of children with acute lymphoblastic leukemia: a Children's Oncology Group study

Smita Bhatia,[1] Wendy Landier,[1] Lindsey Hageman,[1] Heeyoung Kim,[1] Yanjun Chen,[1] Kristine R. Crews,[2]

- Adherence lower in African Americans (87%) and Asian Americans (90%) than non-Hispanic whites (95%)
- Explained by sociodemographic features, eg, household income, maternal education
- 20.5% were <90% adherent

Bhatia S, et al. *Blood.* 2014;124(15):2345-2353; Bhatia S, et al. *JAMA Netw Open.* 2020;3(8):e2015022.

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- Explained by sociodemographic features, eg, household income, maternal education
- 20.5% were <90% adherent

Effect of a Daily Text Messaging and Directly Supervised Therapy Intervention on Oral Mercaptopurine Adherence in Children With Acute Lymphoblastic Leukemia

A Randomized Clinical Trial

Smita Bhatia, MD, MPH; Lindsey Hageman, MPH; Yanjun Chen, MS; F. Lennie Wong, PhD; Elizabeth L. McQuaid, PhD; Christina Duncan, PhD; Leo Mascarenhas, MD;

- No difference in proportion taking >95% of doses
  - 65% (text + education) vs 59% (education alone), *P* = .08)
- Text + education more effective in >12 yr old, esp if baseline adherence <90%
  - Mean adherence 83% vs 75% (*P* = .008)

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Bhatia S, et al. *Blood.* 2014;124(15):2345-2353; Bhatia S, et al. *JAMA Netw Open.* 2020;3(8):e2015022.

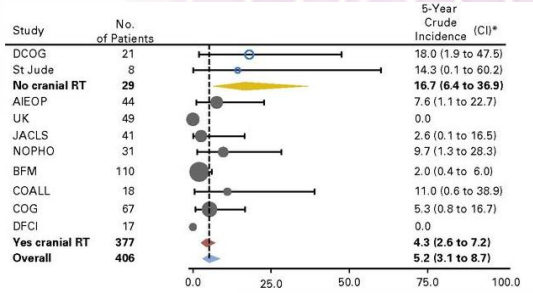
Cranial Irradiation Does Not Influence Survival on Contemporary Pediatric ALL Protocols

Meta-analysis of 10 Cooperative Groups

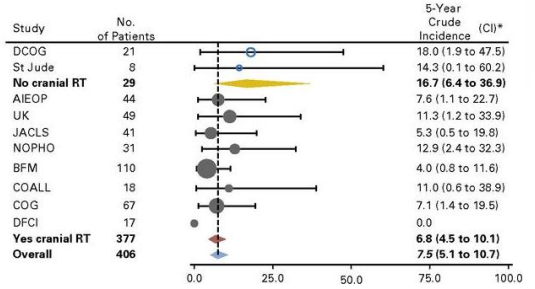
- CRT decreased relapses in the 1970s
  - But ↑ neurocognitive sequalae, endocrinopathy, and second malignancies
- Increasingly replaced by IT chemo (+ MTX, dex, Asp)
- N = 16623, aged 1–18, 1996–2007
- CNS3 was only group to benefit from CRT

Isolated CNS relapse:	4% with CRT vs 17% without
Any CNS relapse (isolated ± BM):	7% vs 17%
Any event:	32% vs 34%

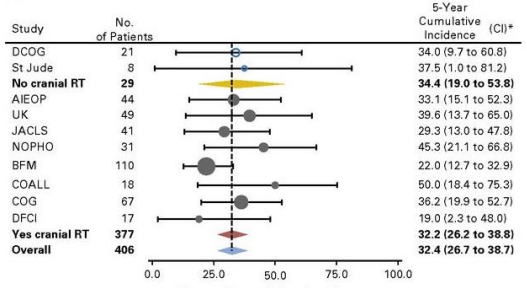
- COG now limits CRT to CNS3
- Several groups omit it completely (eg, St Jude)



Isolated CNS relapse by 5 years



Any CNS relapse



Any event

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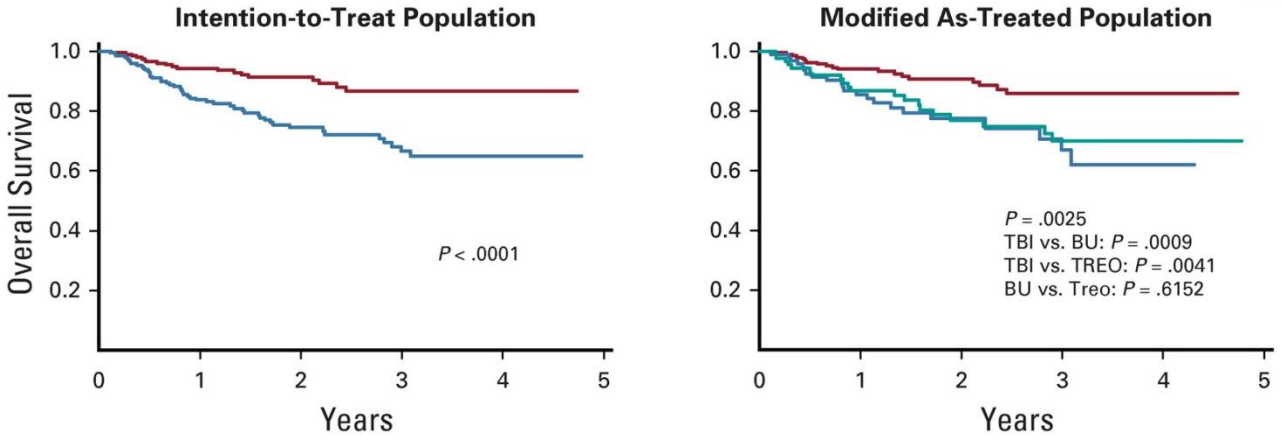
Vora A, et al. *J Clin Oncol.* 2016;34(9):919-926.

FORUM Study: Optimal Conditioning in ALL HSCT

TBI-Etoposide vs Flu-Thiotepa-Bu or Treo



Total body irradiation + etoposide recommended for children aged >4 years undergoing HSCT for high-risk ALL

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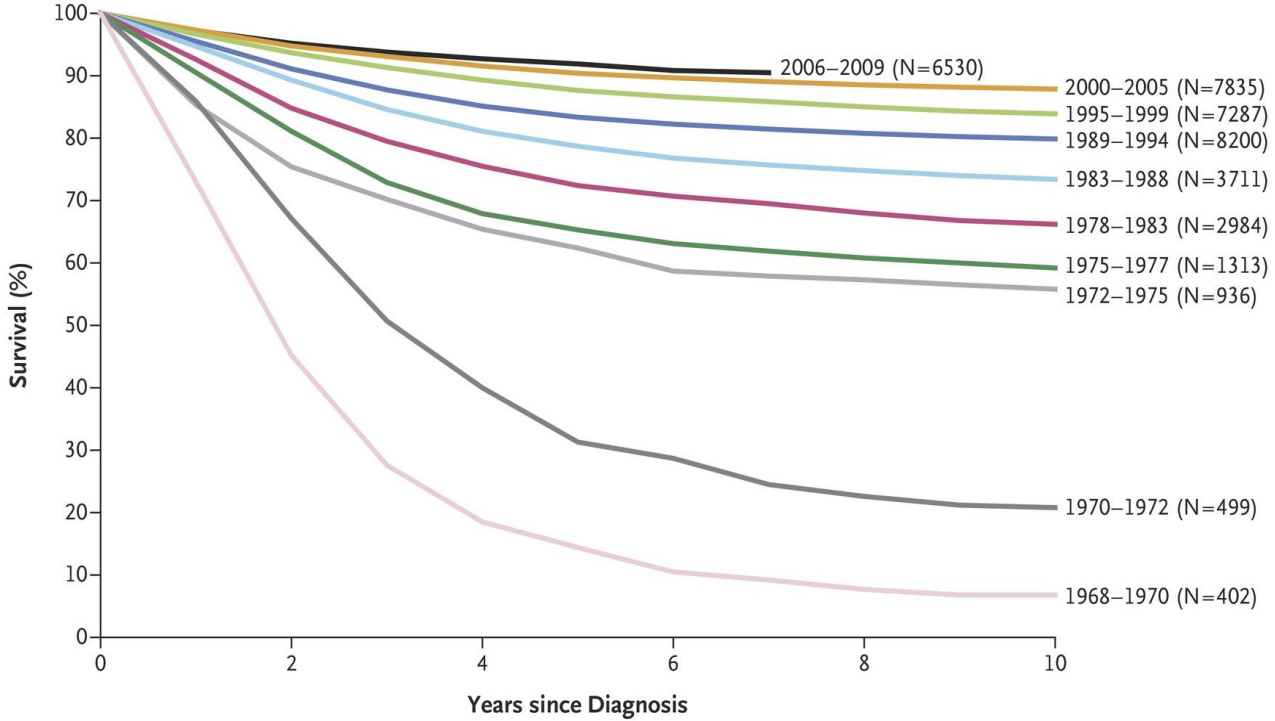
Peters C, et al. *J Clin Oncol*. 2021;39(4):295-307.

Improvements in Survival Are Now Plateauing

So We Need More-Effective, Less-Toxic Therapies



Relapse

Cost of cure

Acute toxicity
Late effects
Psychosocial

Global Leukemia Academy

Hunger SP, Mullighan CG. N *Engl J Med.* 2015;373(16):1541-1552.

Further Improvement in Survival and Toxicity in ALL

More sophisticated
Risk Stratification

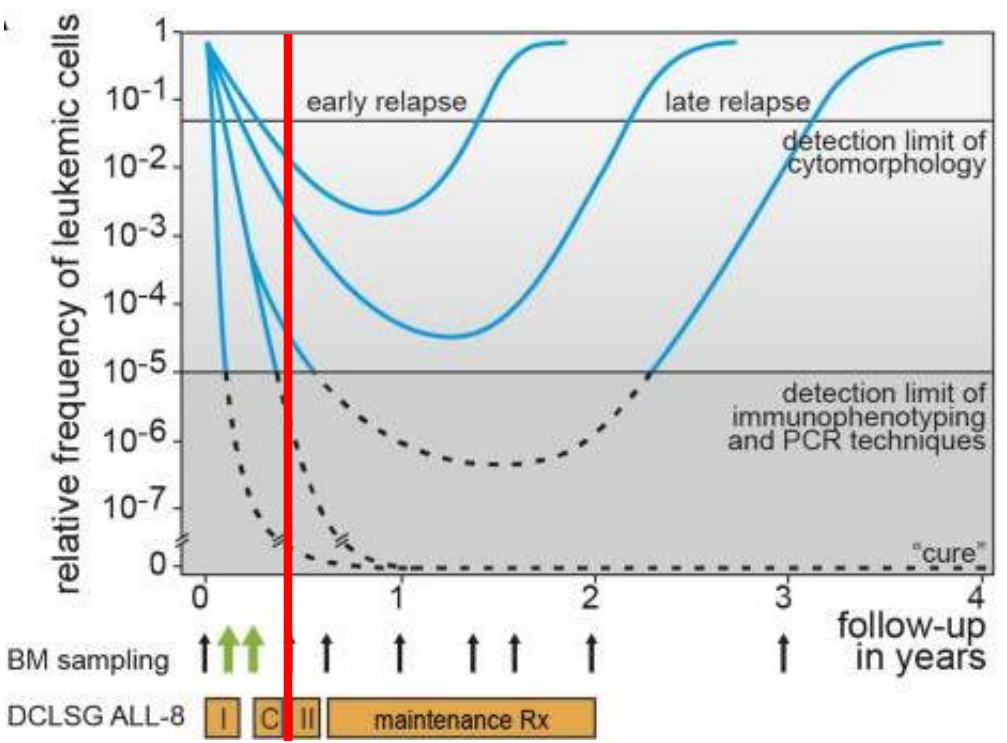
Frontline use of
Immunotherapies

Targeted therapies
based on improved
Understanding of Biology

Optimizing current drugs and pharmacogenomics

Minimal Residual Disease

Low-Level Leukemia Not Detectable by Cytomorphology



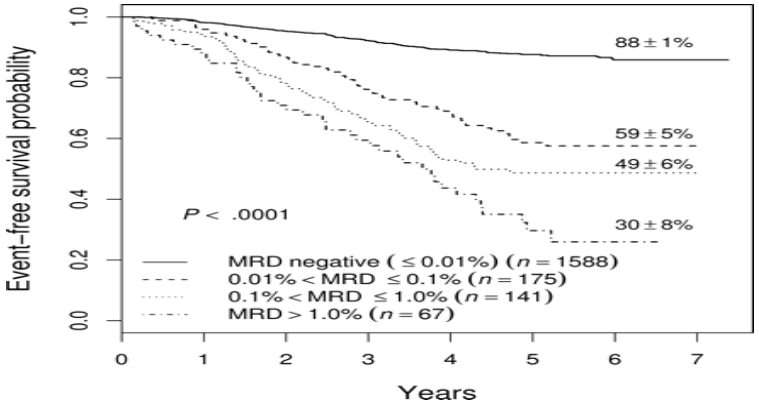
Flow cytometry

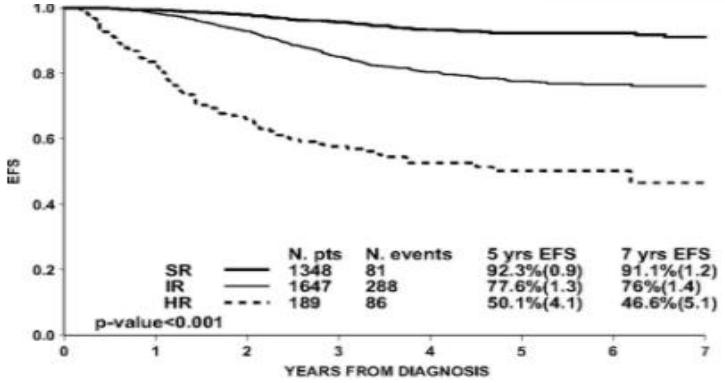
- "Leukemia-associated immunophenotype"
- Sensitivity 10^{-4} (6–8 colors)
- Readily available

IgH/TCR PCR

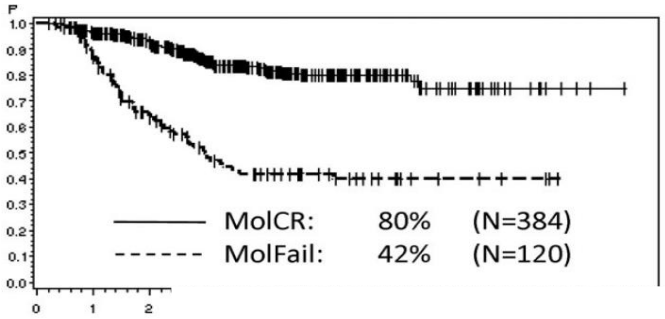
- Leukemia-associated gene rearrangements
- Sensitivity 10^{-4}–10^{-5}
- Centralized to specialized labs

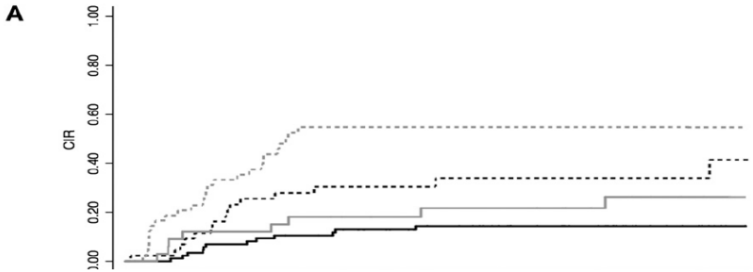
End of Induction MRD Is a Powerful and Independent Predictor of Outcome in ALL





COG: Borowitz MJ, et al. *Blood.* 2008;111(12):5477-5485. **BFM:** Conter V, et al. *Blood.* 2010;115(16):3206-3214.





GMALL: Gökbuget N, et al. *Blood.* 2012;120(9):1868-1876.

GRAALL: Beldjord K, et al. *Blood.* 2014;123(24):3739-3749.

Academy

High-Throughput Sequencing (NGS) MRD

- Targets same leukemic clone-specific *IGH* and *TCR* gene rearrangements as PCR MRD
- Rapid, parallel sequencing with consensus primers

Sensitivity	Strengths	Weaknesses
10^{-5}–10^{-7}	Very sensitive Fast Potential to track small subclones and clonal evolution Identifies precise breakpoints Applicable for >95% of cases	Not yet standardized (although very feasible) Large number of cells/DNA needed (problem in aplastic sample post-Rx; overamplification of rare nonmalignant rearrangements) Requires complex bioinformatics Minimal clinical validation Requires access to pretreatment samples Expensive

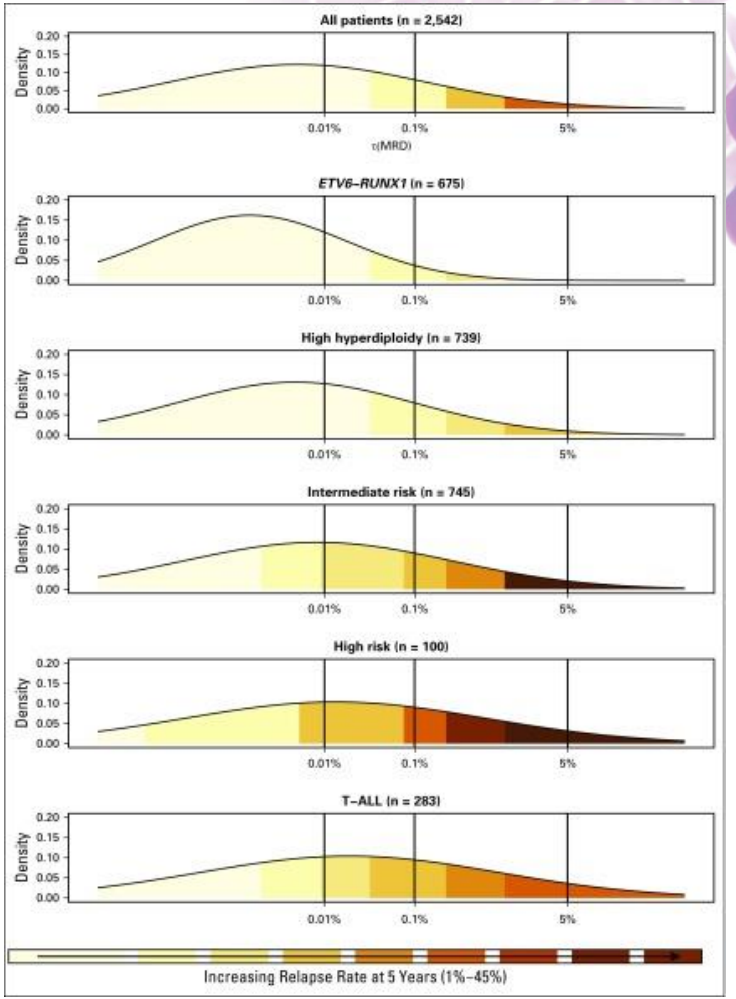
High-Throughput Sequencing (NGS) MRD

- In flow "MRD-neg" patients, HTS distinguished MRD neg from those with MRD 10^{-4}–10^{-6}
- HTS MRD neg at EOI in AALL0331 and AALL0232 had **98.1% DFS**
- Identifies low-risk group suitable for less-intensive Rx

Sensitivity	Strengths	Weaknesses
10^{-5}–10^{-7}	Very sensitive Fast Potential to track small subclones and clonal evolution Identifies precise breakpoints Applicable for >95% of cases	Not yet standardized (although very feasible) Large number of cells/DNA needed (problem in aplastic sample post-Rx; overamplification of rare nonmalignant rearrangements) Requires complex bioinformatics Minimal clinical validation Requires access to pretreatment samples Expensive

Genotype-Specific MRD Interpretation Improves Stratification in Pediatric ALL

- UKALL2003, N = 3113
- Examined MRD within genetic subgroups
- In each group, MRD correlated with relapse risk, *but* absolute relapse rate that was associated with a specific MRD value or category varied significantly by genetic subtype
- Future algorithms should incorporate **genotype-specific MRD thresholds** rather than a single cut-off



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O'Connor D, et al. *J Clin Oncol*. 2017;36(1):34-43.

Further Improvement in Survival and Toxicity in ALL

More sophisticated
Risk Stratification

Frontline use of
Immunotherapies

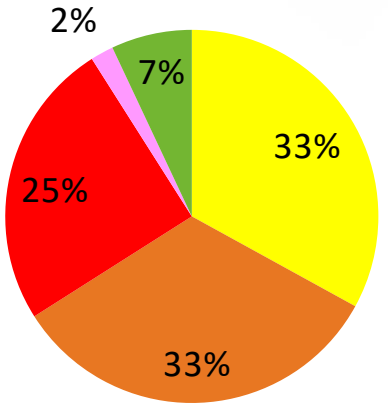
Targeted therapies
based on improved
Understanding of Biology

Optimizing current drugs and pharmacogenomics

Frontline Use of Immuno- or Molecular Therapies

Children's Oncology Group Strategy

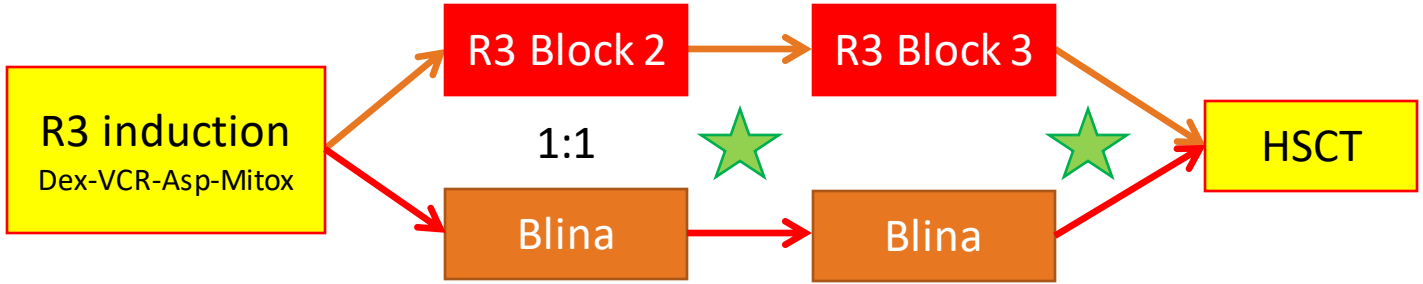
Risk Group	Projected 5-yr DFS	Protocol	Therapeutic Question
SR-favorable	>95%	AALL1731	Standard therapy with 2-year duration for both boys and girls
HR-favorable	>94%	AALL1732	
SR-Av and high	~89%	AALL1731	Blinatumomab
High risk	~80%	AALL1732	Inotuzumab
Very-high risk	<50%	AALL1721	CAR T cells in CR1
Ph+, Ph-like	60-85%	AALL1631 AALL1521 AALL1131	Molecularly targeted therapy (dasatinib or ruxolitinib in Ph-like)



Global Leukemia Academy

These indications are not approved in Australia outside clinical trials.

Blinatumomab vs Chemo in First Relapse
COG AALL1331: HR/IR



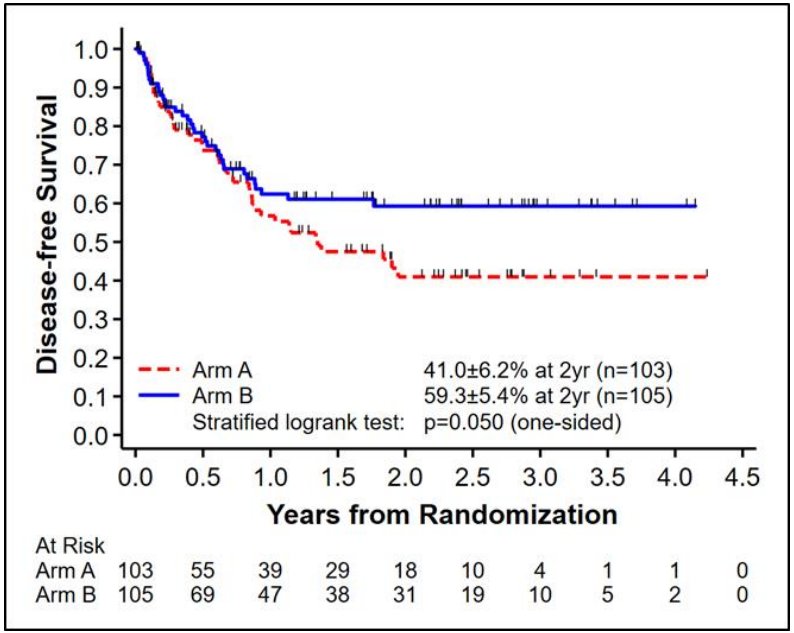
Arm A: UKALL R3
Block 2: Vinc-Dex (wk 1), ID MTX-PEG-Asp (wk 2); Cyclo-Etop (wk 3); IT MTX or ITT
Block 3: Vinc-Dex (wk 1), HD-Ara-C-Erwinia (wk 1, 2); ID MTX-Erwinia (wk 4); IT MTX or ITT

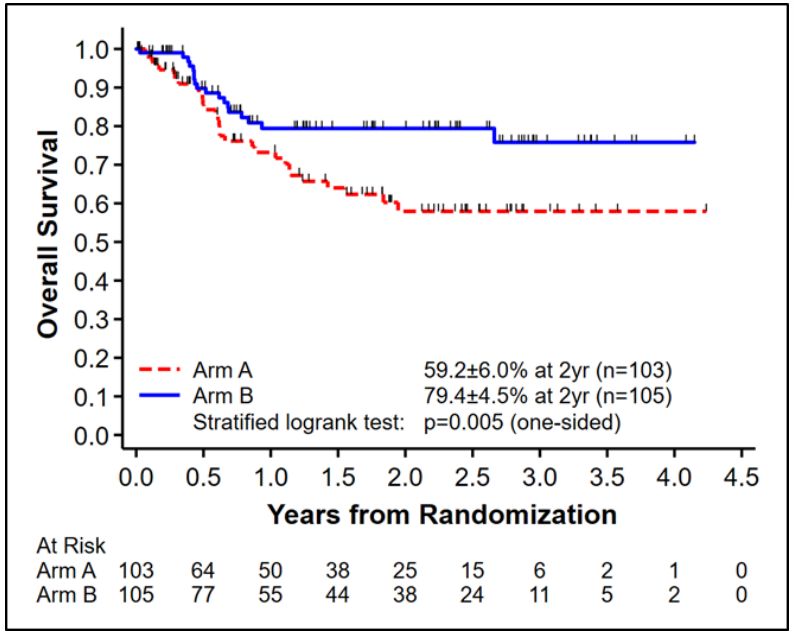
Arm B: Blinatumomab
Cycle 1 and 2: 15 ug/m^2/day × 28 days, then 7 days off

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

Blinatumomab vs Chemo in First Relapse

COG AALL1331: HR/IR



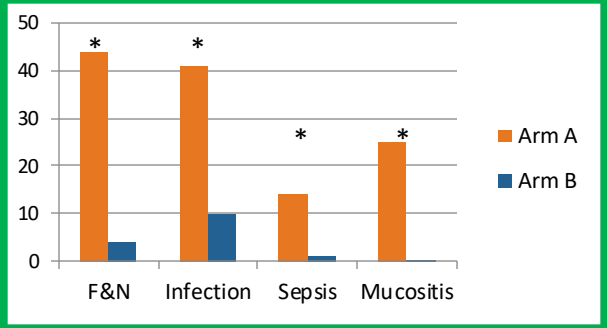


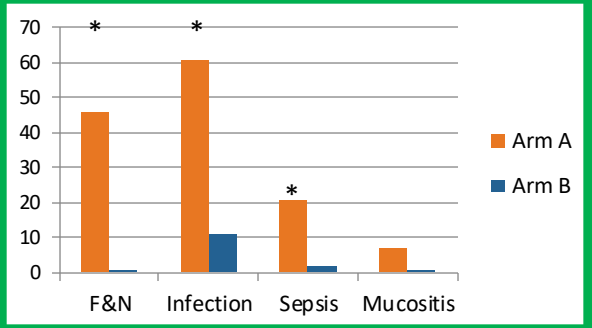
Brown PA, et al. *JAMA*. 2021;325(9):833-842.

Blinatumomab vs Chemo in First Relapse

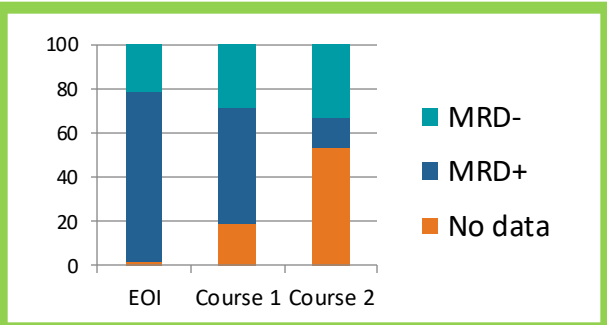
COG AALL1331: HR/IR

Blinatumomab **tolerated** better
(**P* <.001)

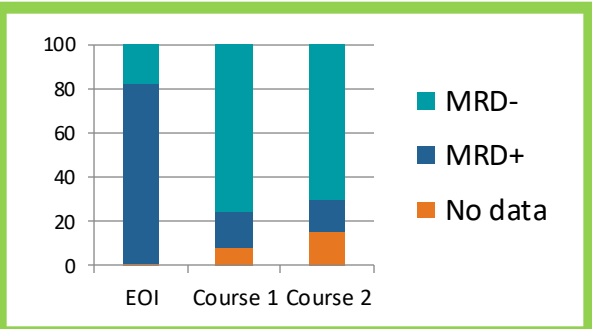




Blinatumomab **cleared MRD** better



Arm A: Chemo



Arm B: Blinatumomab

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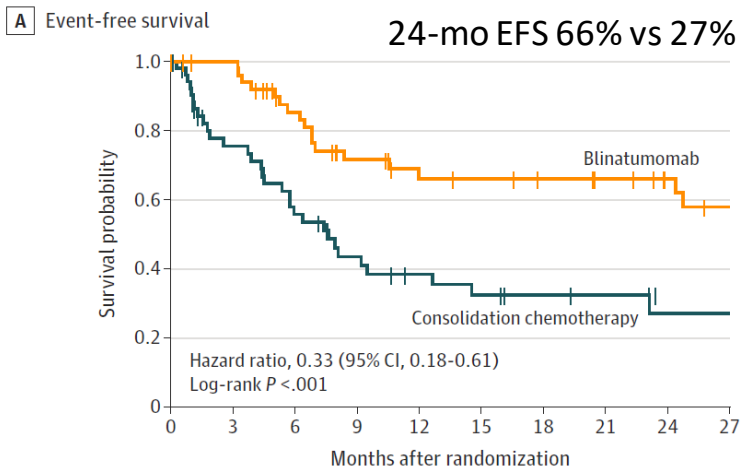
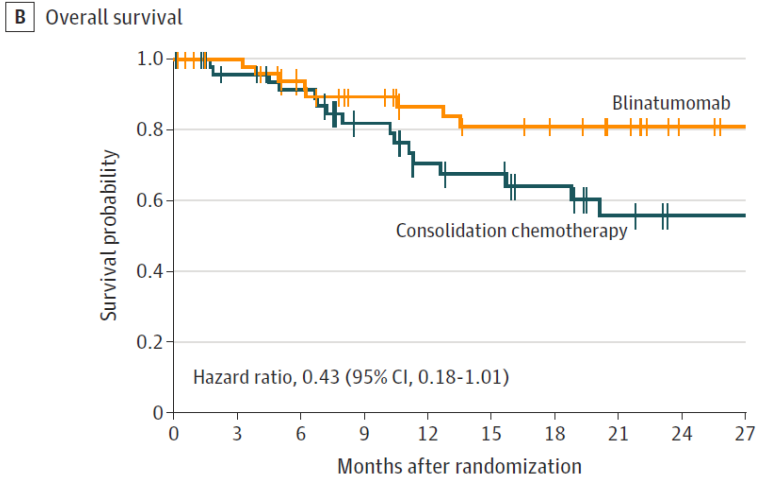
Brown PA, et al. *JAMA*. 2021;325(9):833-842.

IntReALL HR 2010

Blinatumomab vs HR Blocks as Postinduction Therapy



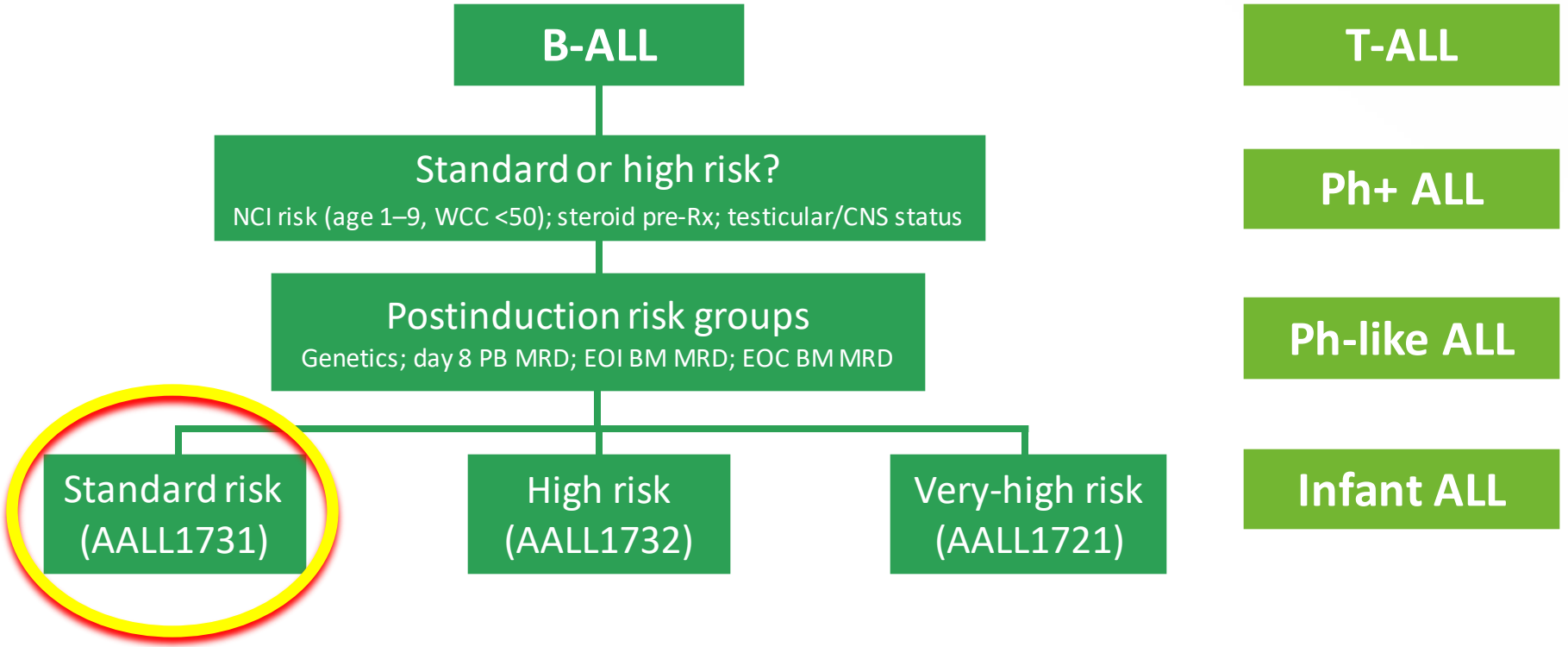


Better MRD response ($<10^{-4}$) with blinatumomab: 90% vs 54%
Subgroup with MRD $>10^{-4}$ at baseline converting to MRD $<10^{-4}$: 93% vs 24%
Less SAEs with blinatumomab: 24% vs 43%

Global Leukemia Academy

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

Children's Oncology Group Approach



AALL1731

A Phase III Trial Investigating Blinatumomab in Combination With Chemotherapy in Patients With Newly Diagnosed Standard-Risk or Down Syndrome B-ALL and the Treatment of Patients With Localized B-LLy

Risk Group	Therapeutic Question
SR-Fav and SR-Av^{HTSneg}	Will standard therapy with **2.25-year** duration for **both boys and girls** maintain DFS >93%?
SR-Av^{HTSpos}	Will randomized addition of 2× **blinatumomab** cycles to standard therapy improve DFS?
SR-High	Will randomized addition of 2× **blinatumomab** cycles to **augmented BFM** improve DFS?*

Global Leukemia Academy

*Nonrandom assignment to blina if EOC MRD >0.1%.

AALL1731

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SR-High	Will randomized addition of 2× **blinatumomab** cycles to **augmented BFM** improve DFS?*

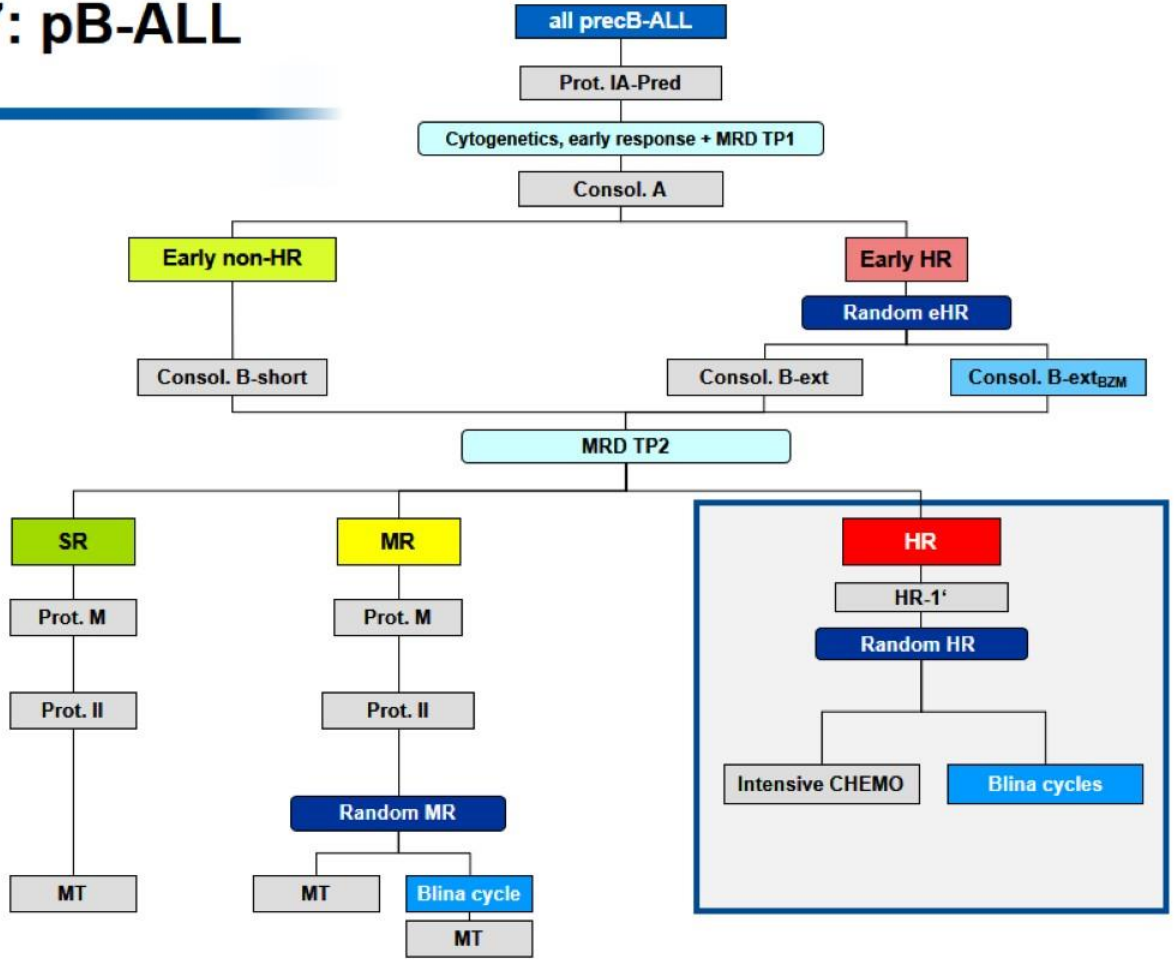
- **DNA-based MRD:** high-throughput sequencing of IgH
- **Genotype-specific threshold for EOI MRD**
  - 0.1% for double trisomy (+4, +10) vs 0.01% for all others
- **Down syndrome** included
  - DS-SR-High: nonrandomly assigned to blina on a less-toxic chemo backbone
- **B-lymphoblastic lymphoma**: Murphy stage I/II treated with COG standard therapy (no blina)
  - CNS 2/3 not eligible (treated on AALL1732)

*Nonrandom assignment to blina if EOC MRD >0.1%.

AIEOP-BFM ALL 2017: pB-ALL

Overview of treatment

- Randomized study of blinatumomab vs intensive chemotherapy in HR group
- Incorporates **“IKZF1+”** into risk stratification



Blinatumomab is not licensed for frontline use in paediatric ALL.

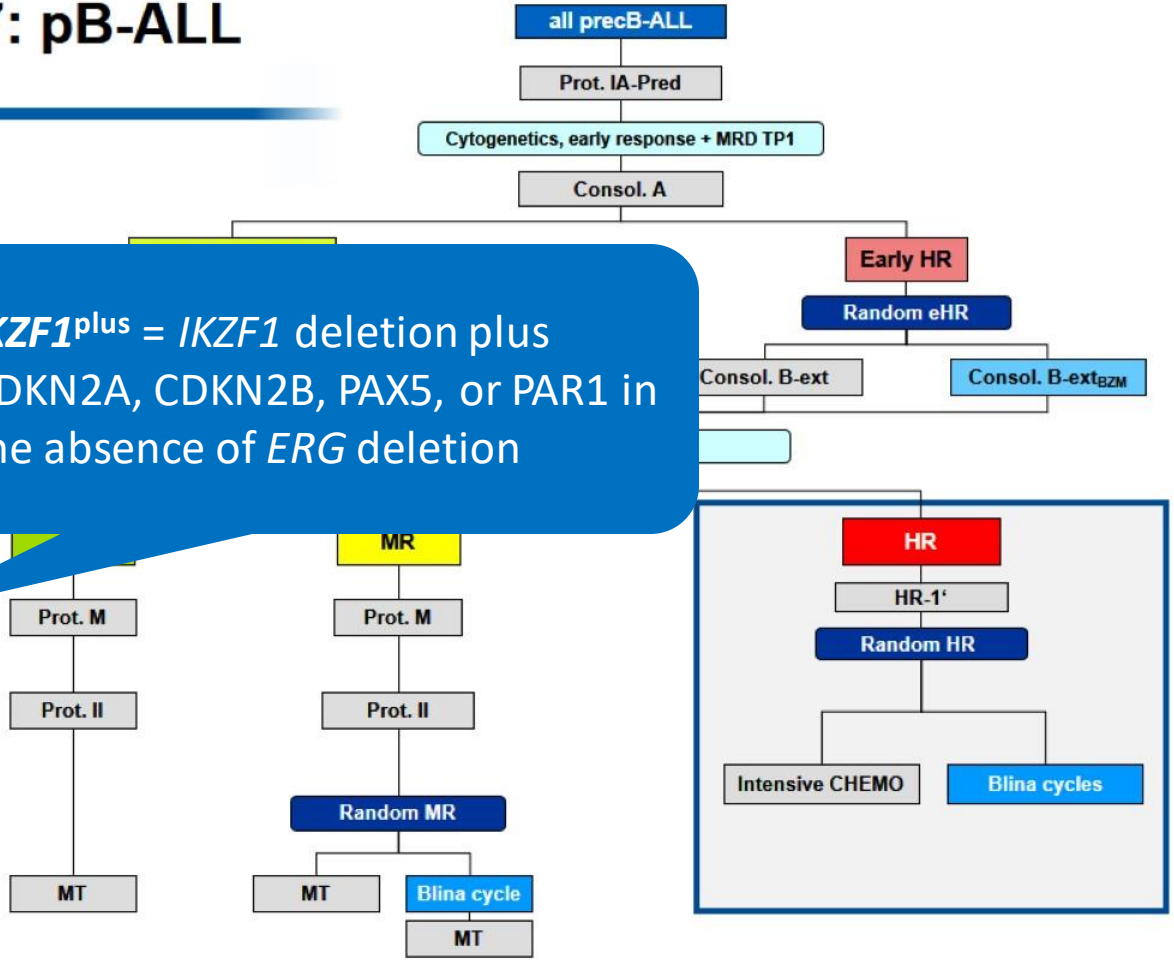
These indications are not approved in Australia outside clinical trials.

AIEOP-BFM ALL 2017: pB-ALL

Overview of treatment

- Randomized study of blinatumomab vs intensive chemotherapy in HR group
- Incorporates **"IKZF1+"** into risk stratification

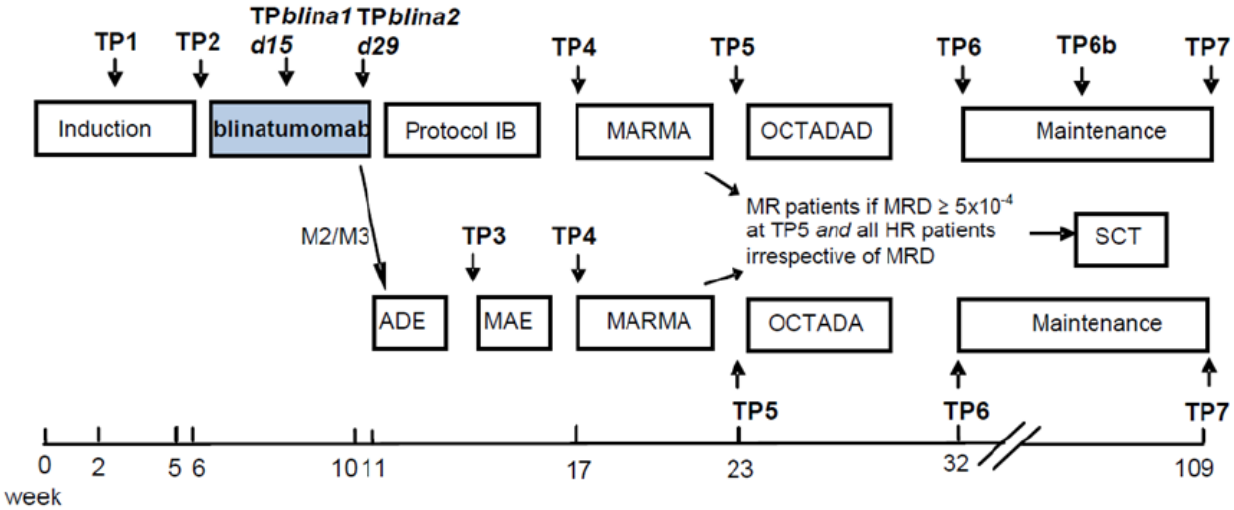
***IKZF1*^{plus}** = *IKZF1* deletion plus CDKN2A, CDKN2B, PAX5, or PAR1 in the absence of *ERG* deletion



Blinatumomab is not licensed for frontline use in paediatric ALL.

These indications are not approved in Australia outside clinical trials.

A Pilot Study to Test the Feasibility, Safety, and Efficacy of the Addition of the BiTE Antibody Blinatumomab to the Interfant-06 Backbone in Infants With MLL-Rearranged ALL

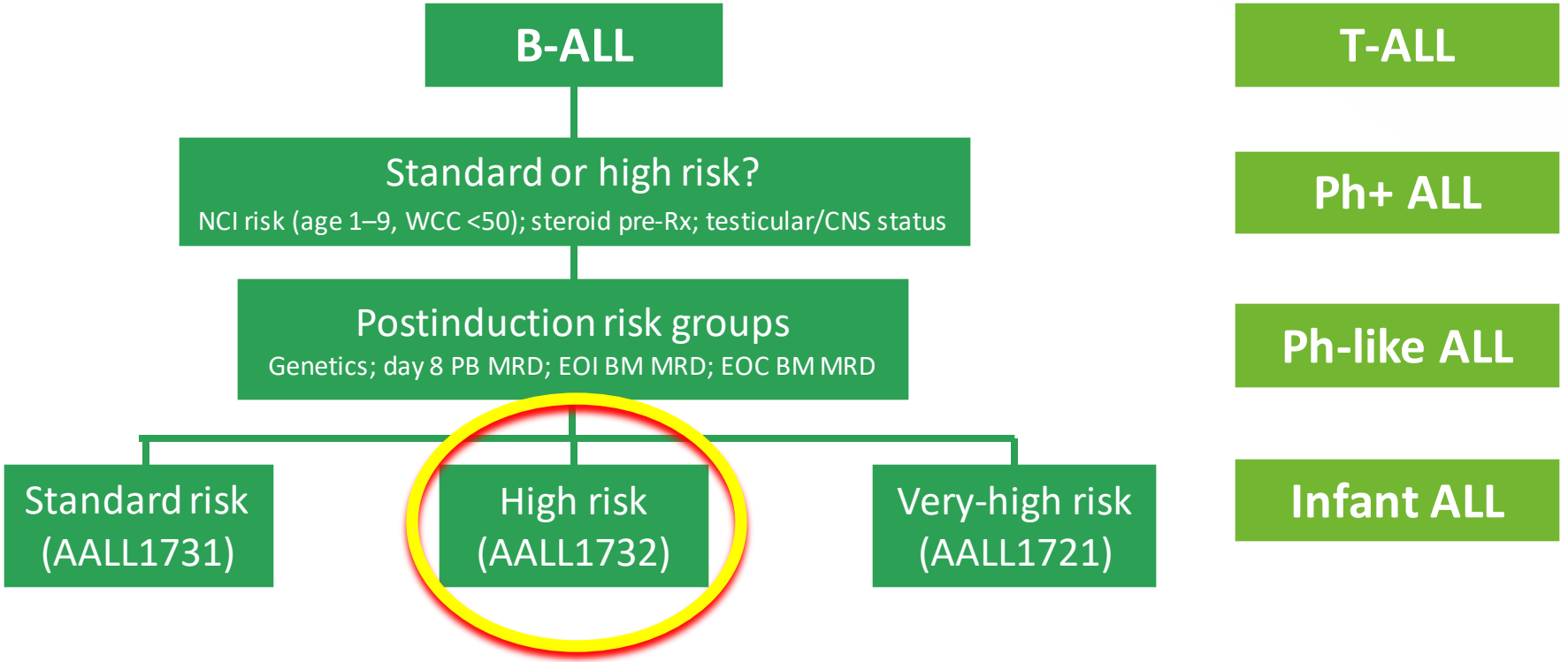


1-year **EFS 90%** (vs 55% in Interfant-06)
1-year **OS 93%** (vs 70% in Interfant-06)

Global Leukemia Academy

Van der Sluis I, et al. ASH 2021. Abstract 361.

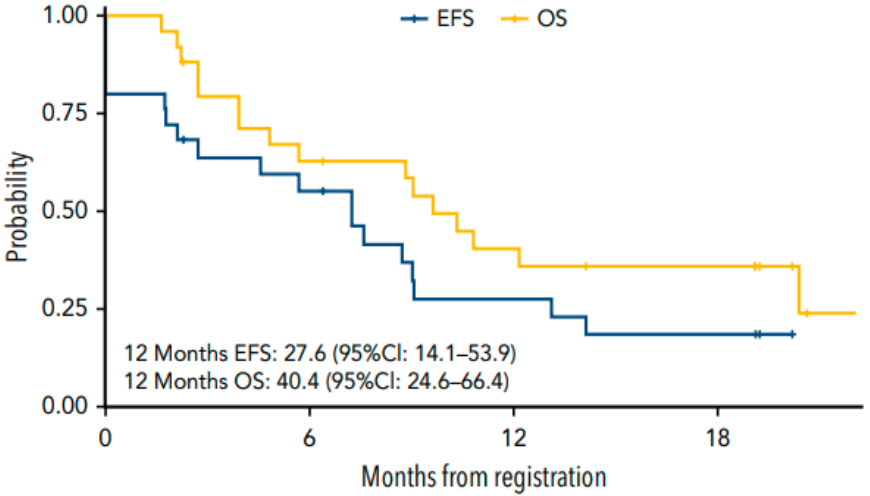
Children's Oncology Group Approach



A Phase I Study of Inotuzumab Ozogamicin in Pediatric Relapsed/Refractory Acute Lymphoblastic Leukemia ITCC-059: Brivio E, Locatelli F, Lopez-Yurda M, et al

- 25 children with multiple R/R ALL
- CR in 80%
  - 75% with 1.4 mg/m^2
  - 85% with 1.8 mg/m^2
- 84% of responders MRD negative
- 12-mo OS 40%

- No SOS during Ino, but 2 in subsequent Rx
- Better tolerated than conventional chemo
  - Fever 64%, ↓plts 60%, ↓neutrophils 56%, anemia 44%
  - Hepatic (grade 3–4): ↑ bilirubin 12%, transaminitis ~20%



Global Leukemia Academy

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

AALL1732

A Phase III Randomized Trial of Inotuzumab Ozogamicin for Newly Diagnosed High-Risk B-ALL; Risk-Adapted Postinduction Therapy for High-Risk B-ALL, MPAL, and Disseminated B-LLy

Risk Group	Therapeutic Question
HR-favorable	No randomization. Modified BFM with 2.25-year duration for males and females
High risk	Will randomized addition of 2× **inotuzumab** cycles to mBFM therapy improve DFS?
MPAL, BLLy (stage III/IV)	No randomization. mBFM with 2× interim maintenance (HDMTX then Capizzi) in MPAL

AALL1732

A Phase III Randomized Trial of Inotuzumab Ozogamicin for Newly Diagnosed High-Risk B-ALL; Risk-Adapted Postinduction Therapy for High-Risk B-ALL, MPAL, and Disseminated B-LLy

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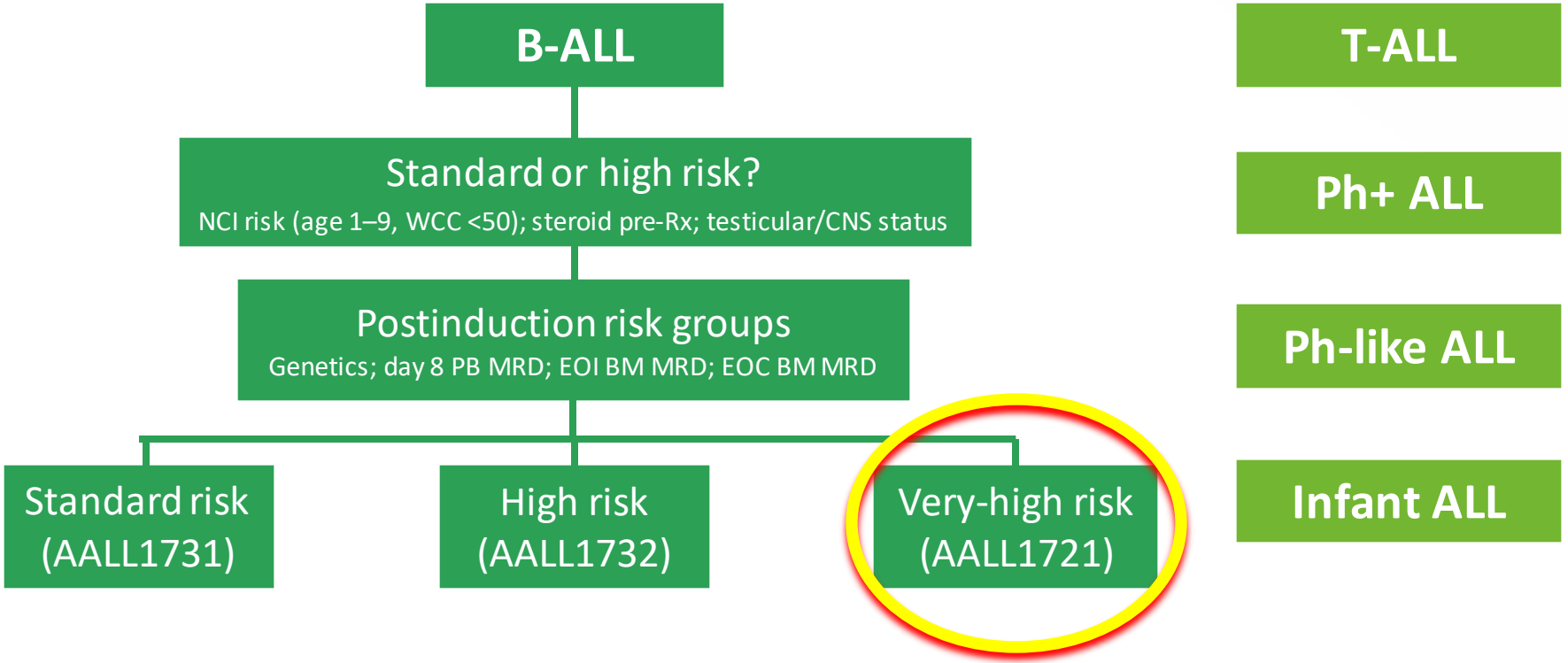
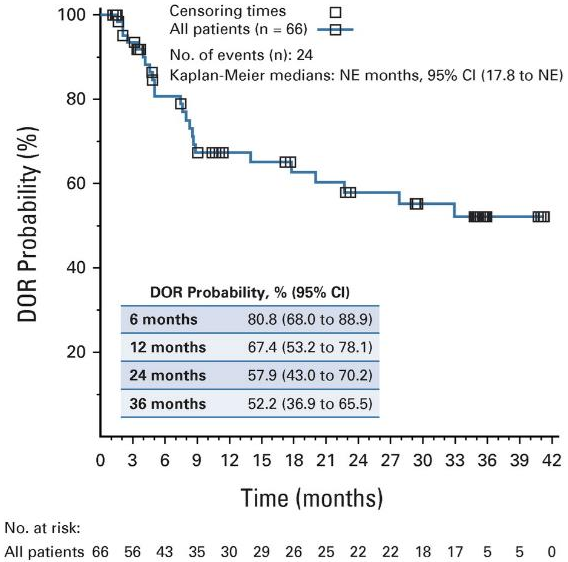
High risk	Will randomized addition of 2× **inotuzumab** cycles to mBFM therapy improve DFS?
MPAL, BLLy (stage III/IV)	No randomization. mBFM with 2× interim maintenance (HDMTX then Capizzi) in MPAL

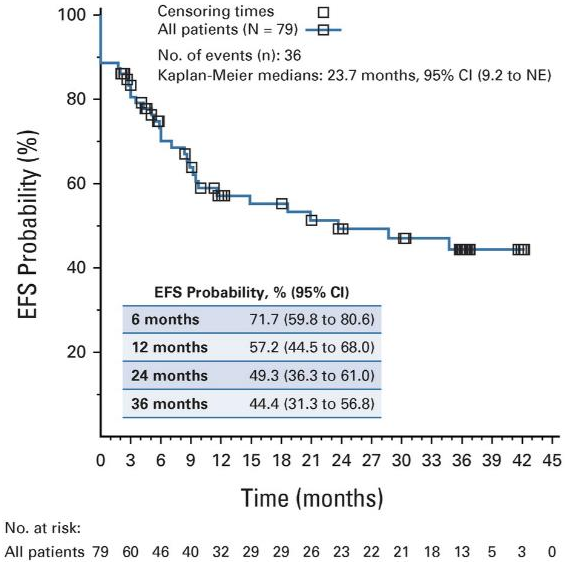
- **InO**
  - Documentation of CD22 expression required for InO randomization
- **MPAL** included
  - No previous frontline MPAL studies. Aim is to establish EFS in a prospective study of ALL-based therapy
- **Intensive interventions to improve adherence to 6-MP in AYA**
  - ACCL1033: Multimedia education, web-based scheduling, text message reminder
  - Intervention package vs intensified IP (real-time feedback) vs patient/parent-established IP

Children's Oncology Group Approach



3-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory ALL in the ELIANA Trial





113 screened
↓
97 enrolled
↓
79 infused
↓
65 CR/CRi (82%)
↓
64 MRD– in 3 mo

Median duration of response not reached
36-mo EFS 44%, OS 63%

Global Leukemia Academy

Laetsch TW, et al. *J Clin Oncol.* 2022. Online ahead of print.

AALL1721/Novartis CCTL019G2201J

A Phase II Trial of Tisagenlecleucel in First-Line High-Risk (HR) Pediatric and Young Adult Patients With B-ALL Who Are MRD Positive at the End of Consolidation (EOC) Therapy

Risk Group	Therapeutic Question
VHR (MRD ≥0.01% at EOC)	Efficacy of tisagenlecleucel as measured by 5-year DFS

AALL1721/Novartis CCTL019G2201J

A Phase II Trial of Tisagenlecleucel in First-Line High-Risk (HR) Pediatric and Young Adult Patients With B-ALL Who Are MRD Positive at the End of Consolidation (EOC) Therapy

39% 5-yr DFS in AALL0232

Risk Group	Therapeutic Question
VHR (MRD ≥0.01% at EOC)	Efficacy of tisagenlecleucel as measured by 5-year DFS

AALL1721/Novartis CCTL019G2201J

A Phase II Trial of Tisagenlecleucel in First-Line High-Risk (HR) Pediatric and Young Adult Patients With B-ALL Who Are MRD Positive at the End of Consolidation (EOC) Therapy

39% 5-yr DFS in AALL0232

Risk Group	Therapeutic Question
VHR (MRD ≥0.01% at EOC)	Efficacy of tisagenlecleucel as measured by 5-year DFS

- Also articulates with European ALLTogether first-line trial, DFCI 2016 (high risk), DCOG ALL-11, EORTC-CLG 58081 (variant 1), UKALL2011
  - Not available in Australia/New Zealand
- Interim maintenance with HDMTX during manufacture
- No stem cell transplant
- Second dose for patients whose B-cell aplasia recovers in <6 months
- Exclusions include M2/M3 at EOC, hypodiploid, Ph+, prior TKI, prior anti-CD19 Rx, etc

Further Improvement in Survival and Toxicity in ALL

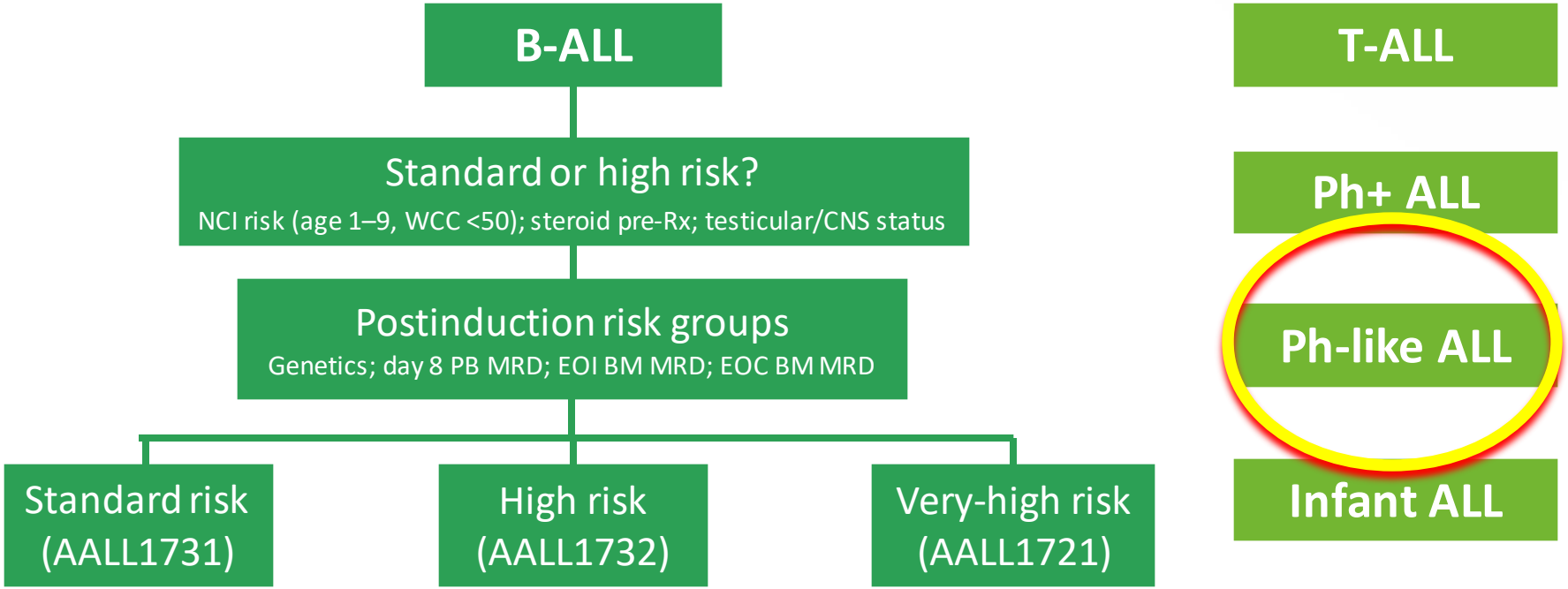
More sophisticated
Risk Stratification

Frontline use of
Immunotherapies

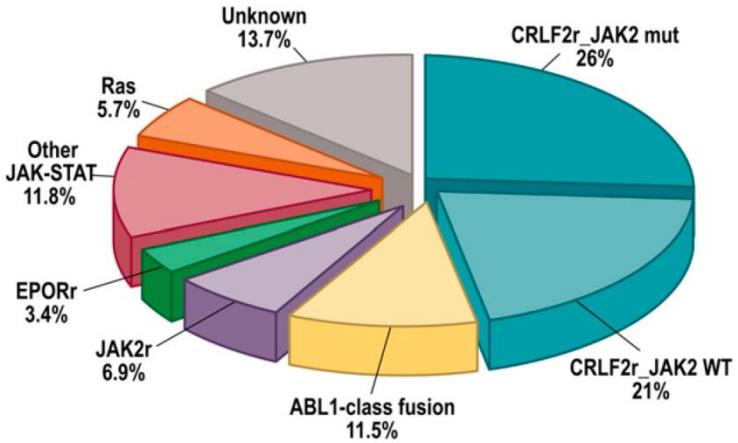
Targeted therapies
based on improved
Understanding of Biology

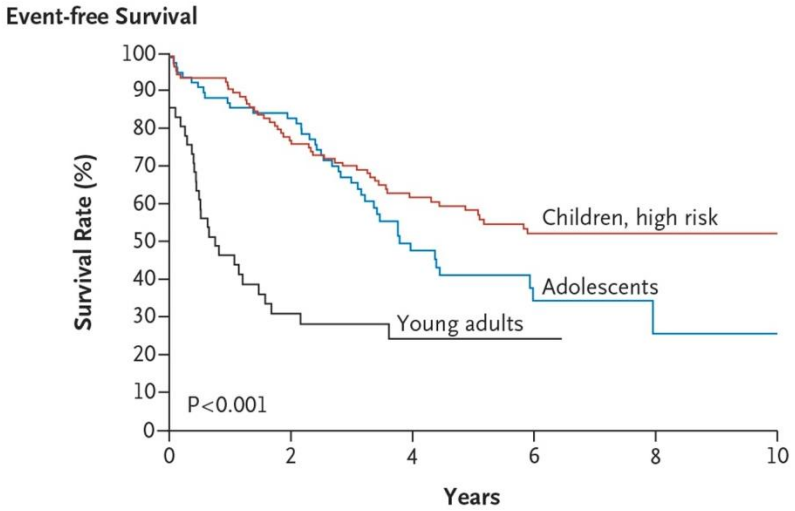
Optimizing current drugs and pharmacogenomics

Children's Oncology Group Approach



Ph-like ALL





- Gene expression profile similar to Ph+ ALL
- Alterations in B-lymphoid transcription factor genes
  → Dysregulation of cytokine receptor and tyrosine kinase signaling
- Worse prognosis
- **Case reports of response to dasatinib and speculation about other small molecules**

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Roberts KG, et al. *N Engl J Med.* 2014;371(11):1005-1015; Weston et al. *J Clin Oncol.* 2014.

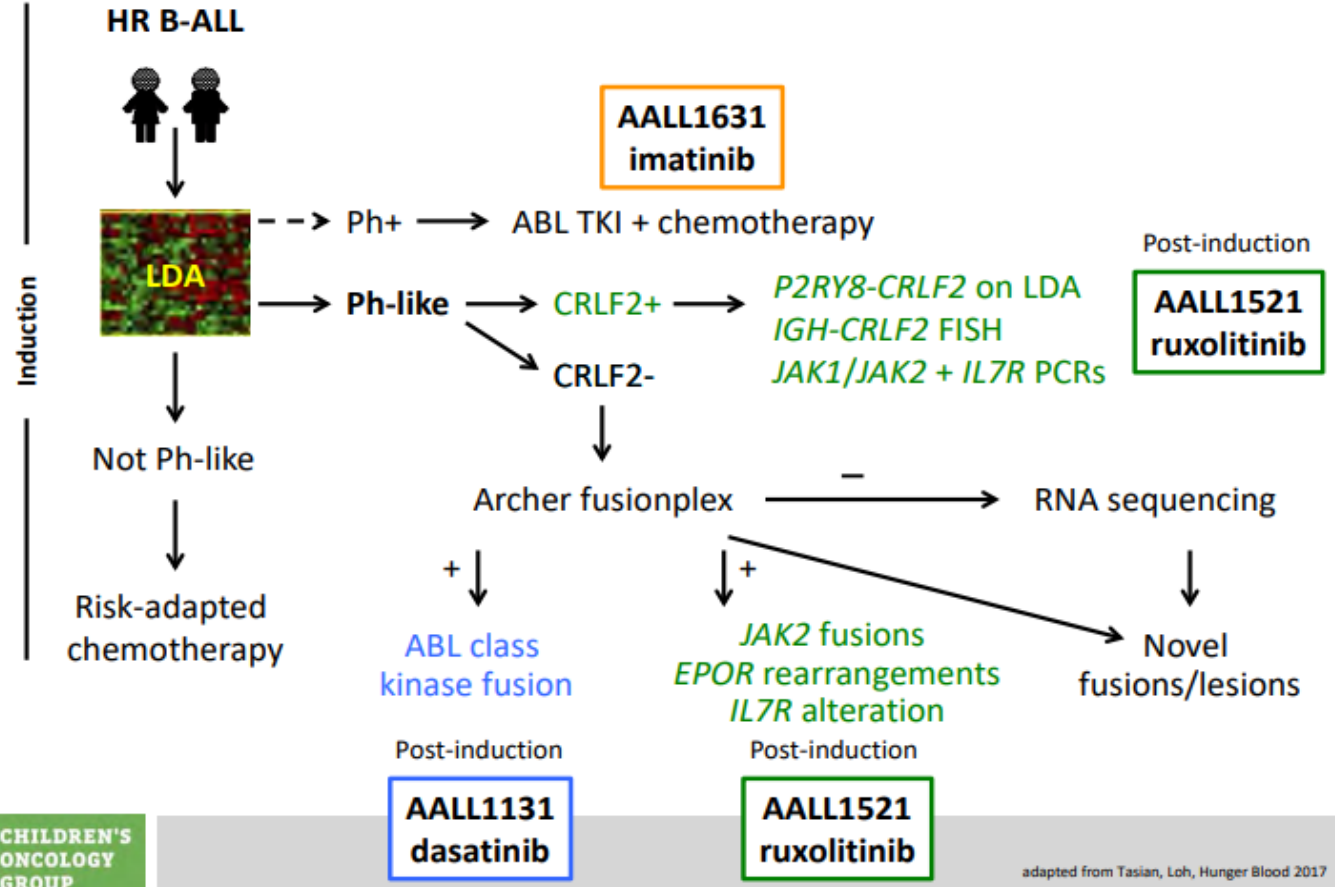
AALL1131 (closed Aug 9, 2019)

A Phase III Randomized Trial for Newly Diagnosed High-Risk B-ALL Including a Stratum Evaluating Dasatinib in Patients With Ph-like Tyrosine Kinase Inhibitor-Sensitive Mutations

Risk Group	Therapeutic Question
HR and VHR: Ph-like with predicted TKI-sensitive mutation	To describe the results of nonrandomized postinduction treatment with dasatinib on a MBFM-IMHDM backbone

> Identified by LDA card and targeted RNA-seq

Ph-like ALL Genetic Stratification for Trials



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WE STRONGLY ENCOURAGE SUBMISSION OF APEC14B1 SPECIMENS FOR PH-LIKE ALL TESTING, WHICH MUST BE REQUESTED WITHIN 72H OF SAMPLE SUBMISSION.

AALL1521

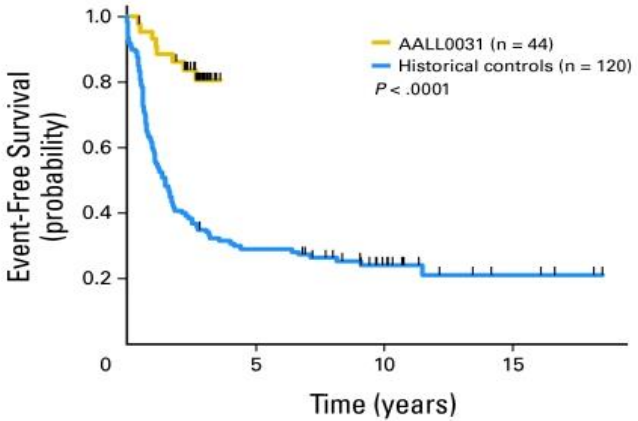
A Phase II Study of the JAK1/JAK2 Inhibitor Ruxolitinib With Chemotherapy in Children With De Novo High-Risk *CRLF2*-Rearranged and/or *JAK* Pathway-Mutant ALL

Risk Group	Therapeutic Question
HR/VHR with *CRLF2* rearrangement and/or *JAK*-mutant	**Part 1 (pilot/safety phase)** Evaluate safety and tolerability and define RP2D of ruxolitinib in combination with multiagent chemotherapy in children and AYAs with newly diagnosed high-risk *JAK* pathway-mutant Ph-like B-ALL **Part 2 (efficacy phase)** Determine the efficacy of ruxolitinib + chemotherapy in children and AYAs with newly diagnosed high-risk *JAK* pathway-mutant Ph-like B-ALL

- Dose of ruxolitinib 50 mg/m^2 BID × 14 days on/14 days off was selected for part 2
- Treatment responses may differ across subgroups, so are stratified into cohorts
  - A. *CRLF2*-R, *JAK1*- or *JAK2*-mutant and MRD ≥0.01%
  - B. *CRLF2*-R, *JAK1*- and *JAK2*-wild-type and MRD ≥0.01%
  - C. *JAK2* fusion, *EPOR* fusion, *SH2B3*-deleted, *IL7R*-mutant and MRD ≥0.01%
  - D. Any genomic lesion in cohorts A, B, C and MRD <0.01%

Ph+ ALL in Children

TKIs Have Decreased Need for Transplant, but Chemo Remains Toxic



- **AALL0331**: imatinib + intensive chemo
  - 5-yr EFS 70% with no benefit from HSCT
- **AALL0622**: dasatinib + intensive chemo
  - 5-yr EFS 61% (standard risk) and 67% (high risk); OS 87%–89%
  - Dasatinib no better than historical results with imatinib
  - *IKZF1* mutations prognostic
- **AALL1122**: dasatinib + EsPhALL chemo
  - 5-yr EFS 55%; OS 82%, ie, noninferior

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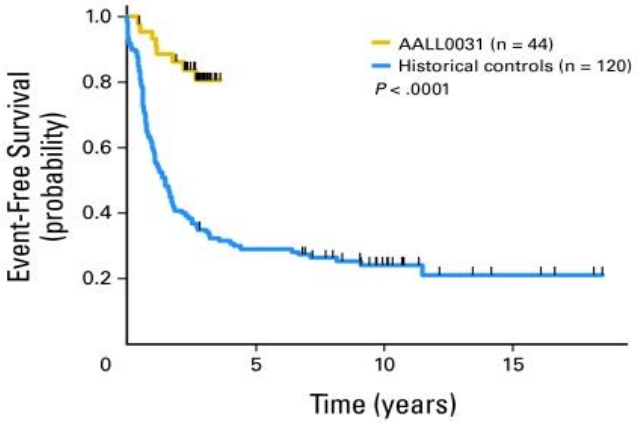

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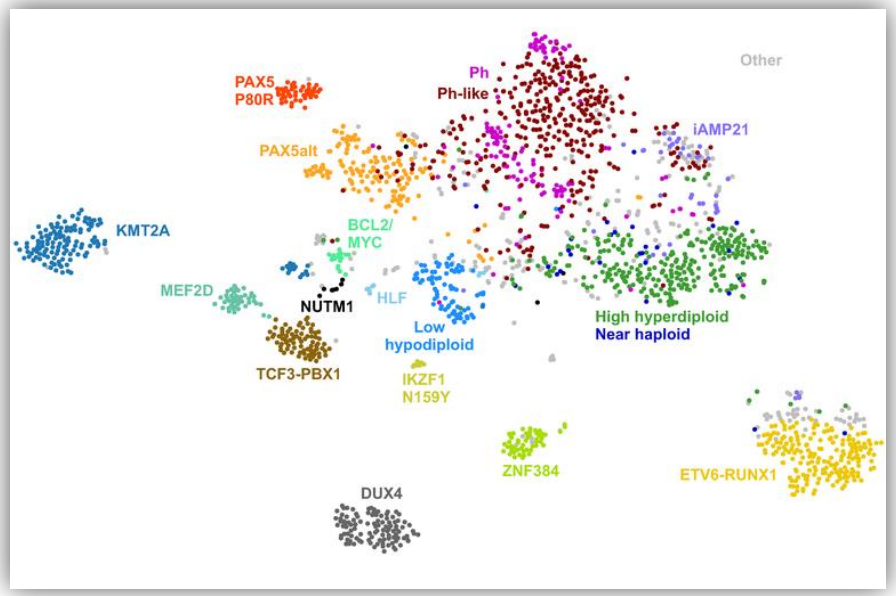
  - 5-yr EFS 55%; OS 82%, ie, noninferior

Study	Therapeutic Questions
AALL1631/EsPhALL	Can chemotherapy be further **de-intensified** in standard-risk patients? **MRD <5 × 10^{-4}** after block 2: randomized to **intensive** AALL1122 **vs less-intensive** BFM2000 **Posttransplant imatinib**
AALL1922	Phase I/II study of **ponatinib** in relapsed/refractory/intolerant Ph+ ALL

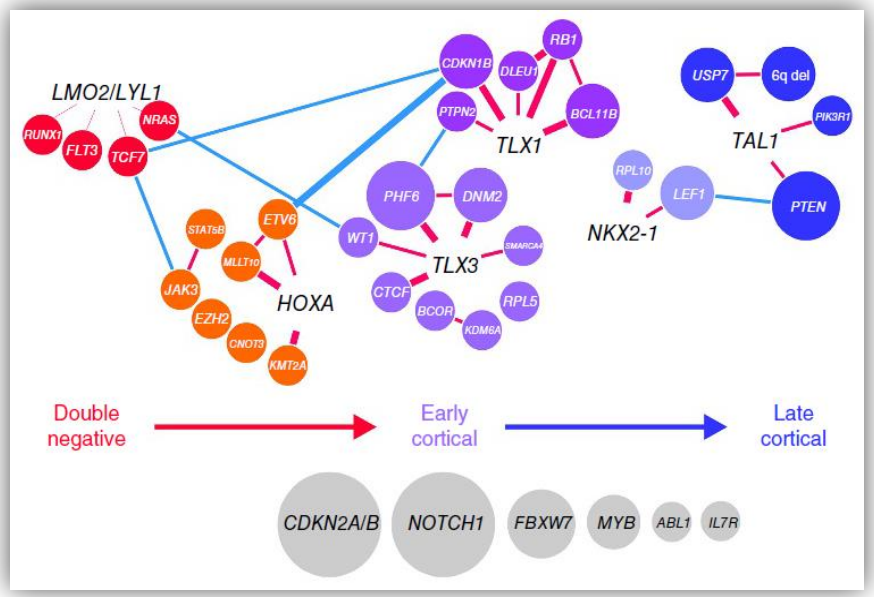
Genomics Has Improved Our Understanding of Molecular Biology

. . . and May Facilitate Precision Therapies for Specific Subgroups

B-ALL Genomic Landscape



T-ALL Genomic Landscape



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Gu Z, et al. *Nat Genet.* 2019;51(2):296-307; Liu Y, et al. *Nat Genet.* 2017;49(8):1211-1218.

Further Improvement in Survival and Toxicity in ALL

More sophisticated
Risk Stratification

Frontline use of
Immunotherapies

Targeted therapies
based on improved
Understanding of Biology

Optimizing current drugs and pharmacogenomics

Optimizing Current Drugs

Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions

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

- PEG-Asparaginase infusion reactions occur in 10%–30%
- Asp discontinuation worsens EFS (hazard ratio 1.5)
- Historical concern that premeds masked silent inactivation
- Trial of premed with anti-H1 and anti-H2
  - Low rate of silent inactivation
  - All completed doses yielded excellent SAA
  - Erwinia substitution in 7% (premeds) vs 17.2% (without)
  - Infusion reactions 5.9% vs 17.2%
  - Grade 4 infusion reactions 15% vs 0%
  - Cost savings US $12,402 per premedicated patient

Allopurinol use during pediatric acute lymphoblastic leukemia maintenance therapy safely corrects skewed 6-mercaptopurine metabolism, improving inadequate myelosuppression and reducing gastrointestinal toxicity

Cohen G, et al. *Pediatr Blood Cancer.* 2020;67(11):e28360.

- Inadequate myelosuppression in maintenance worsens EFS
- Skewed metabolism of 6MP to hepatotoxic 6MMP decreases levels of the antileukemic metabolic 6TGN
- Trial of allopurinol in inadequate myelosuppression/hepatotoxicity
  - ↓6MMP and ↑6TGN
  - ↓ hepatotoxicity and GI toxicity
  - ↑ time with neutrophils in target range (0.5–1.5 × 10^9/L)

AYAs With Cancer Have Complex Medical and Psychosocial Challenges

Which Impact Treatment Outcomes and Quality of Survivorship

Unique spectrum of tumors
- Worse outcome in some subtypes
- Unique biology

Lack of critical mass
Dispersed across several adult hospitals and pediatric hospitals

Complex psychosocial issues
- Marked developmental changes
- Social transitions
  - Education → employment
  - Peers and romantic relationships
  - Risk-taking behavior

Poor accrual to clinical trials
- Slows improvements in therapy
- Limits understanding of biology

12 of 13 Retrospective Studies Show Improved Outcomes for Adolescents Treated on Pediatric Protocols

	No of patients	Age Range	CR	EFS (5-years)	OS (5-years)
France					
FRALLE-93	77	15 – 20	94%	67%	78%
LALA-94	100		83%	41%	45%
USA				7 years	7 years
CCG	197	16 - 20	90%	63%	67%
CALGB	124		90%	34%	46%
Netherlands					
DCOG	47	15 - 18	98%	69%	79%
HOVON	44		91%	34%	38%
United Kingdom					
MRC ALL97	61	15 - 17	98%	65%	71%
UKALLXII/E2993	67		94%	49%	56%
Finland					
NOPHO	128	10 – 16	96%	67%	77%
Finnish Leuk Group	97	17 - 25	97%	60%	70%

Boissel, *JCO*, 2003; Stock, *Blood*, 2008; de Bont, *Leukemia*, 2004; Ramanujachar, *Ped Blood Can*, 2007; Usvasalo, *Hematologica*, 2008

Prospective Studies From UK, US, Spain, France, and Others Confirm That Pediatric Protocols Improve Outcomes in AYA ALL

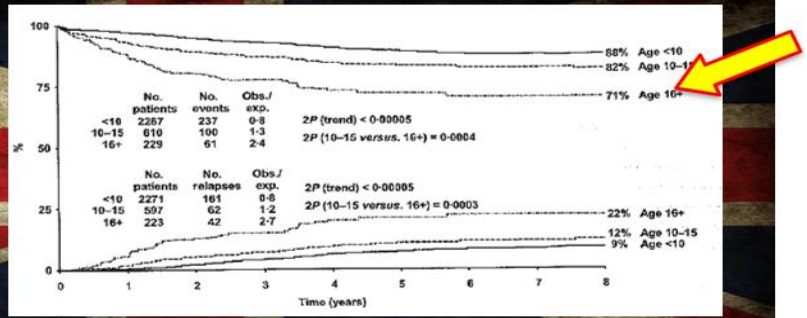
UKALL2003

N= 229 aged 16-24

5y EFS 72%

More high MRD in TYA

More toxicity in >10yo



C10403

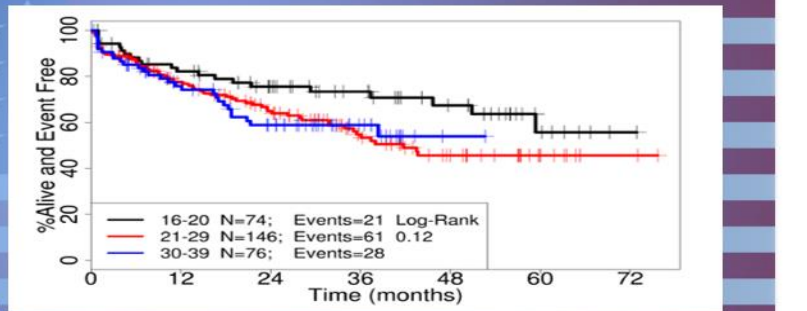
N= 296 aged 16-39

2y EFS 66%

Worse outcome if:

BMI >40

Ph-like / High CRLF2



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White VM, et al. *Pediatr Blood Cancer*. 2018;65(11):e27349; Muffly L, et al. *Cancer*. 2017;123(1):122-130.

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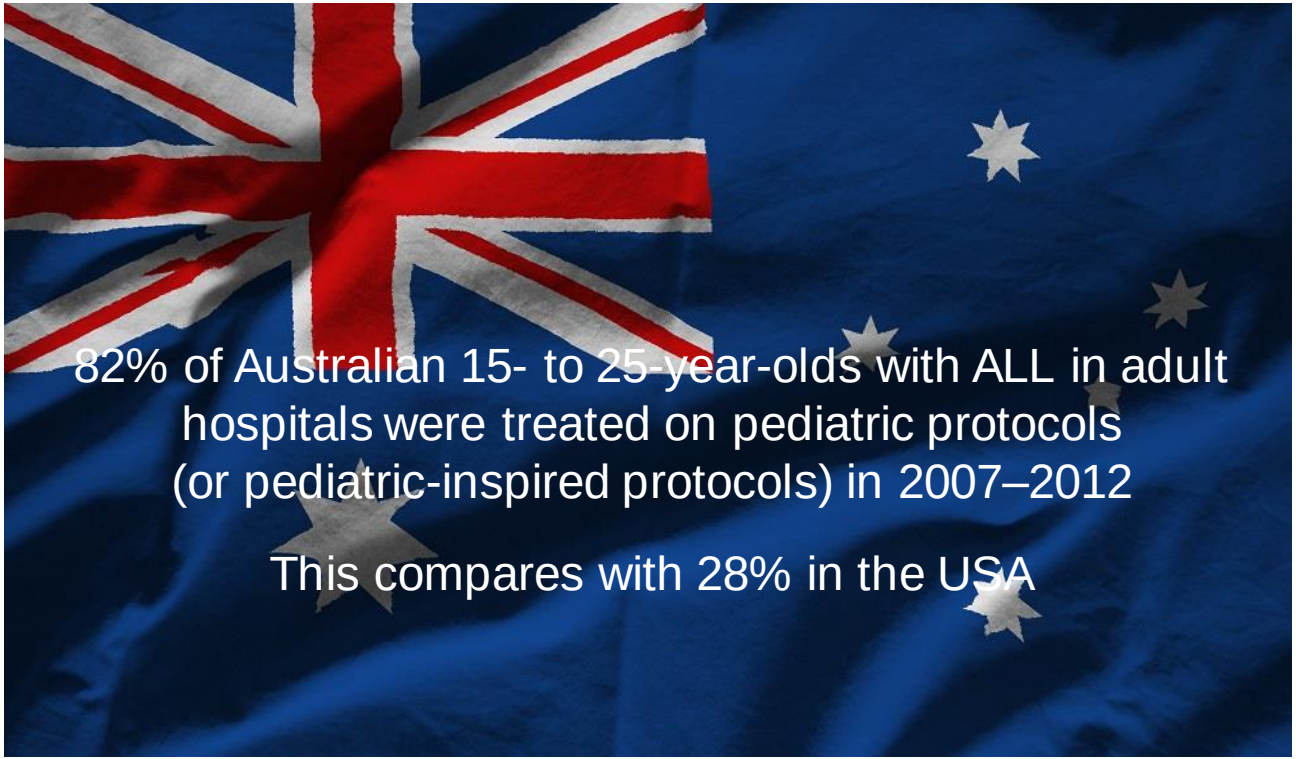

Global Leukemia Academy

White VM, et al. *Pediatr Blood Cancer*. 2018;65(11):e27349; Muffly L, et al. *Cancer*. 2017;123(1):122-130.

AYAs Treated on Pediatric Protocols Experience More Toxicities Than Younger Children

> AYAs experience more

- Hyperglycemia
- Hyperbilirubinemia
- Thrombosis
- Sepsis
- Pancreatitis
- Methotrexate encephalopathy
- Osteonecrosis

Global Leukemia Academy

Advani AS, et al. *Blood Adv.* 2021;5(2):504-512; Hough R, et al. *Br J Haematol.* 2016;172(3):439-451.

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Most evident during **induction**

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Most evident during **induction**

Obese AYAs have more toxicity
Consider lower asparaginase dose (500 U/m^2) ± SAA

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COG ACCL1931: Does **levocarnitine** prevent asparaginase-induced hepatotoxicity in induction?

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Consider lower asparaginase dose (500 U/m^2) ± SAA

More common in teenagers (**20%**) than children
Infrequent in young adults

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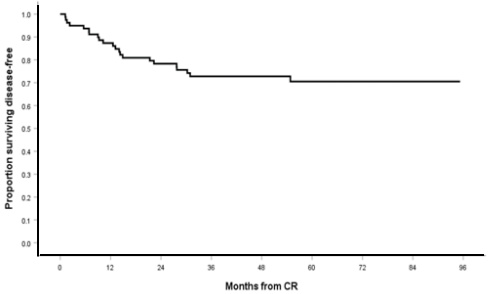
Advani AS, et al. *Blood Adv.* 2021;5(2):504-512; Hough R, et al. *Br J Haematol.* 2016;172(3):439-451.

ALL06: An MRD-Stratified Pediatric Protocol Is as Deliverable in AYAs as Children With ALL

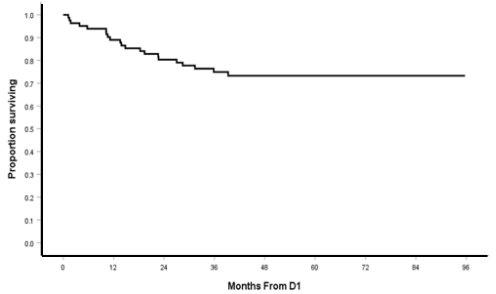
- N = 82, aged 16–38 years, 2012–2018
- Compared deliverability of induction/consolidation to children in ANZCHOG Study 8
- **41%** of AYAs vs **39%** of children started Protocol M by day 94
- Suggests worse outcome in AYAs on pediatric protocols is due to adverse biology rather than intolerance of treatment

Adverse Factors	Overall Survival
MRD at day 79 (pos vs neg)	92% vs 61%
BMI (<30 kg/m^2 vs >30 kg/m^2)	81% vs 49%

3y DFS **72.8%** (95% CI, 62.8 – 82.7)



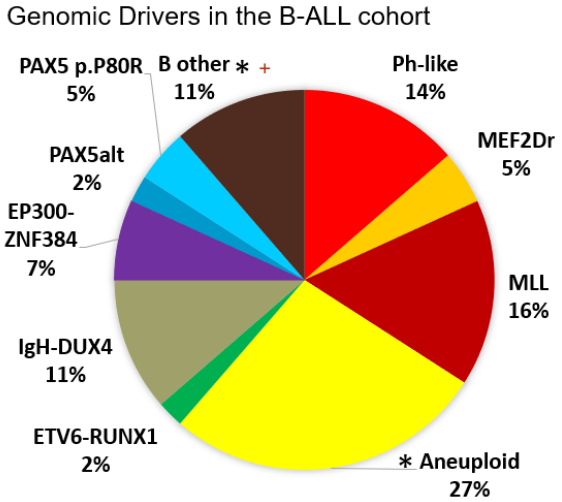
3y OS **74.9%** (95% CI, 65.3 – 84.5%)

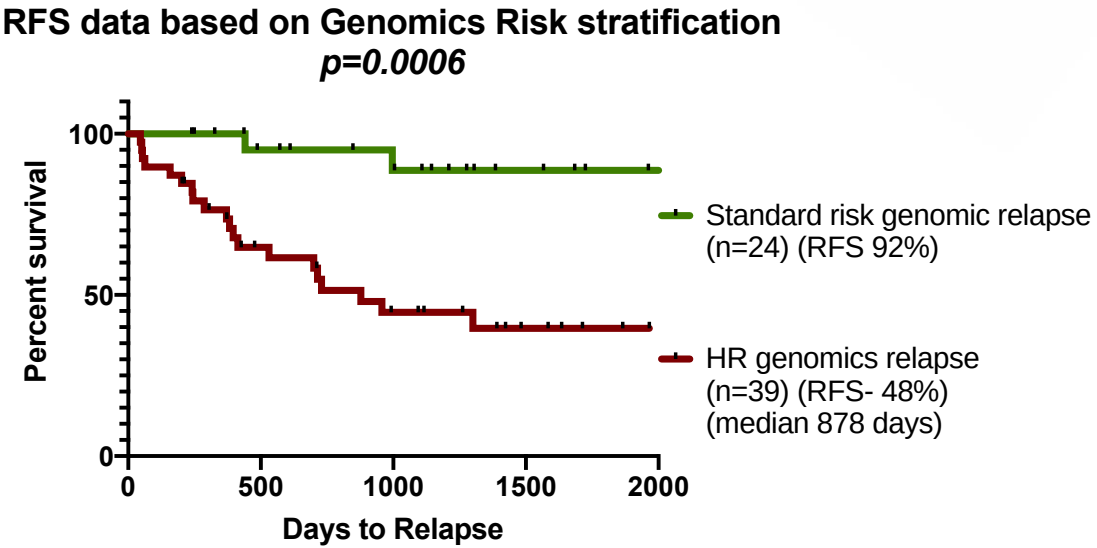


Global Leukemia Academy

Greenwood M, et al. *Blood Adv*. 2022;5(24):5574-5583.

High-Risk Genomic Alterations Identified at the Time of Diagnosis Are Strongly Associated With MRD and Subsequent Poor Outcomes in AYA ALL Patients Treated on a Pediatric-Inspired Chemotherapy Regimen





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Yeung DT, et al. ASH 2019. Abstract 3949.

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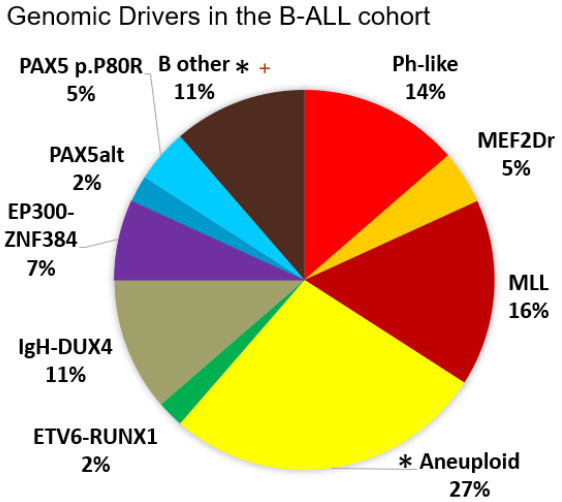

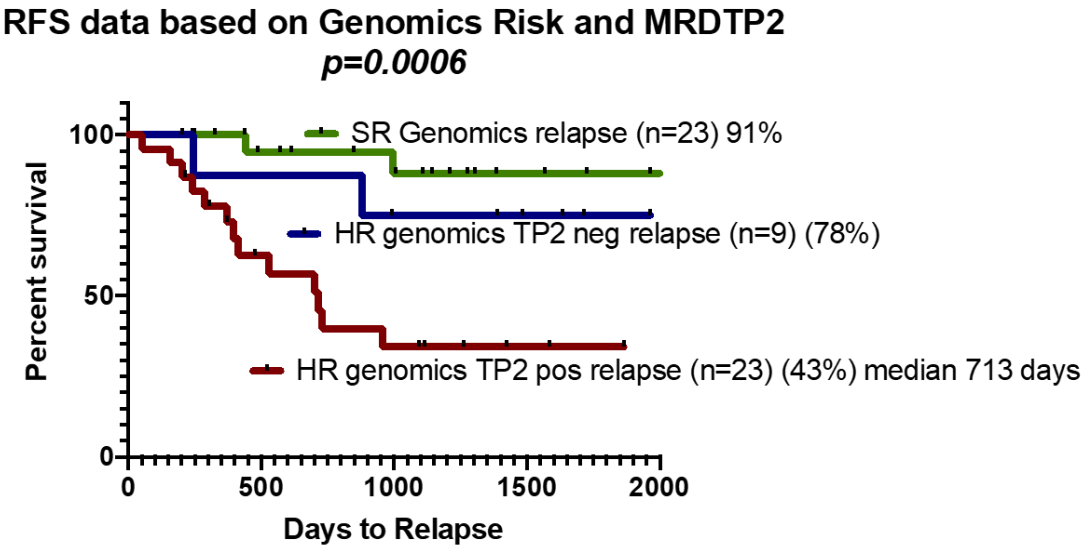

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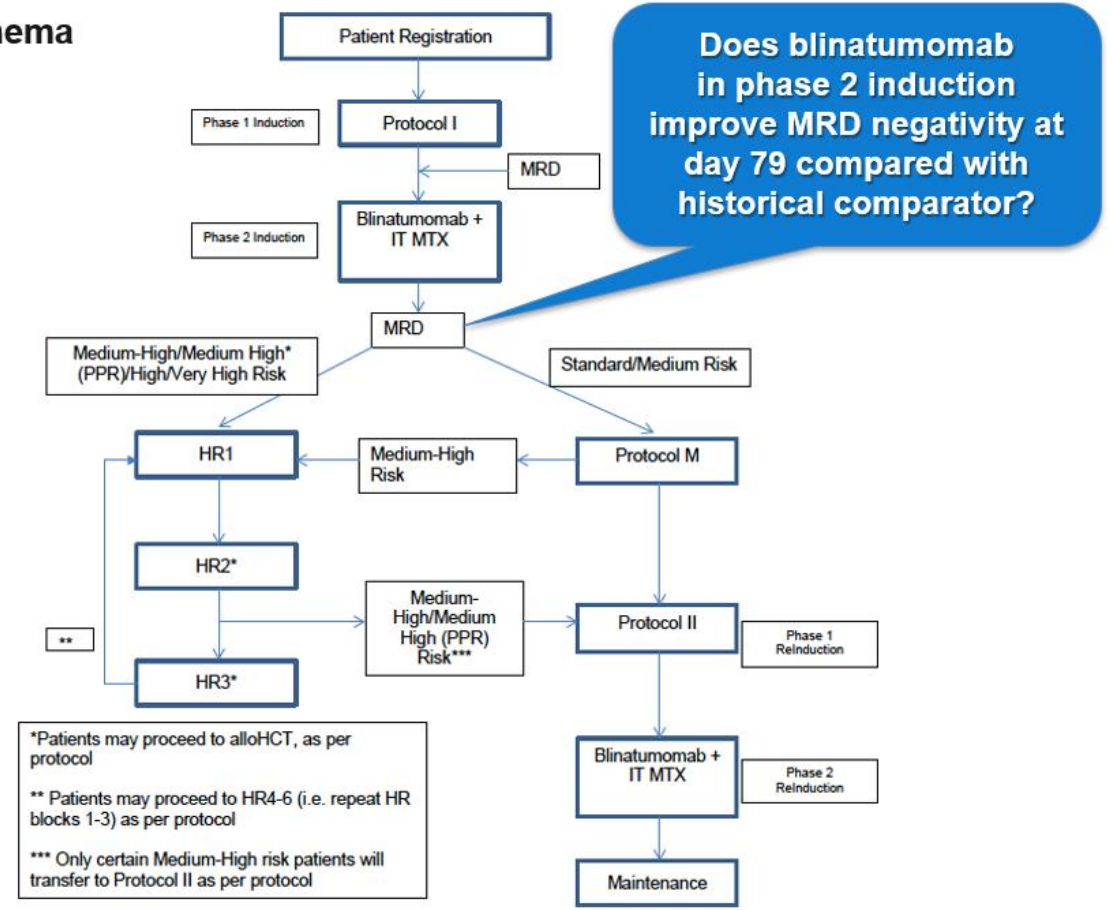
Yeung DT, et al. ASH 2019. Abstract 3949.

ALL09 trial schema

CI: M.Greenwood



ALLG Leukaemia & Lymphoma Group

Better treatments...
Better lives.

Greenwood M, et al. *Blood.* 2022;140(suppl 1):8971-8972.

ALL09 trial schema

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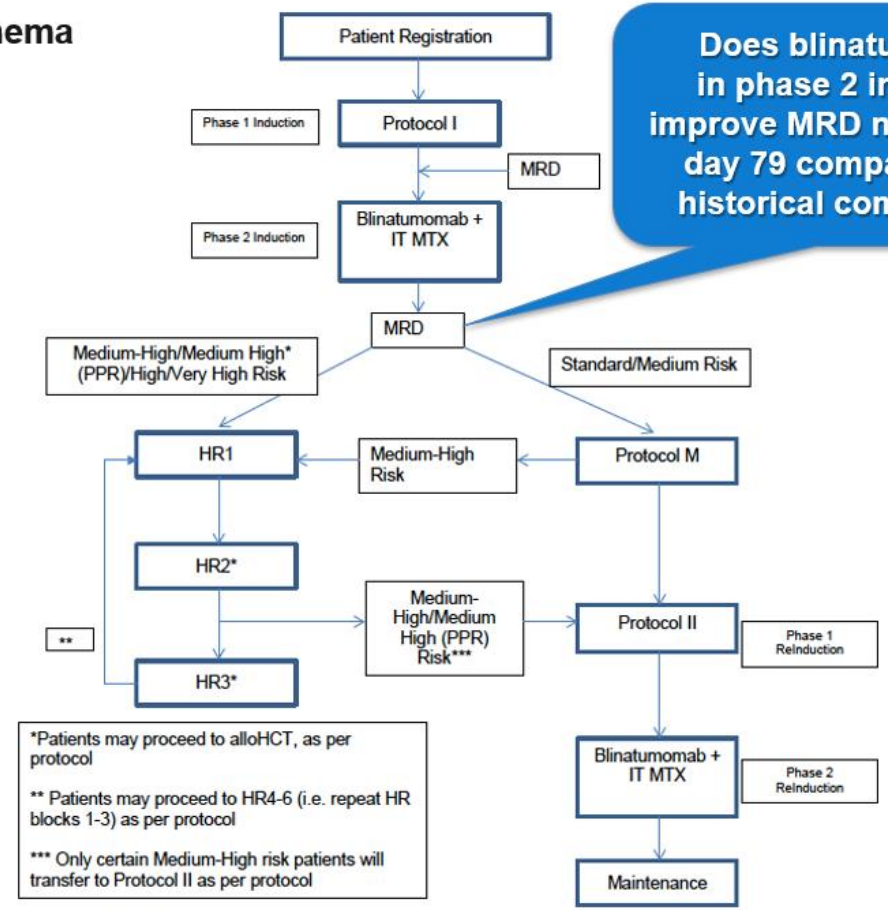

	MRD negative %	
Study	**Day 33**	**Day 79**
ALL06	19%	56%
ALL09	34%	71%

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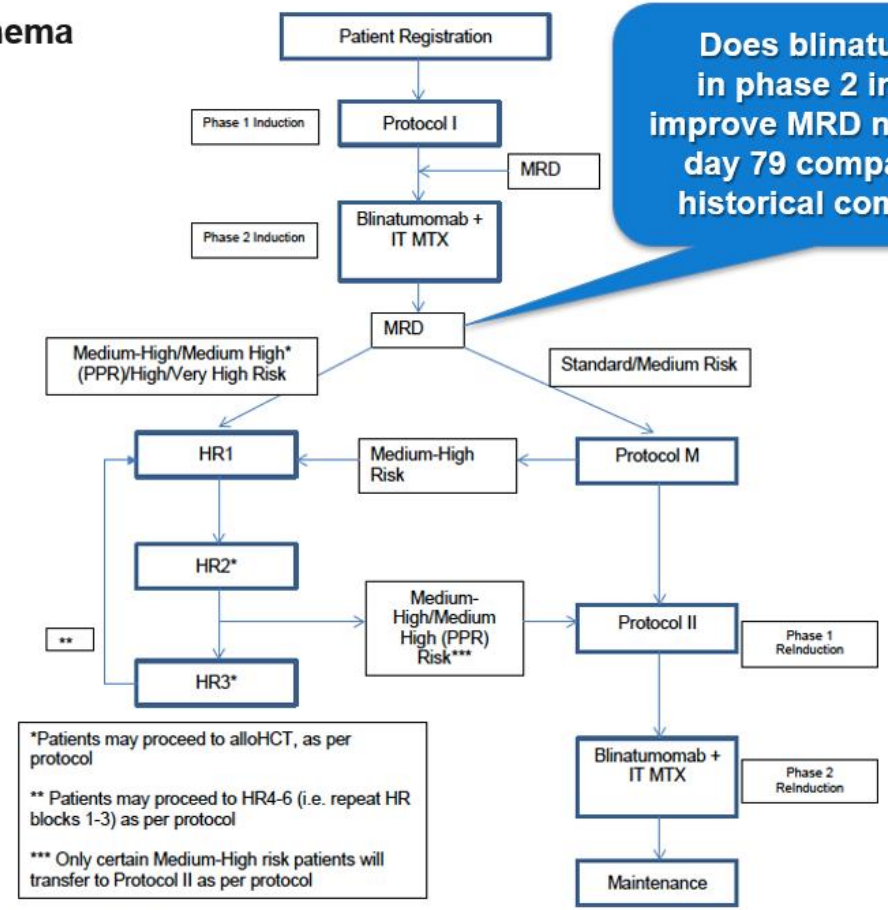

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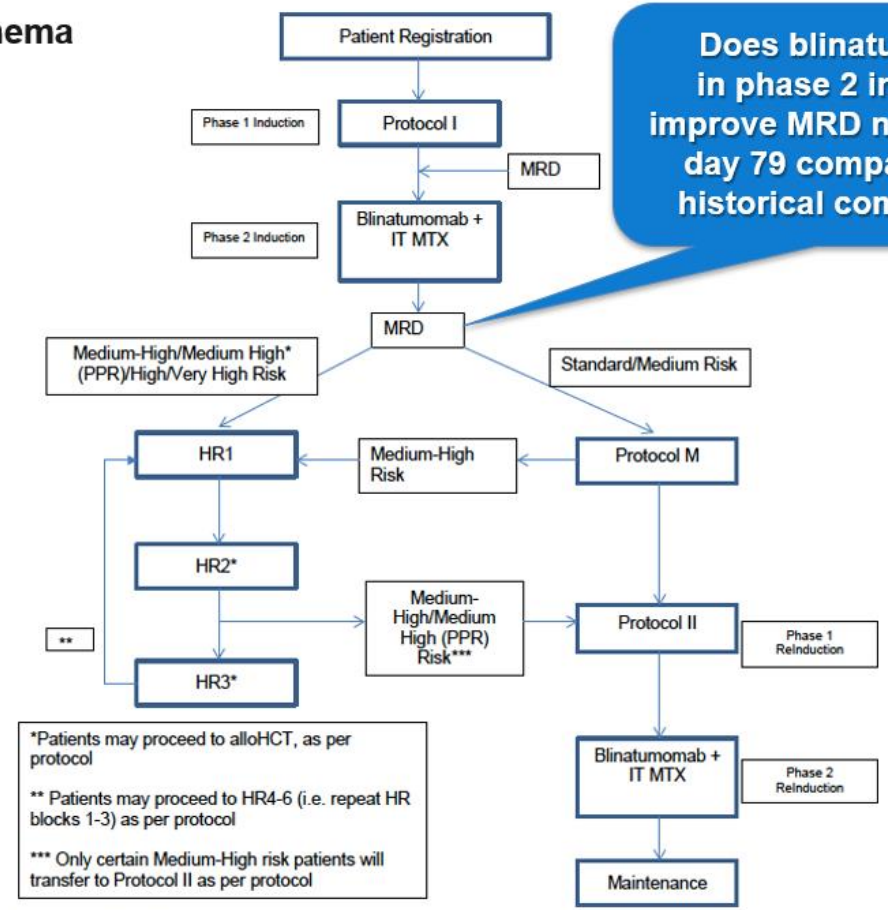

	MRD negative %	
Study	**Day 33**	**Day 79**
ALL06	19%	56%
ALL09	34%	71%

Selected Grade 3/4 Toxicities	
Cytokine release syndrome	4%
Neurological	15%
Febrile neutropenia/sepsis	6%

ALLG Australasian Leukaemia & Lymphoma Group

Better treatments... Better lives.

Greenwood M, et al. *Blood.* 2022;140(suppl 1):8971-8972.

Improvements in Survival Are Now Plateauing

So We Need More-Effective, Less-Toxic Therapies . . .

. . . With Strategies to Improve Outcomes for LMICs

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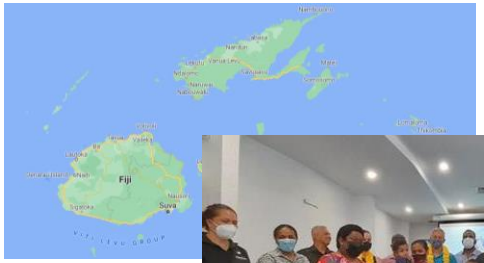
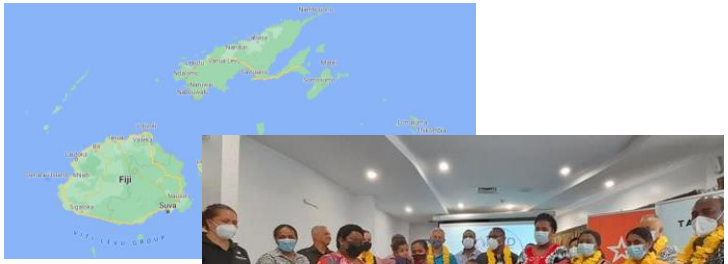
Strategies to Improve Outcomes in LMICs

> Twinning programs



Strategies to Improve Outcomes in LMICs

> Twinning programs



> Adjusted protocols for LMICs

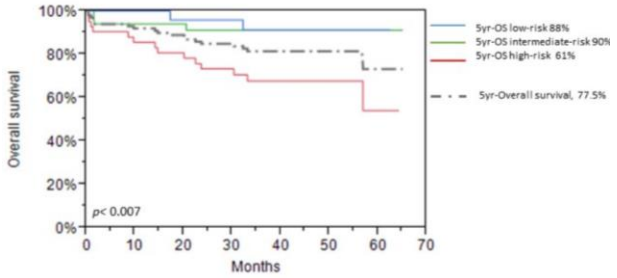
Pediatric Blood & Cancer

GLOBAL ONCOLOGY: RESEARCH ARTICLE

Childhood acute lymphoblastic leukemia: Four years evaluation of protocols 2013 and 2016 in a single center in Indonesia, a lower-middle-income country

Sutaryo Sutaryo, Pudjo Hagung Widjajanto, Sri Mulatsih, Bambang Ardianto, Alexandra Widita Swipratami Pangarso, Eddy Supriyadi, Ignatius Purwanto ... See all authors

> **Feasibility and Improvement in Survival with a Risk-Adapted Treatment Regimen for Childhood Acute Lymphoblastic Leukemia in a Limited Resource Setting.** Jimenez-Antolinez YV, et al. ASH 2022. Abstract 2731.



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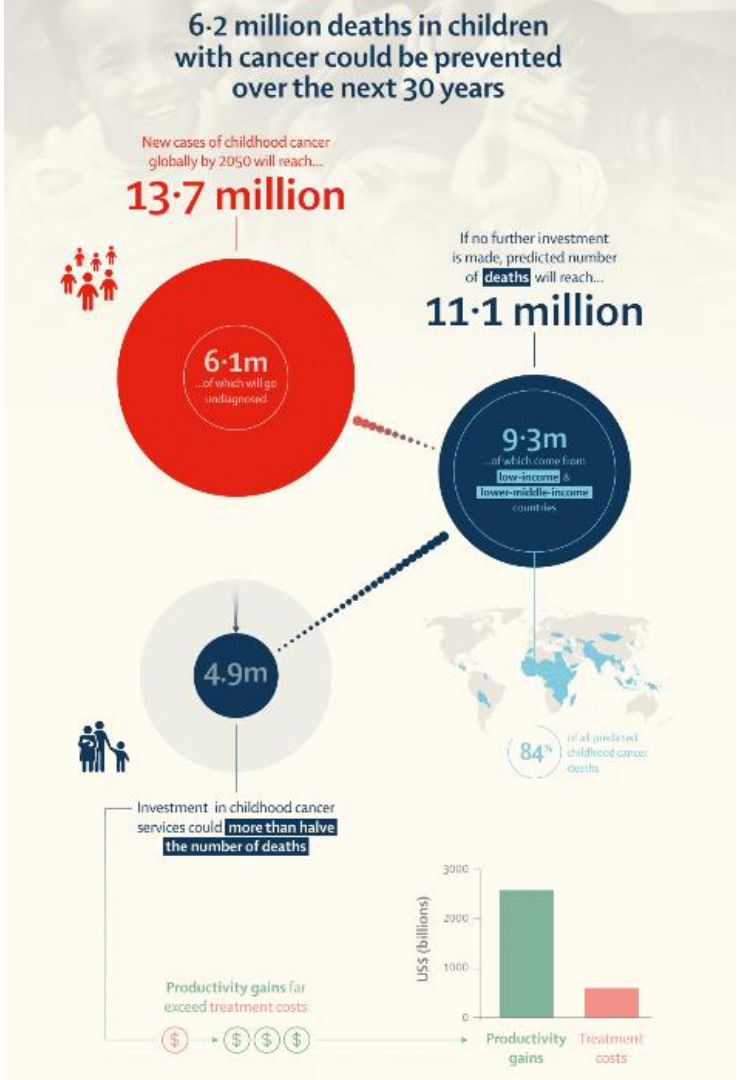
"The world is clearly failing to meet the needs of children with cancer in low-to-middle income countries. Yet there is hope. Many cost-effective interventions could be used to expand access to cancer prevention, treatment, and care . . . averting more than 6 million deaths."

APTITUDE HEALTH



LMICs

- Health systems not ready to meet this challenge
- Burden has historically been on infectious diseases
- Decreased infection-related mortality in <5 yr old associated with more children with cancer
- Childhood cancer managed as a charitable activity at best
- Needs to become an integral part of universal health care

No reliable data on

- Current and future burden of childhood cancer
- Cost of effective interventions
- Current coverage levels for diagnostic, treatment, and care services
- Cost, feasibility, or health and economic benefits of scaling-up effective coverage

Misconceptions

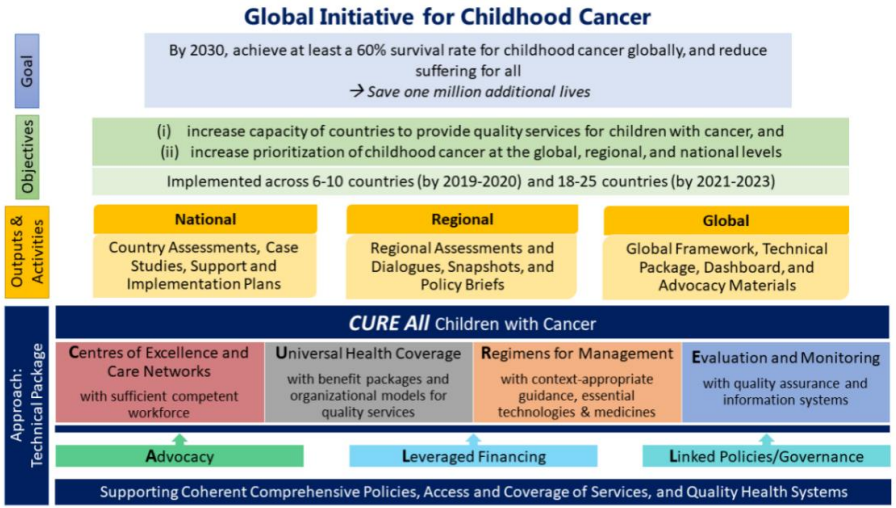
- *Myth 1:* Complex/not manageable
  - Fact: We understand childhood cancers now more than ever and can manage this burden with the right healthcare system
- *Myth 2:* Not treatable
  - Fact: Effective diagnostics and treatment exists, and many childhood cancers are curable
- *Myth 3:* Not affordable
  - It is affordable—and new modelling in this Commission proves this

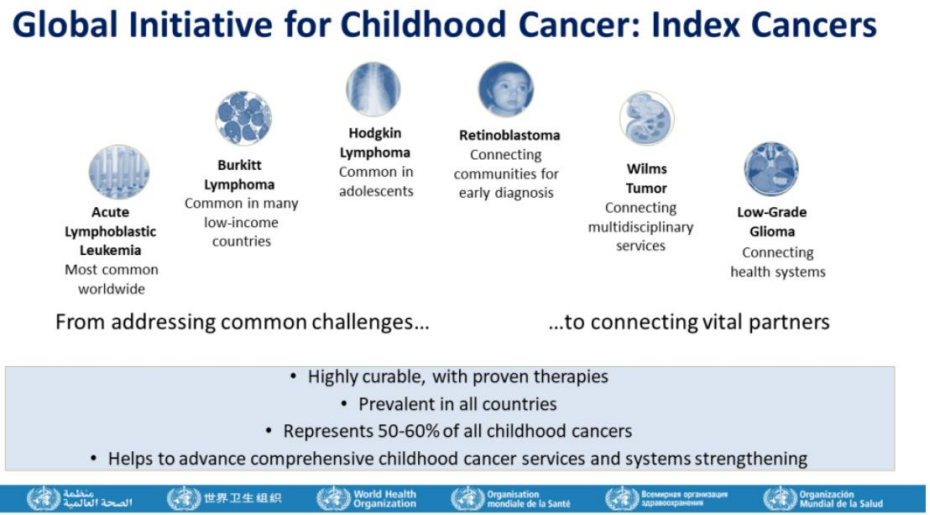
Atun R, et al. *Lancet Oncol*. 2020;21(4):e185-e224.

	Major Actions	Targets
Action 1	Incorporate childhood cancers into **essential benefits** packages when expanding **universal health coverage**	80% of LMICs by 2030, ensuring finances to provide this
Action 2	Develop **national cancer control plans** and provide **predictable financing**, to ensure the expansion of sustainable care for children with cancer	80% of LMICs by 2030, with processes to create the fiscal space to fund it
Action 3	**Eliminate out-of-pocket expenditures** for children with cancer to halt catastrophic expenditures and abandonment of treatment	80% of LMICs by 2030
Action 4	Expand access to effective services for childhood cancers by establishing **cancer networks**	Effective services (human resources, diagnostics, Rx, surgery, radiotherapy, pall care and social support) for 80% and pain control for 100% by 2030
Action 5	Invest in the development of **cancer registries** that incorporate childhood cancers	80% by 2030
Action 6	Invest in **research, development, and innovation**	UN-led global coalition to mobilize US $100 million per year

WHO/St Jude Global Initiative for Childhood Cancer

US $200 Million Over 6 years





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SIOP OCEANIA

- Improve **knowledge** about childhood cancer, and its management, in Oceania countries.
- Advocate for children with cancer across Oceania, including sharing **advocacy and technical expertise** to improve childhood cancer services
- Promote **research** to improve outcomes for childhood cancer patients in Oceania
- Facilitate **education and training opportunities** for SIOP Oceania members, including coordinating regional education initiatives for medical, nursing, and allied health professionals
- Strengthen **strategic partnerships** in our region, including working in close partnership with the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG)
- Support implementation of the goals and objectives of SIOP in our region

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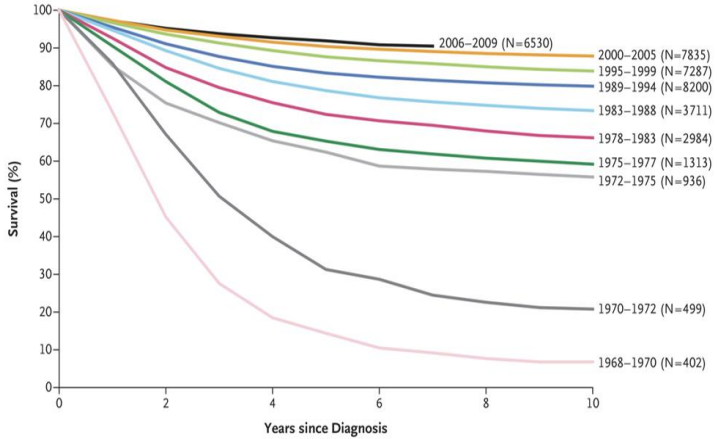
oceania@siop-online.org

Acute Lymphoblastic Leukemia

Optimizing Frontline Treatment for Children and AYAs



Relapse

Cost of Cure:

Acute toxicity
Late effects
Psychosocial

More sophisticated **Risk Stratification**

Frontline use of **Immunotherapies**

Targeted therapies based on improved **Understanding of Biology**

Optimizing current drugs and **pharmacogenomics**

Global and Regional Partnerships

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Optimal Management and Treatment Coordination of Long-term Toxicities in Pediatric ALL

Stephanie Dixon

APTITUDE HEALTH

Global Leukemia Academy

Case 1: Frontline Setting

Savenaca Seduadua

APTITUDE HEALTH

Overview

- Fiji: population 900,000; 400,000 <15 yr
- Paediatric Oncology Unit – Colonial War Memorial (CWM) and Lautoka Hospital
- 20–30 new cases annually
- Twinning program: Children's Haematology and Oncology Centre, NZ
- ALL is the most common childhood cancer
- PI ALL protocol: standard to intermediate risk (unable to risk stratify)
- Treatment offered: only chemotherapy and surgery


PACIFIC OCEAN
MYANMAR
VIETNAM
LAOS
THAILAND
CAMBODIA
PHILIPPINES
Guam
(United States)
Palau
Marshall Islands
MALAYSIA
SINGAPORE
Federated States
of Micronesia
Kiribati
Nauru
Solomon Islands
INDONESIA
TIMOR-LESTE
Tokelau
(New Zealand)
Tuvalu
Pāpua-
New Guinea
American Samoa
(United States)
Samoa
Vanuatu
New Caledonia
Fiji
Tonga
Niue
(New Zealand)
INDIAN
OCEAN
Australia
Norfolk Island
(Australia)
New
Zealand
Adobe Stock | #298421073


180° Meridian
Inset: Rotuma
177°E
16°30'S
Labasa
Rabi
Ringold Isles
VANUA LEVU
Savusavu
Qamea
Laucala
Yasawa Islands
Yadua
Taveuni
Nabowalu
Vanuabalavu
BLIGH WATER
Yacata
Lomaloma
Koro
Rakiraki
Makogai
Vatu Vara
Mago
Tavua
Ba
Mamanuca Islands
Lautoka
Wakaya
Ovalau
KORO SEA
Tuvuca
Cicia
Nadi
Korovou
Batiki
Nairai
VITI LEVU
Nausori
Nayau
18° S
Gau
Sigatoka
SUVA
Lakeba
Navua
Beqa
Oneata
Vatulele
Moala
Moce
Namuka-i-lau
Ono
Totoya
Vunisea
Kabara
Kadavu
Matuku
Fulaga
0
50 km

- TS is a 3-yr-old FI who presented to CWM with
  - Abdominal pain × 1/12
  - Incidental finding of severe bicytopenia

- Child has been well
- Early in the year, mother noticed he was losing weight
- Around September, he was less active than usual
- His abdominal pain began as intermittent, generalized pain; but the day of presentation, more localized to RUQ
- USS: at the HC, hypoechoic mass noted within liver
- ROS: fever ±; dry cough (+); no SOB; normal bowel and urine; no easy bruising; no vomiting; no nausea; reduced appetite; weak (+)

- PMHs: no past hospitalization; no comorbid condition; no allergies; not on any medication
- Pediatric history: FTNVD; 3.15 kg; immunization completed; normal development and growth
- Social history
  - He has 9-yr-old brother, well
  - Parents both work
  - They live 20-min drive from CWM in their own house with nuclear family
  - They do not have health insurance

Physical Examination

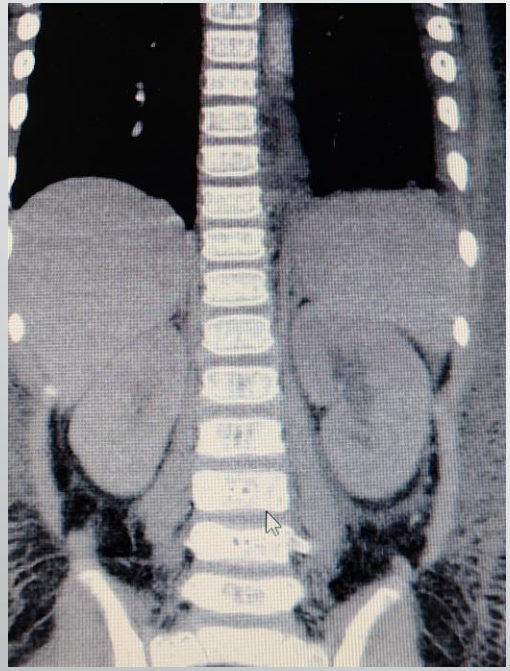
- O/E: nondysmorphic child; pale looking; mild respiratory distress on oxygen Nprongs
- HEENT: periorbital puffiness(+); no LN; no oral mucosal lesions; neck: supple
- Chest: mild creps bilaterally on lung fields; CVS: S1S2; no murmur
- Abdomen: distended; liver 4 FB BRCM; tipped spleen; not tender; generally soft
- Extremities: edema of all 4 limbs; good volume pulses; no neurocutaneous lesions; symmetrical movement of all 4 limbs

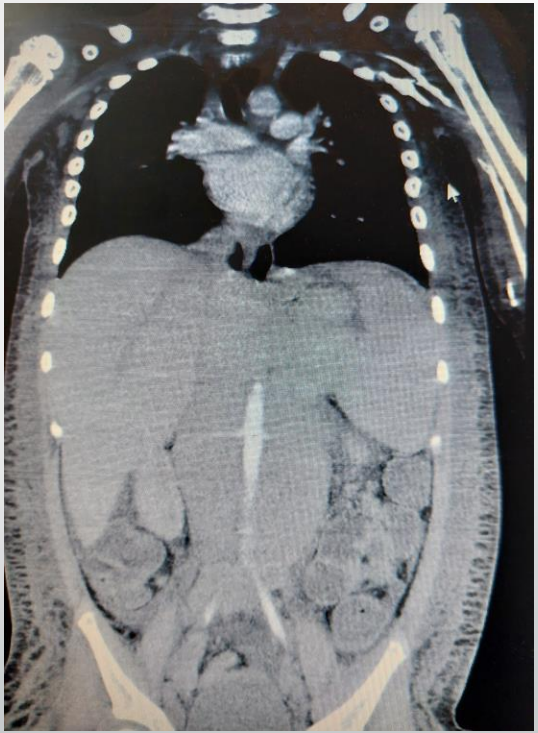
Investigations

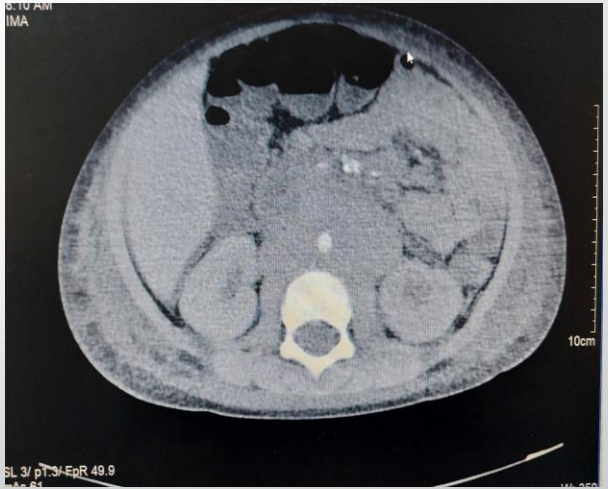
- Blood film (8/11/22): consistent with lymphoproliferative disorders
- RBC shows a predominating normocytic, normochromic picture with macrocytes also seen. Occasional fragmented cells seen
- WBC shows marked absolute lymphocytosis (90%) with absolute neutropenia. These cells are homogenous with regular nucleus with no nucleoli and scant cytoplasm. Few cells with cleaved nuclei and smudge cells are seen
- Platelets are low in numbers but normal in morphology

Date	8/11/22	Normal Range
Hb	3.4	
WBC	35200 N 4%	
P/M	11/93	
Plt	35000	
COAGS	PT C12 T14 APTT C28 T29	
ESR	55	
U	6.5	2.8–8.5
Cr		58-110
Na	130	135–148
K	4.4	3.5–5.2
Cl	105	90–100
Ca		2.2–2.65
Mg		0.73–1.06
Phos		0.81–1.45
TB	10	
DB	5	
AST	32	<40
ALT	3	<45
ALP	102	30–120
TP	50	66–83
Alb	31	35–53
Glob	19	20–35
Urates		
LDH		<248

CT Scan







Bone Marrow Aspiration

- BMA showed >90% lymphoblast featuring marked increase in nuclear cytoplasmic ratio, minimal nuclear pleomorphism and hyperchromasia, and prominent nucleoli
- All other hematopoietic cells are markedly suppressed
- Diagnosis: ALL FAB L1

Final Diagnosis

- Acute lymphoblastic leukemia – L1

Management Plan

- Admitted to oncology unit
- Parents counseled during family conference: diagnosis, treatment options
- Counseling session with counselor
- Registration with WOWS Kids Fiji – child cancer support NGO
- Hyperhydration 125 mL/m^2/h started
- Allopurinol 100 mg/m^2/d in 3 divided doses
- TLS monitoring
- Child started on Pacific Island ALL protocol

CHALLENGES

- Inability to do proper risk stratification
- No health insurance for parents
- PEG-asparaginase not in stock
- Low survival rate for ALL (approximately 49%)
- Chemotherapy shortage
- No qualified pediatric oncologist on-site

Global Leukemia Academy

Case 2: Management of Long-term Toxicities

Claudia Toro

APTITUDE HEALTH

Clinical Background

- 5-yr-old boy
- No significant past medical history
- History: 6 weeks blocked nose, 3 weeks ear pain and sore throat, developed lump to temple and presented to PED
- Family history of insulin-dependent diabetes
- Burkitt lymphoma – nasopharyngeal, stage 4B, CNS positive but CSF negative (CN involvement)
- Treated according to C1 arm of ANHL01P1

ANHL01P1

TREATMENT 4 GROUP C Pilot (≅37 Patients): CNS Involvement and/or Bone Marrow >25%

REDUCTION COP-R (Rasburicase) ♣

↓

1St Evaluation

↓

INDUCTION COM(8)R(Rituximab)AP 1*♣

↓

COM(8)R(Rituximab)AP 2**♣

↓

2nd Evaluation

↓

CONSOLIDATION CYVE-RM-(Rituximab)1(+ HD MTX in CNS positive patients only) ♣♣

↓

CYVE-RM-(Rituximab) 2

↓

3RD Evaluation

No Residual disease----------Residual disease

↓ ↓

OFF STUDY

MAINTENANCE MI COPADM(8) 3***♣

MAINTENANCE M2 Cytarabine/etoposide

MAINTENANCE M3 COPD

MAINTENANCE M4 Cytarabine/etoposide

* Cyclophosphamide 250 mg/m^2 bid x 3days
**Cyclophosphamide 500 mg/m^2 bid x 3days
*** Cyclophosphamide 500 mg/m^2 qd x 2days
♣ Please note IT medications in Treatment 4 (Group C Pilot) patients in courses COP-R, COM(8)RAP 1 & 2, CYVE-RM 1, COPADM(8) 3 vary from Treatment 1(Group B Sub-Pilot) patients in courses COP-R, COM(3)RAP 1 & 2, CYM-RM 1, COPADM(3) 3
♣♣ Additional note to investigators: IT medications vary for Treatment 4 (Group C Pilot) patients that are CNS negative and patients that are CNS positive in Consolidation course CYVE-RM1.

The Royal Children's Hospital Melbourne

Clinical Progress

- Echo post-COM(8)RAP1

MMode Measurements & Calculations

IVSd: 0.60 cm	LVEDd: 4.0 cm
LVPWd: 0.55 cm	LVESd: 2.7 cm
	FS: 33.3 %
	EF (Teich): 62.5 %

- Conclusion: Normal biventricular systolic function. Mild biventricular and LA dilatation. Structurally normal heart. TDI parameters normal range for age

What Next?

A: Reduce dose of doxorubicin

B: Continue the same dose of doxorubicin but add dexrazoxane (cardioprotectant)

C: Cease further anthracycline

D: Continue doxorubicin without change in dose or use of cardioprotectant

Clinical Progress

Post-COM(8) RAP2

- Conclusion: mildly dilated LV with normal LV and RV systolic function

Post-M2 (Ara-C–etop)

- LV has a globular appearance but normal dimensions. Normal biventricular systolic function

MMode Measurements & Calculations

IVSd: 0.59 cm	LVEDd: 4.0 cm
LVPWd: 0.47 cm	LVESd: 2.6 cm
	FS: 34.3 %
	EF (Teich): 63.8 %

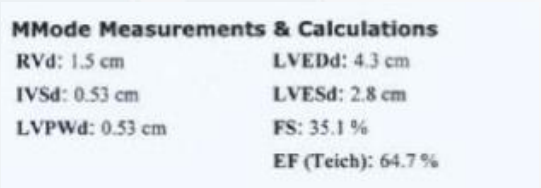
MMode Measurements & Calculations

RVd: 1.4 cm	LVEDd: 4.3 cm
IVSd: 0.60 cm	LVESd: 2.7 cm
LVPWd: 0.39 cm	FS: 35.7 %
	EF (Teich): 65.5 %

Clinical Progress

End of treatment

- Mildly dilated LV with normal systolic function. Slightly reduced TDI parameters



MMode Measurements & Calculations

RVd: 1.5 cm	LVEDd: 4.3 cm
IVSd: 0.53 cm	LVESd: 2.8 cm
LVPWd: 0.53 cm	FS: 35.1 %
	EF (Teich): 64.7 %

Dexrazoxane – The Evidence

Original Article

Late Health Outcomes After Dexrazoxane Treatment: A Report From the Children's Oncology Group

Eric J. Chow, M
Yuan-Shung V. Hua
Smita Bhatia, M
Wendy M. Leisenring, Sc
[3]; David R. Doody, MS[1];
[5]; K. Scott Baker, MD, MS[1];
Lisa M. Kopp, DO, MPH[9];
[10]; and Steven E. Lipshultz, MD[11]

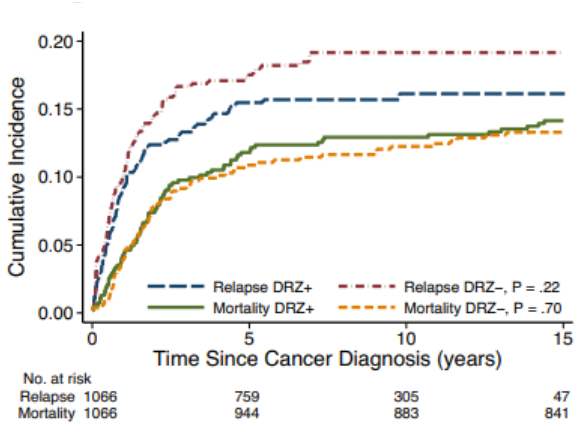


Figure 1. Cumulative incidence of relapse and all-cause mortality among patients treated in randomized clinical trials of DRZ (P9404, P9425, P9426, and DFCI 95-01) by their DRZ status. DFCI indicates Dana-Farber Cancer Institute; DRZ, dexrazoxane.

BACKGROUND: The obje
were treated in dexrazoxan
P9426 (Hodgkin lymphoma
and 2001: 1066 were rando
to receive dexrazoxane. Tr
the Pediatric Health Inform
(CCSS; n = 495; no dexraz
Cox regression, and Fine-
median follow-up, 18.6 ye
0.63-1.13), second cancers
(HR, 1.45; 95% CI, 0.41-5.16
follow-up, 16.6-18.4 years),
CCSS osteosarcoma surviv
serious cardiovascular out
commonly with dexrazoxa
P = .35). **CONCLUSIONS:**
Cancer 2022;128:788-796.

n newly diagnosed with cancer who
kemia/lymphoma [ALL]), P9425 and
enrolled 1308 patients between 1996
P9754) were nonrandomly assigned
ement and Transplantation Network,
e Childhood Cancer Survivor Study
assessed with cumulative incidence,
doxorubicin dose, 100-360 mg/m^2;
0.84; 95% confidence interval [CI],
78-1.47), or cardiovascular mortality
xorubicin, 450-600 mg/m^2; median
ar heart transplantation rate among
= .13). Among randomized patients,
ed by PHIS/Medicaid occurred less
es alone did not differ (4.4% vs 8.1%;
t-free survival, or second cancer risk.

KEYWORDS: adolescent, cancer survivors, cardiotoxicity, child, second malignancy, survivorship.

Case Considerations

- February 2020: Severely dilated LA, mildly dilated LV with good systolic function. Diastolic dysfunction with abnormal LV filling
- August 2020: Severely dilated LA. Normal LV size with preserved LV systolic function. Abnormal diastolic function

MMode Measurements & Calculations

RVd: 1.8 cm	LVEDd: 5.4 cm
IVSd: 0.61 cm	LVESd: 3.9 cm
LVPWd: 0.60 cm	FS: 28.5 %
	EF (Teich): 54.5 %

MMode Measurements & Calculations

IVSd: 0.74 cm	LVEDd: 5.0 cm
LVPWd: 0.66 cm	LVESd: 3.7 cm
	FS: 26.7 %
	EF (Teich): 52.0 %

The Patient Voice

Slow down mummy

I had no idea how this would affect him

You'll do whatever it takes

The Royal Children's Hospital Melbourne

Future Considerations

- Standardized pediatric guidelines
  - International Late Effects of Childhood Cancer Guideline Harmonization Group
  - Australian Cardio-Oncology Registry (ACOR)
- Pharmacogenomics

References

- Armenian SH, Armstrong GT, Aune G, et al. Cardiovascular disease in survivors of childhood cancer: Insights into epidemiology, pathophysiology, and prevention. *J Clin Oncol*. 2018;36(21):2135-2144
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- Chow EJ, Asselin BL, Schwartz CL, et al. Late mortality after dexrazoxane treatment: A report from the Children's Oncology Group. *J Clin Oncol*. 2015;33(24):2639-2345

The Royal Children's Hospital Melbourne

Thank You!

Patients and Families

The Baker Heart and Diabetes Institute

My supervisors
Prof David Elliott
A/Prof Rachel Conyers
Prof David Ritchie
Prof Michael Sullivan
Dr Kanika Bhatia
Prof Andre La Gerche

ACOR National Co-ordinator
Ms Emma Masango

ACOR Academic pharmacist
Mr Ben Felmingham

Murdoch Children's Research Institute, Cardiac Regeneration Laboratory
Professor Melissa Little
A/Prof Enzo Porrello
Dr David Elliott

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- Children's Cancer Foundation (ACTive study)
- The Kids Cancer Project (ACOR)
- The Royal Australasian College of Physicians (ACOR)
- The Royal Children's Hospital Foundation (ACOR)

Global Leukemia Academy

ALL Case-Based Panel Discussion

Moderators: Michael Osborn and Elizabeth Raetz

APTITUDE HEALTH

Global Leukemia Academy

Break

APTITUDE HEALTH

Global Leukemia Academy

Current Treatment Options for Relapsed ALL in Children

Elizabeth Raetz

APTITUDE HEALTH

HASSENFELD
CHILDREN'S
HOSPITAL
AT NYU LANGONE

Current Treatment Options for Relapsed ALL in Children

Global Leukemia Academy

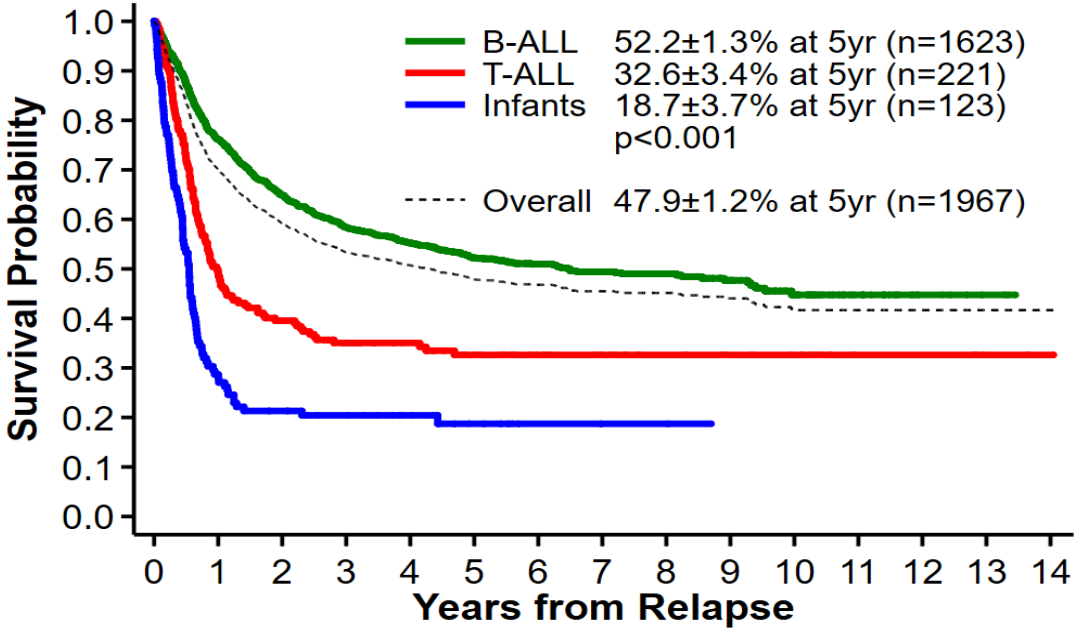
Elizabeth Raetz, MD

December 5, 2022

Outline

- Outcomes
- Prognostic factors
- Risk stratification
- Treatment options
  - Targeted therapy and immunotherapy
- Future directions

Overall Survival Post-relapse



At Risk

B-ALL	1623	1184	962	807	681	540	375	259	185	108	55	23	8	3	0
T-ALL	221	101	74	55	45	35	26	21	15	12	10	4	4	2	1
Infants	123	35	25	20	15	8	3	2	2	0	0	0	0	0	0
Overall	1967	1320	1061	882	741	583	404	282	202	120	65	27	12	5	1

CHILDREN'S ONCOLOGY GROUP

Rheingold SR, et al. ASCO 2019. Abstract 10008; Loh M, et al. SIOP 2019. Abstract FP004.

Recently Completed Phase III Trials for First ALL Relapse

Trial	Years of Accrual	Patient Age, Years	Number of Patients	Outcomes
UKALL R3 NCT00967057	2003-2009	1-18	239 (216 randomized)	3-yr PFS 65%; 3-yr OS 69% (mitoxantrone arm)
ALL-REZ-BFM 2002 NCT00114348	2003-2012	1-18	538 (420 randomized)	5-yr EFS 60%; 5-yr OS 69% (Prot II-IDA arm)
COG AALL0433 NCT00381680	2007-2013	1-30	275* (271 eligible)	3-yr EFS 64%; 3-yr OS 72%
COG AALL1331 NCT02101853	2014-2019	1-30	220** (208 randomized)	2-yr DFS 59%; 2-yr OS 79% (blinatumomab arm)

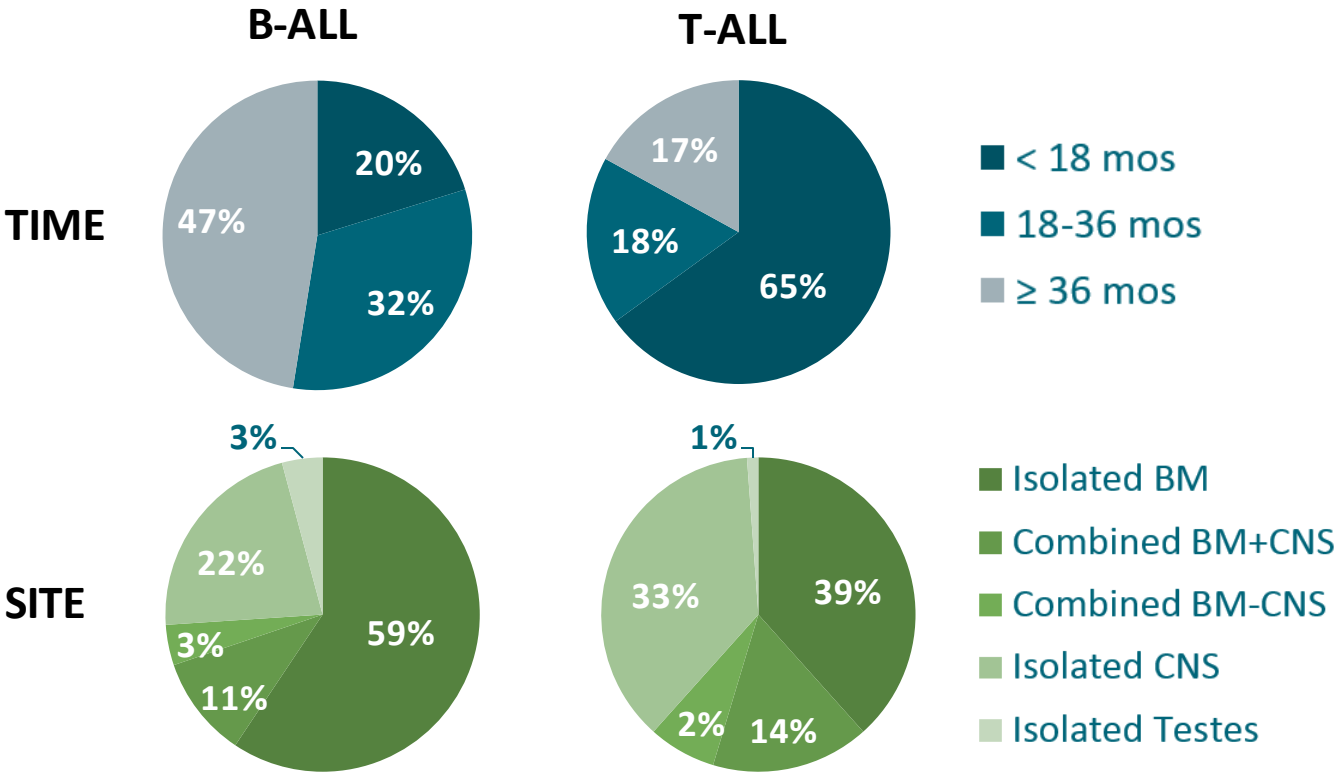
*Late isolated or combined marrow and very early isolated CNS.
**Intermediate and high risk only.

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

Prognostic Factors at Relapse

- *Timing*
  - The earlier relapse occurs relative to the time of initial diagnosis, the worse the outcome
- *Site*
  - Prognosis for isolated extramedullary relapse is better than that for bone marrow relapse
- *Blast immunophenotype and cytogenetics*
  - Inferior outcomes with T-cell disease and unfavorable genetics
- *MRD response*
  - Early favorable responses portend better outcomes

Time and Site of Relapse



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Rheingold SR, et al. ASCO 2019. Abstract 10008; Loh M, et al. SIOP 2019. Abstract FP004.

Median Duration of First Remission

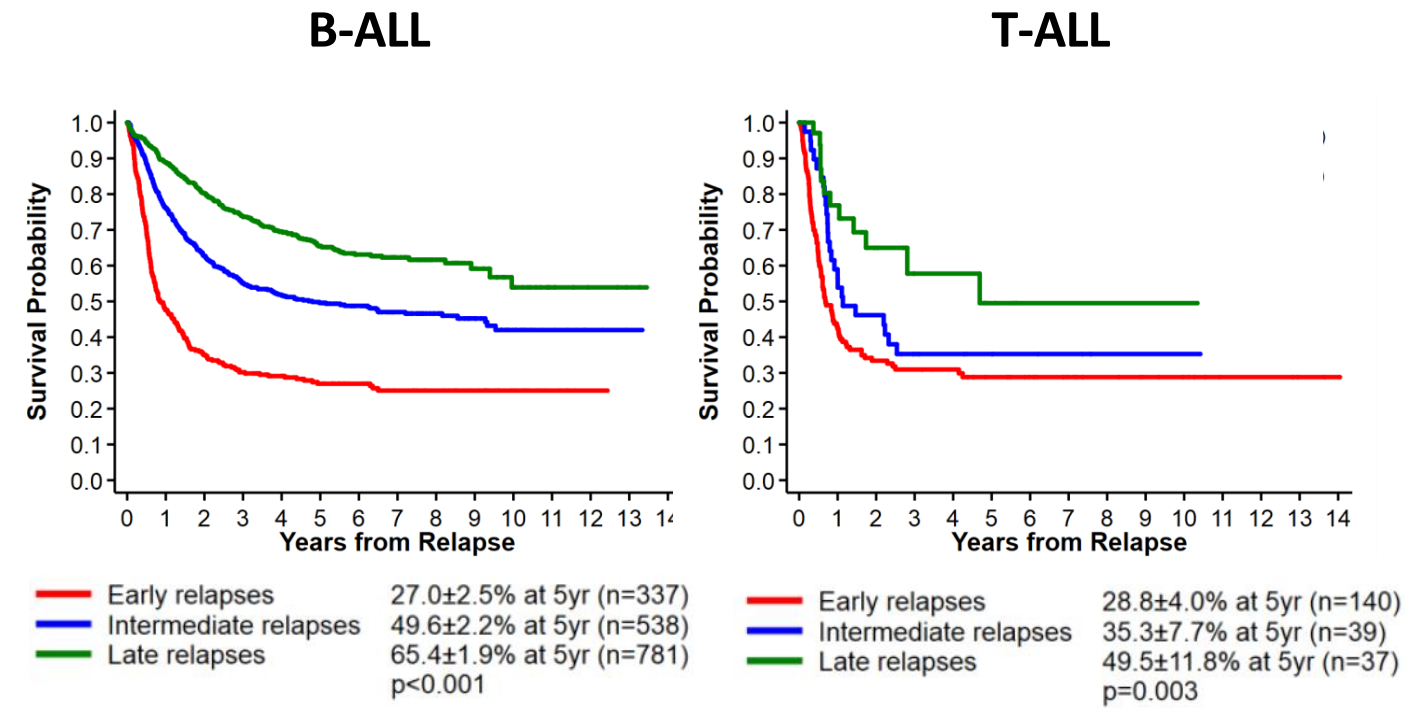
	Median (range) CR1 Duration in Months
B-lineage (non-infants)	34.3 (2.1-186)
• NCI SR	36.3 (2.1-186)
• NCI HR	31.7 (2.2-123)
T-lineage	13.8 (1.1-133)
Infants (at initial dx)	13.8 (3.4-57.5)

71% of infants relapse by 18 months
97% of infants relapse by 36 months

CHILDREN'S ONCOLOGY GROUP

Rheingold SR, et al. ASCO 2019. Abstract 10008; Loh M, et al. SIOP 2019. Abstract FP004.

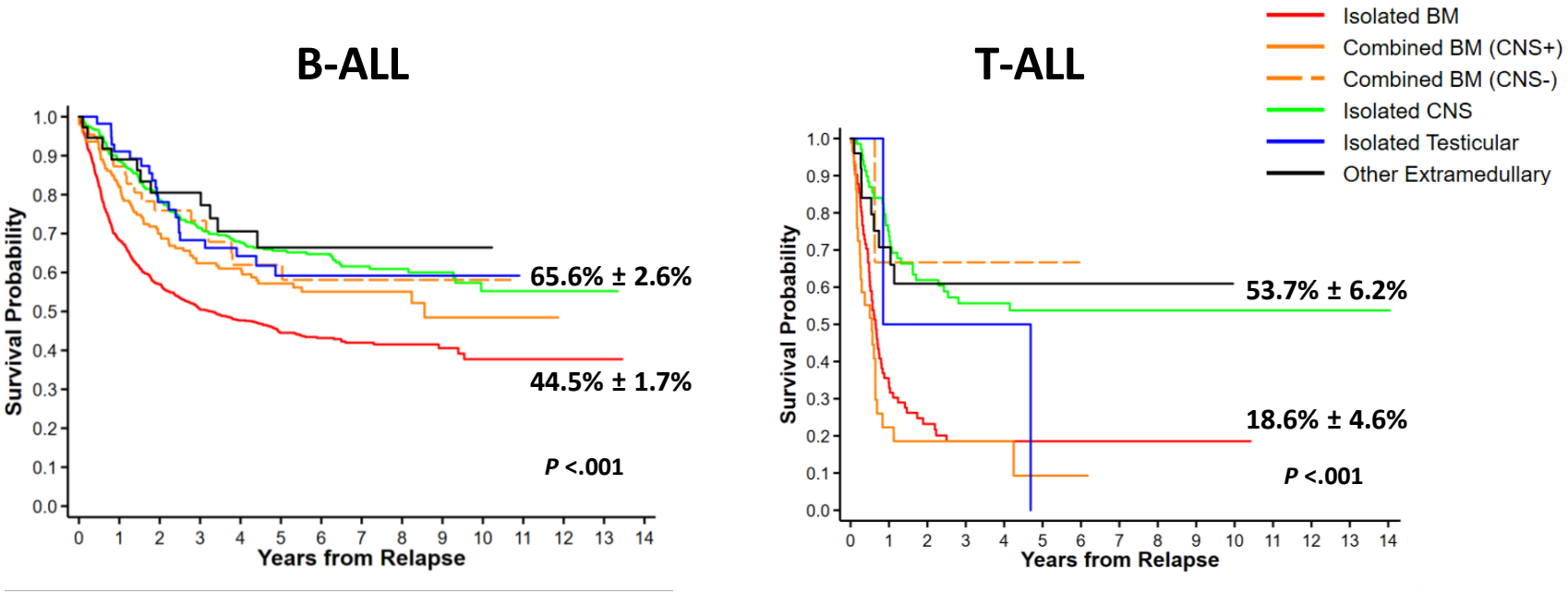
Survival According to Timing of Relapse



CHILDREN'S ONCOLOGY GROUP

Rheingold SR, et al. ASCO 2019. Abstract 10008; Loh M, et al. SIOP 2019. Abstract FP004.

Survival According to Site of Relapse

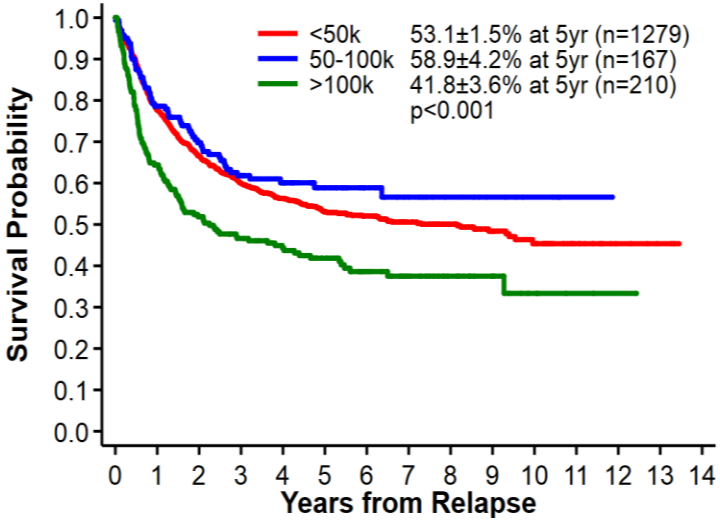


CHILDREN'S ONCOLOGY GROUP

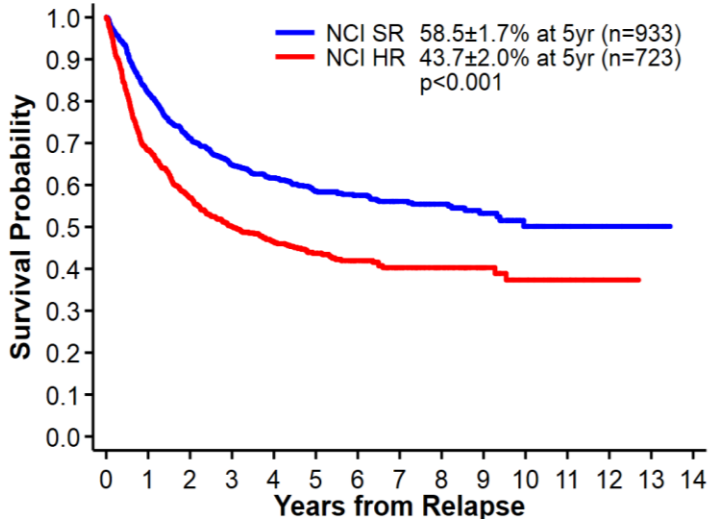
Rheingold SR, et al. ASCO 2019. Abstract 10008; Loh M, et al. SIOP 2019. Abstract FP004.

WBC at Diagnosis and NCI Risk Group Predict Survival Post-relapse in B-ALL

WBC at initial diagnosis



NCI risk stratification



CHILDREN'S ONCOLOGY GROUP

Rheingold SR, et al. ASCO 2019. Abstract 10008; Loh M, et al. SIOP 2019. Abstract FP004.

Cytogenetics Influence Relapse Timing and Outcomes in B-ALL

	Number of Patients	Number of Relapses (%)	5 Yr From Dx EFS ± SE	Median CR1, mo	5 Yr Post-relapse OS ± SE
ETV6-RUNX1	2017	127 (14)	92.4% ± 0.6%	42.9	74.1% ± 4.1%
Trisomy 4 and 10	2567	165 (14)	92.7% ± 0.5%	43.3	70.6% ± 3.8%
E2A-PBX1	392	52 (4)	83.1% ± 2.0%	18.1	31.8% ± 6.6%
iAMP 21	176	52 (5)	67.7% ± 3.7%	44.0	51.9% ± 8.8%
BCR-ABL1	261	58 (4)	62.2% ± 3.2%	33.5	47.3% ± 6.9%
Hypodiploid	182	37 (3)	58.9% ± 3.9%	12.6	16.8% ± 6.4%

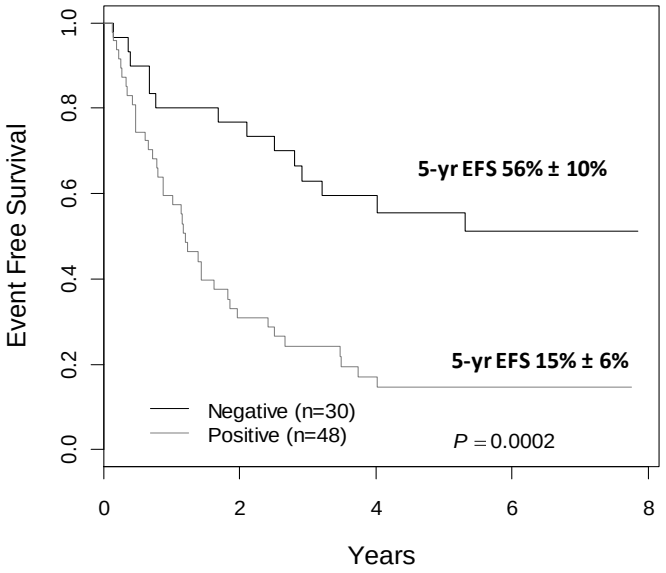
All *P* <.001 except *BCR-ABL1* and iAMP21.

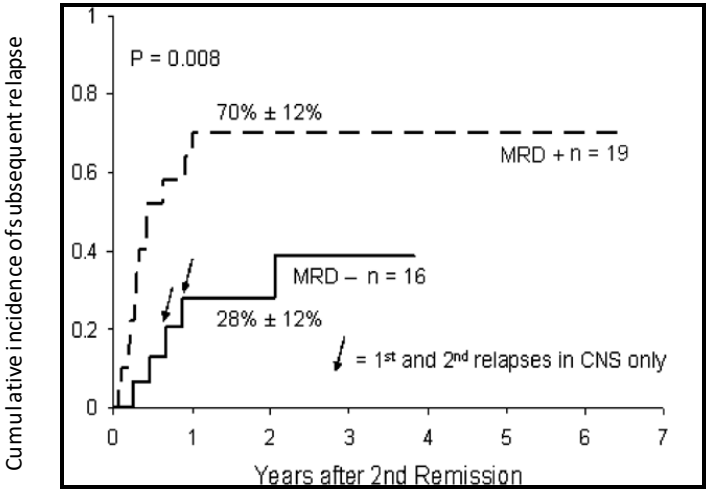
CHILDREN'S ONCOLOGY GROUP

Rheingold SR, et al. SIOP 2022. Abstract O185.

Prognostic Impact of MRD

All B-lymphoblastic patients with CR by MRD (0.01%)





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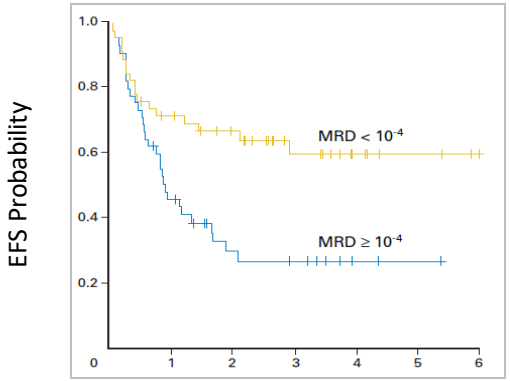
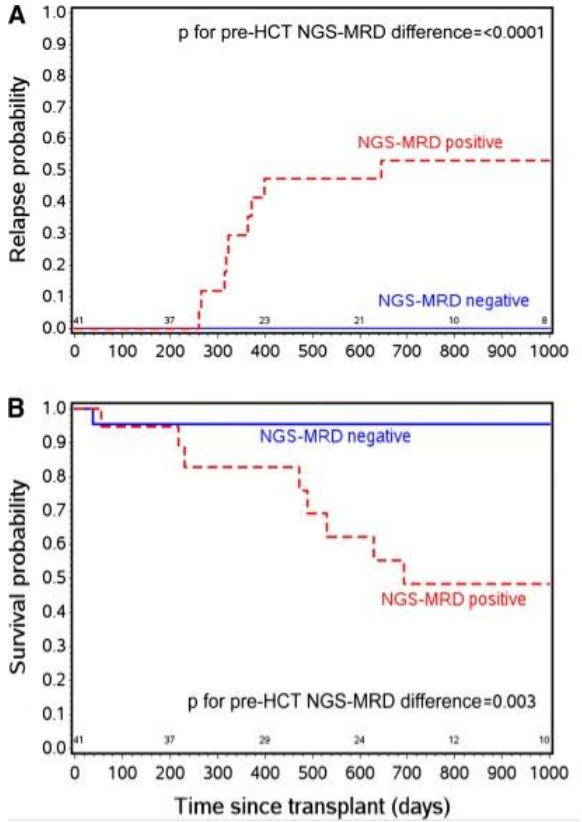
Prognostic Significance of MRD Prior to SCT





Bader P, et al. *J Clin Oncol.* 2009;27(3):377-384; Pulsipher MA, et al. *Blood*. 2015;125(22):3501-3508.

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Prognostic Factors: Summary

- 5-year overall survival for patients who relapse on contemporary protocols has improved
- T-ALL relapses occur earlier than B-ALL (<18 months) and involve the marrow and CNS equally
- Risk factors for worse survival post-relapse include time to relapse <18 months, marrow site, age <1 or >10 years, T-lineage, and NCI high-risk B-ALL at diagnosis
- No improvement in survival for infants post-relapse

Risk Stratification

Risk Stratification at First Relapse

Children's Oncology Group

Risk Status	Definition
Low	Late B-ALL marrow, end-Block 1 MRD <0.1% Late IEM, end-Block 1 MRD <0.1%
Intermediate	Late B-ALL marrow, end-Block 1 MRD ≥0.1% Late IEM, end-Block 1 MRD ≥ 0.1%
High	Early B-ALL marrow Early IEM T-ALL, any site and timing

BFM Group

Risk Status	Definition
Low (S1)	Late IEM relapses
Intermediate (S2)	Very early and early IEM relapses Late B-ALL isolated marrow relapses Early/late B-ALL combined relapses
High (S3 and S4)	Very early and early B-ALL marrow relapses Very early B-ALL combined relapses T-ALL marrow relapses, any timing

Cancer Research UK Children's Cancer Group

Risk Status	Definition
Standard	Late IEM relapses
Intermediate	Early IEM relapse Late isolated B-ALL marrow relapse Early/late combined B-ALL marrow relapse
High	Very early IEM relapse B-ALL early isolated marrow relapse B-ALL very early marrow or combined relapse T-ALL, marrow or combined relapse, any timing

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

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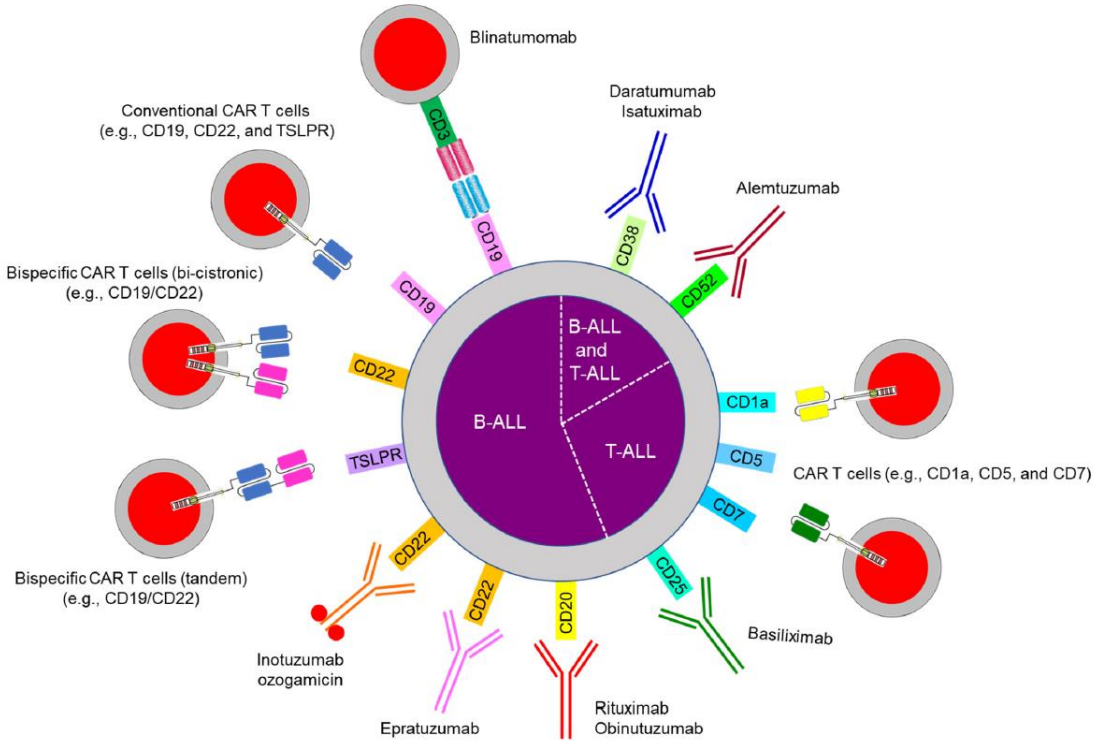
Treatment

Novel Immunotherapeutic Approaches



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HASSENFELD CHILDREN'S HOSPITAL AT NYU LANGONE

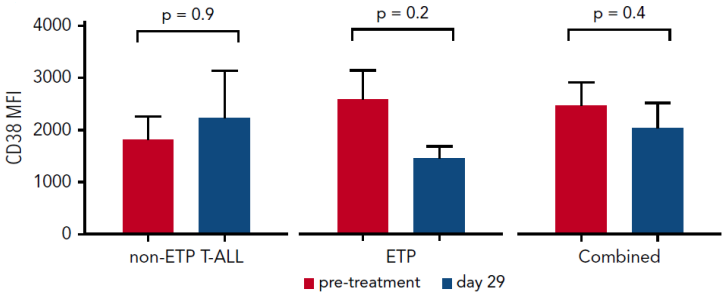
Promising New Immunotherapies for B-ALL

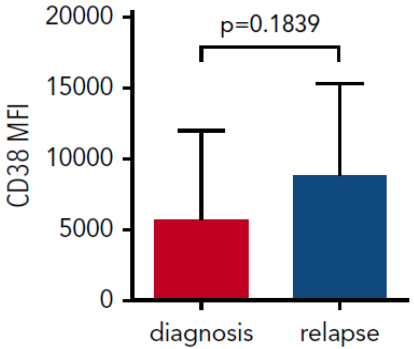
Immune Therapy	Mechanism of Action	Patient Population Studied	Outcome
Blinatumomab	Bispecific T-cell receptor engager (BiTE) that redirects CD3+ T cells to CD19+ blasts	Children and adults with R/R B-ALL Children and adults with MRD >0.1%	39% CR 80% MRD clearance
Inotuzumab	CD22-directed humanized moAb conjugated to calicheamicin	Adults with CD22+ R/R B-ALL	80.7% CR/CRi
CAR T cells	T cells transduced ex vivo with chimeric anti-CD19 receptor	Children with CD19+ R/R B-ALL	83% CR/CRi

Kantarjian H, et al. *N Engl J Med*. 2016;375(8):740-753; Maury S, et al. *N Engl J Med*. 2016;375(11):1044-1053; Topp M, et al. EHA 2016. Abstract 149; Topp MS, et al. *Blood*. 2016;128(22):222; Grupp SA, et al. *Blood*. 2016;128(22):221.

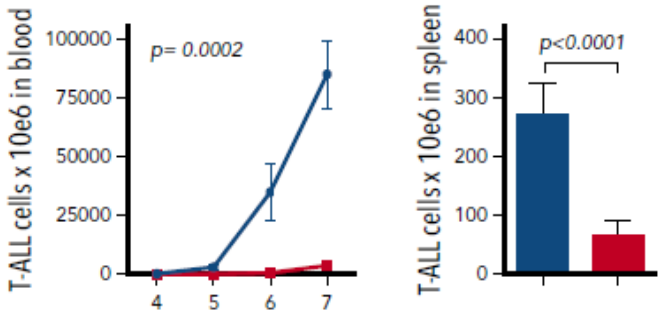
Daratumumab

- Fully humanized monoclonal antibody targeting CD38
- Expression of CD38 in T-ALL is similar to CD19 and CD22 in B-ALL
- Received accelerated FDA approval for relapsed/refractory multiple myeloma
- Well-tolerated in adults





In vivo efficacy of daratumumab*



Fourteen out of 15 responses to single-agent daratumumab.

Bride KL, et al. *Blood.* 2018;131(9):995-999.

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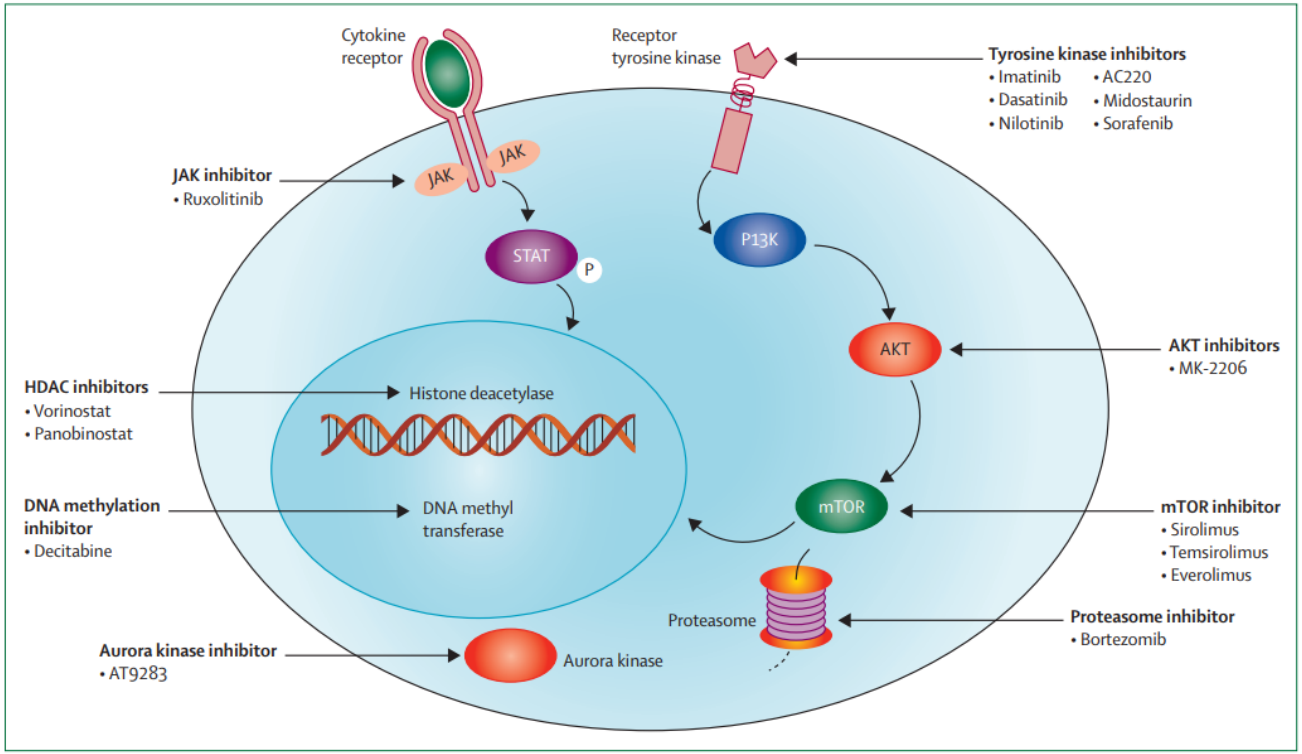
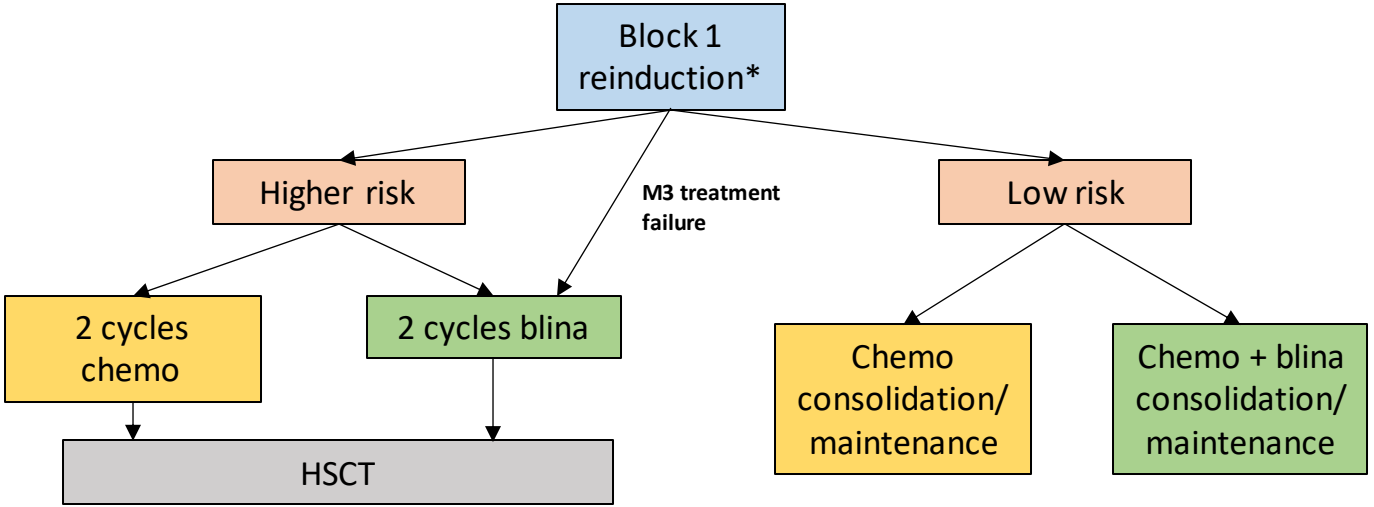
Molecular Targets in ALL



Bhojwani D, Pui CH. *Lancet Oncol.* 2013;14(6):e205-e217.

COG AALL1331: Blinatumomab vs Chemotherapy for First B-ALL Relapse



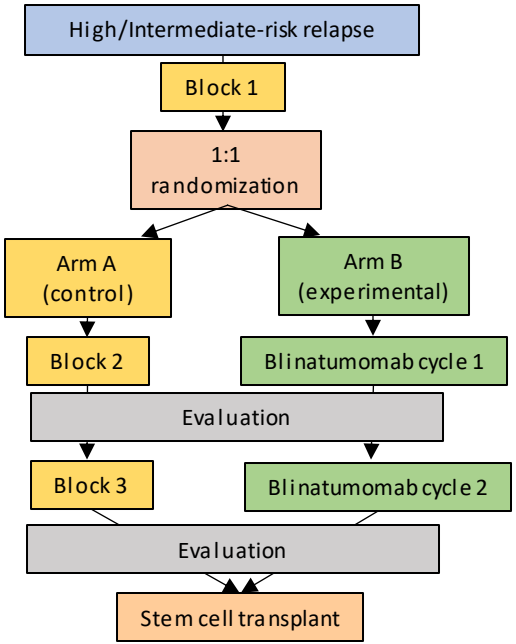
*UKALLR3.

CHILDREN'S ONCOLOGY GROUP

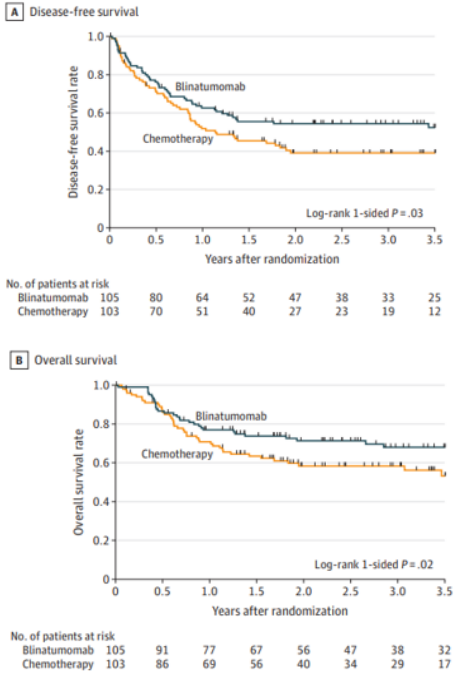
ClinicalTrials.gov Identifier: NCT02101853

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

COG AALL1331: Blinatumomab vs Chemotherapy for First B-ALL Relapse



Improved survival outcomes



CHILDREN'S ONCOLOGY GROUP

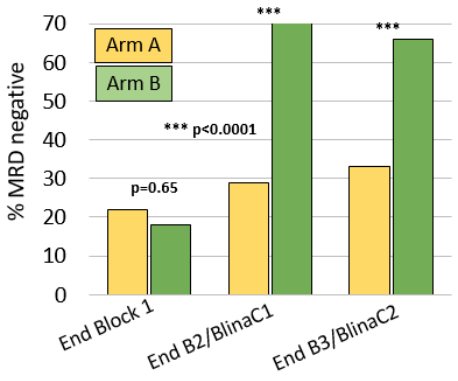
ClinicalTrials.gov Identifier: NCT02101853

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

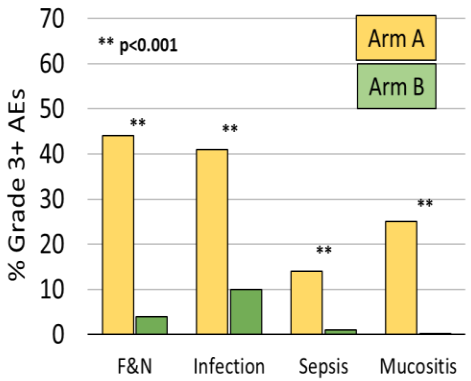
COG AALL1331: High/Intermediate Risk

Blinatumomab arm was superior

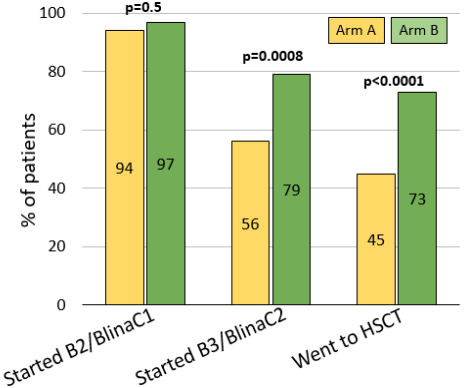
Better MRD clearance



Fewer adverse events



Bridge to transplant



Arm A: Chemo

Arm B: Blina

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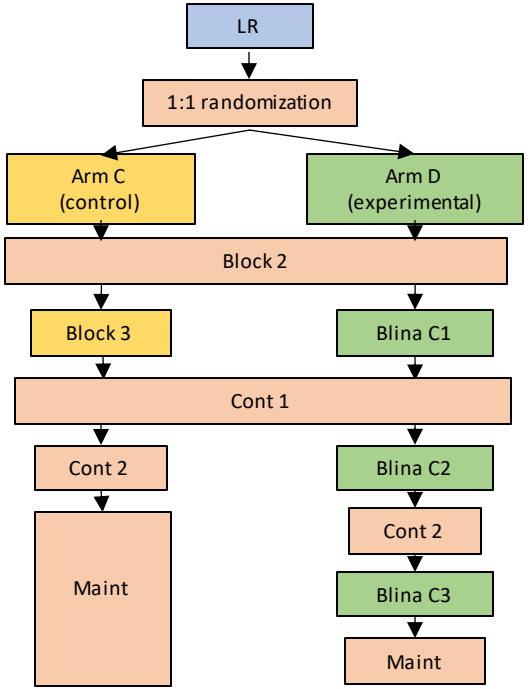
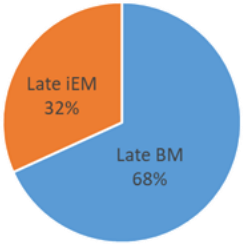
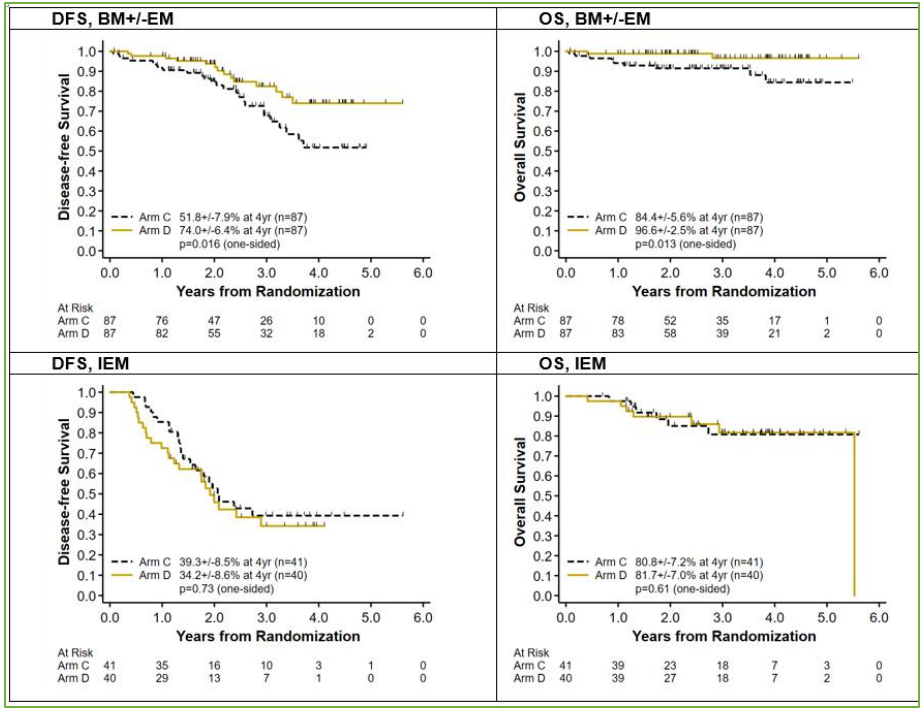
ClinicalTrials.gov Identifier: NCT02101853

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

COG AALL1331: Low-Risk B-ALL Relapse





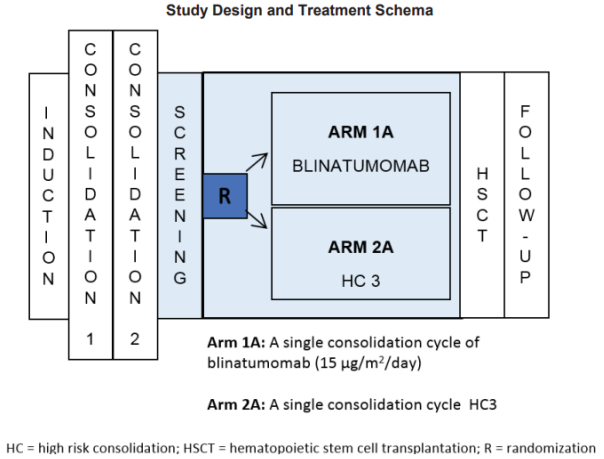


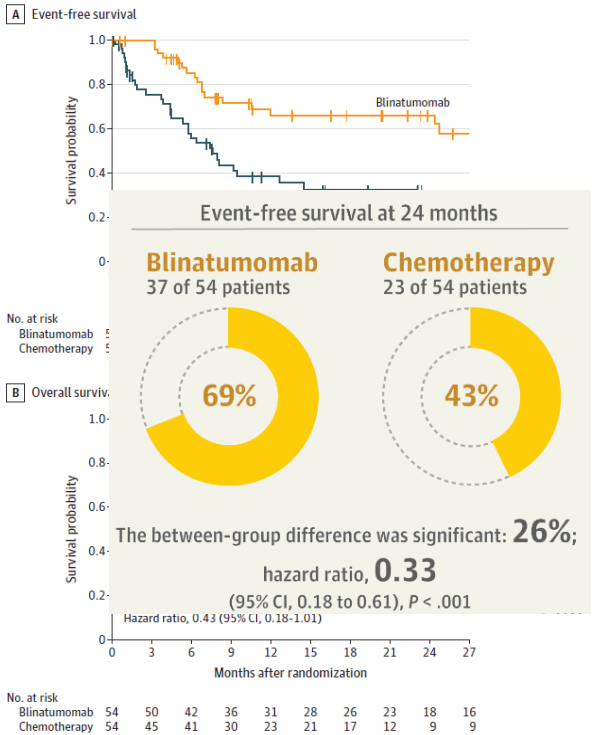
CHILDREN'S ONCOLOGY GROUP

ClinicalTrials.gov Identifier: NCT02101853

Brown PA, et al. *Blood.* 2021;138(suppl 1): abstract 363.

Blinatumomab vs Chemotherapy for First Relapse





In blinatumomab vs chemotherapy groups

- Higher rates of MRD-negative remission (90% vs 54%)
- More proceeded to HSCT (88.9% vs 70.4%)
- Lower rates of grade 3+ AEs

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

ClinicalTrials.gov Identifier: NCT02393859.

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Daratumumab

- DELPHINUS (NCT03384654) phase II study of DARA plus standard of care in patients aged 1-30 years with relapsed/refractory T-ALL or LL

Dosing schedule (≤2 28-day cycles)

DARA (cycles 1-2)
- 16 mg/kg IV QD on days 1, 8, 15, and 22

VPLD (cycle 1)
- Vincristine: 1.5 mg/m^2 (maximum 2 mg) IV QD on days 1, 8, 15, and 22
- Prednisone: 40 mg/m^2 PO divided BID on days 1 to 28
- PEG-asparaginase: 2500 U/m^2 IM or IV QD on days 2 and 16
- Doxorubicin: 60 mg/m^2 IV QD on day 1

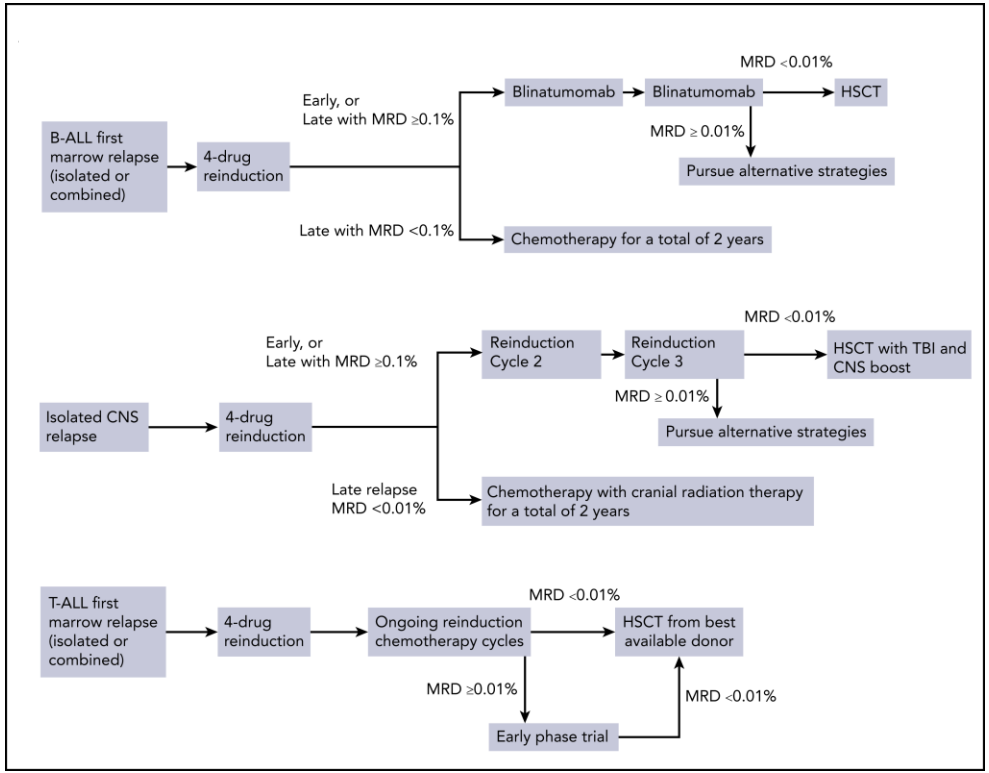
Methotrexate–cyclophosphamide–cytarabine–6-mercaptopurine (cycle 2*)
- Methotrexate: 5 g/m^2 IV QD on day 2
- Cyclophosphamide: 1 g/m^2 IV QD on day 15
- Cytarabine: 75 mg/m^2 IV/SC QD on days 16 to 19 and days 23 to 26
- 6-mercaptopurine: 60 mg/m^2 PO QD on days 15 to 28

*Cycle 2 was optional to allow further treatment for those who did not achieve CR or to consolidate the response prior to HSCT.

- 41.7% CR rate in pediatric T-ALL patients (n = 24) at the end of cycle 1
- 83.3% ORR in pediatric T-ALL patients at any time during treatment
- 41.7% of pediatric T-ALL patients achieved MRD negativity at any time during treatment
- No pediatric T-cell ALL patients discontinued DARA due to AEs

Hogan LE, et al. *J Clin Oncol.* 2022;40(16 suppl): abstract 10001; NCT03384654.

Summary: Approach for First Relapse



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

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Challenges in First Relapse

- Limitations of intensive reinduction chemotherapy
  - High rates of toxic deaths (up to 8%) and serious infections (20%–90%)
  - High rates of MRD positivity despite significant toxicity
    - 75% of patients with early relapse; 50% of patients with late relapse
- ~40% of patients enrolled on COG AALL1331 were unable to proceed to the randomization time point primarily due to toxicities and/or refractory disease and intent-to-treat 2-yr EFS for early BM relapse 25%
- Better strategies for late-isolated CNS relapse are needed

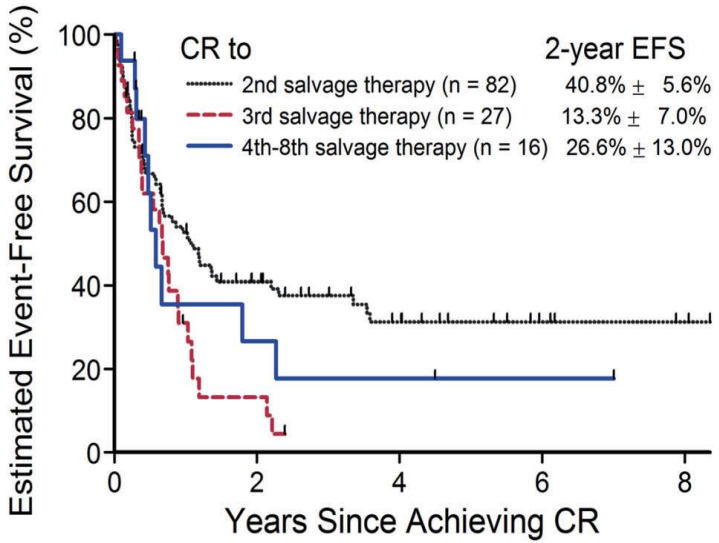
Second or Greater B-ALL Relapse

Historically, outcomes are dismal

325 patients
578 salvage attempts
2005–2013

Relapse, no.	CR Rate
1	69%
2	51%
3	37%
4+	31%

Event-free survival after CR



Sun W, et al. *Leukemia.* 2018;32(11):2316-2325.

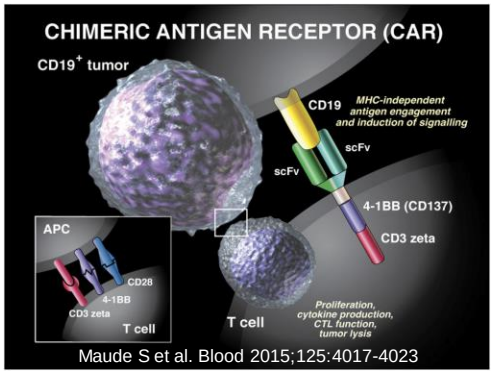
CD19-Directed CAR T-Cell Therapies in Children

The New York Times

HEALTH

F.D.A. Approves First Gene-Altering Leukemia Treatment

- Kymriah (tisagenlecleucel), made by Novartis, was approved to treat children and young adults up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) in August 2017
- More than 550 experimental immunotherapies are being studied → more FDA approvals expected in the near future



Maude S et al. Blood 2015;125:4017-4023

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CD19-Directed CAR T-Cell Therapies in Children

	CHOP/NovartisKymriah	NCI/KITE KTE-C19	Seattle
Co-stim.	4-1BB	CD28	4-1BB
N	75	21	45
MRD-negative CR	81%	60%*	89%*
12-month EFS	50%	NA	50.8%
Cytokine release syndrome	47%	19%	23%
Neurotoxicity (3/4)	13%	19%	21%
Manufacture time	4-6 weeks	1-2 weeks	4 weeks
References	Maude SL, et al. *N Engl J Med.* 2018;378(5):439-448.	Lee DW, et al. *Lancet.* 2015;385(9967):517-528.	Gardner RA, et al. *Blood.* 2017;129(25):3322-3331.

*Intent to treat.

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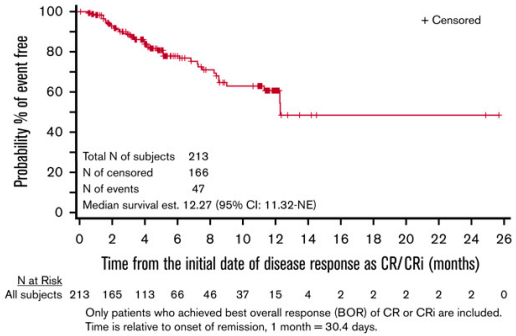
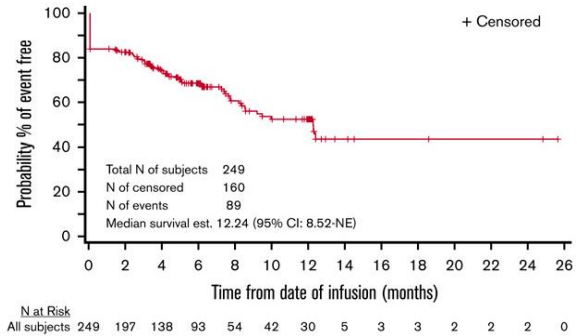
Slide courtesy of Deepa Bhojwani, MD.

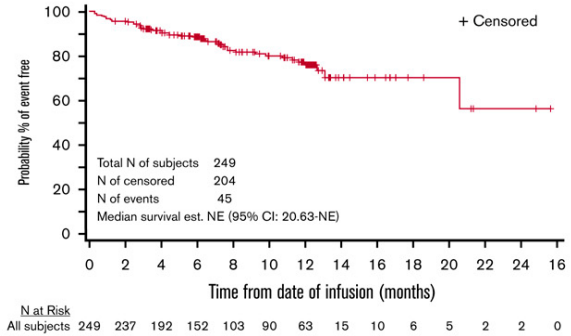
Real-world Experience With Tisagenlecleucel in Pediatric ALL



- CR rate 85.5%
- 12-month duration of response (DOR) 60.9%
- 12-month EFS 52.4%
- 12-month OS 77.2%
- Grade ≥3 CRS and neurotoxicity rates of 11.6% and 7.5%, respectively

➡ Very similar to ELIANA trial that led to approval





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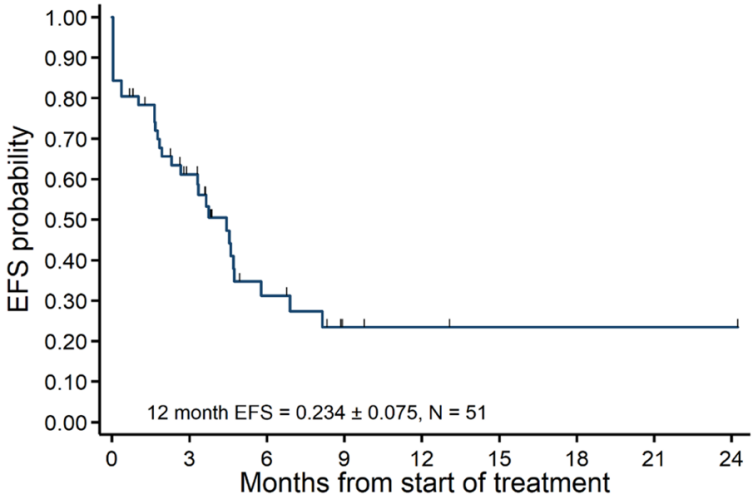
Pasquini MC, et al. *Blood Adv*. 2020;4(21):5414-5424.

Inotuzumab Ozogamicin for Childhood ALL

51 children with R/R ALL treated in the compassionate use program at North American, Australian, and European Centers

- **Clinical activity**
  - 67% complete remission rate
  - 71% MRD negative
- **Safety profile**
- *Most common severe adverse events*
  - Grade 3/4 infection 22%
  - Grade 3 hepatic transaminitis, hyperbilirubinemia 12%
  - Post-transplant hepatic sinusoidal obstruction syndrome 52% (11/21)



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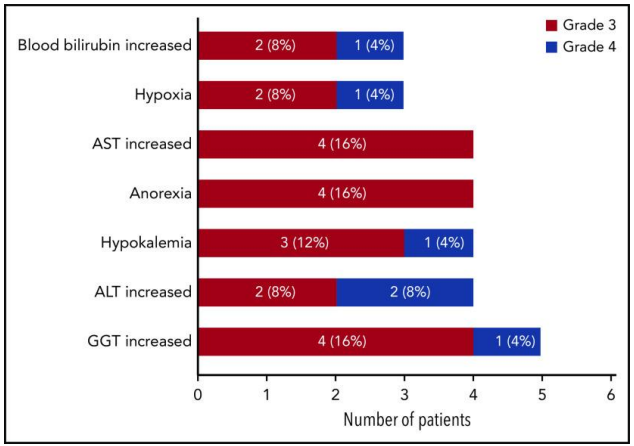
Bhojwani D, et al. *Leukemia.* 2019;33(4):884-892.

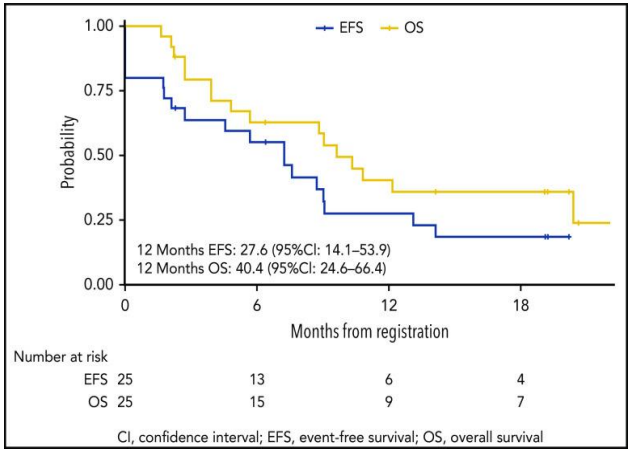
Inotuzumab for Relapsed/Refractory B-ALL

- A phase I study of inotuzumab ozogamicin (InO) in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study)
- The recommended phase II dose of InO for pediatric patients with ALL was established at 1.8 mg/m^2 per course (0.8, 0.5, 0.5 mg/m^2)
- Of the patients with multiple R/R ALL, 85% reached CR after 1 course of single-agent InO at the RP2D, 100% of whom had MRD negativity
- No cases of SOS during InO treatment or among 7 patients who received a transplant after InO

Most common non-hematologic AEs



Overall EFS and OS



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

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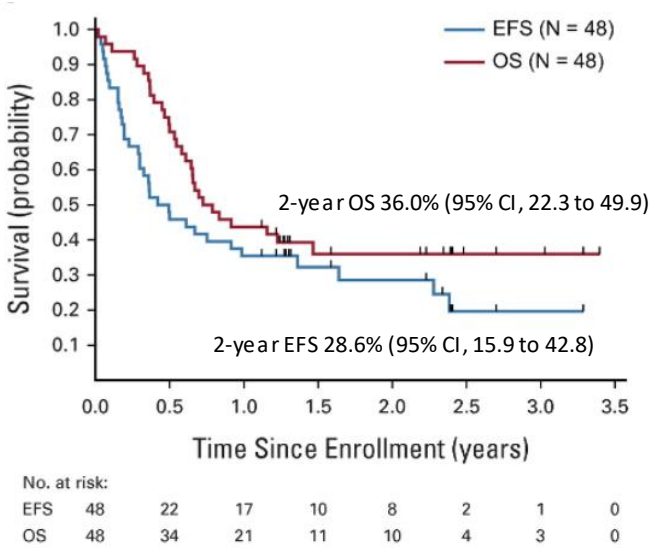
Inotuzumab for Second or Greater Relapse

- COG AALL1621 phase II trial of InO for relapsed or refractory B-ALL
- Single-agent cohort completed (n = 48)
  - 0.8 mg/m^2 on day 1; 0.5 mg/m^2 on days 8 and 15
  - 58% CR/CRi rate
  - 68% MRD <0.01%
  - Post-transplant SOS 29% (6/21)
- Combination cohort activated in April 2021
  - Combined with mBFM consolidation



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ClinicalTrials.gov Identifier: NCT02981628

O'Brien M, et al, *J Clin Oncol.* 2022;40(9):956-967.

Selected Early-Phase Small-Molecule Inhibitor Trials

ClinicalTrials.gov identifier	Phase	Drug Class	Treatment Regimen	Population
NCT00873093	II	Proteasome inhibitor	Bortezomib plus 4-drug reinduction	Relapsed B- and T-ALL
NCT02303821	Ib	Proteasome inhibitor	Carfilzomib plus 4-drug reinduction	Relapsed B- and T-ALL
NCT03817320	I	Proteasome inhibitor	Ixazomib plus 4-drug reinduction	Relapsed B- and T-ALL
NCT03792256	I	CDK4/6 inhibitor	Palbociclib plus 4-drug reinduction	Relapsed B- and T-ALL
NCT03515200	I	CDK4/6 inhibitor	Palbociclib plus reinduction therapy	Relapsed B- and T-ALL
NCT03740334	I	CDK4/6 inhibitor	Ribociclib plus everolimus	Relapsed B- and T-ALL
NCT03236857	I	BCL2 inhibitor	Venetoclax plus chemotherapy	Relapsed B- and T-ALL
NCT03181126	I	BCL2 inhibitor	Venetoclax/navitoclax plus chemotherapy	Relapsed B- and T-ALL
NCT01523977	I	mTOR inhibitor	Everolimus plus 4-drug reinduction	Relapsed B- and T-ALL
NCT04029688	I/II	MDM2 inhibitor	Idasanutlin plus venetoclax	Relapsed B-ALL

Small-Molecule Inhibitors Plus 4-Drug Reinduction

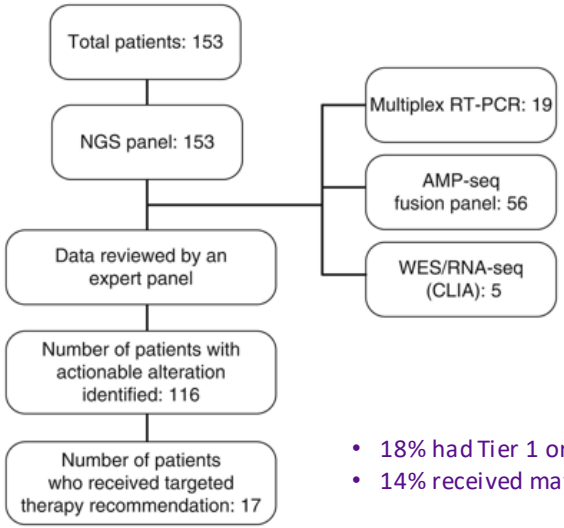
		CR Rate	MRD Response	Outcomes
NCT00873093	COG AALL07P1 (Bortezomib) First early marrow relapse	68% ± 5% B-ALL CR2 68% ± 10% T-ALL CR2	29% <0.01% and 40% <0.1% end of Block 1	3-yr EFS 16%; 3-yr OS 18% very early relapse 3-yr EFS 23%; 3-yr OS 29% early relapse
NCT01523977	DFCI 11-237 (Everolimus) First marrow 18+ months from CR1	86% (21 B-ALL and 1 T-ALL) CR2	68% ≤0.1% end of Block 1	NR
NCT01403415	COG ADVL1114 (Temsirolimus) Second or > relapsed ALL	47% (7 of 15 CR/CRi)	71% (5 of 7) <0.1%	NR
NCT03792256	COG AINV18P1 (Palbociclib) Second or > R/R ALL or first T-ALL	42% (5 of 12 CR/CRi)	80% (4 of 5) <0.1%	NR

Horton TM, et al. *Br J Haematol*. 2019;186(2):274-285; Place AE, et al. *Pediatr Blood Cancer*. 2018;65(7):e27062; Rheingold SR, et al. *Br J Haematol*. 2017;177(3):467-474.

Future Directions

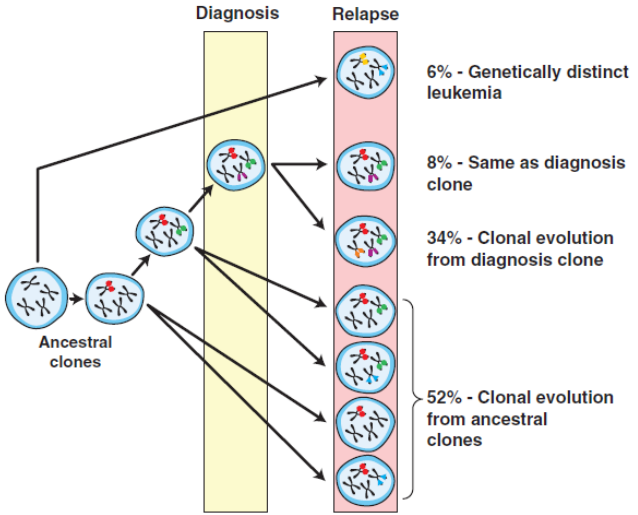
Future Directions

- Precision medicine approaches
  - **LE**ukemi**A** **P**recision-Based Therapy
  - Hem-iSMART



- 18% had Tier 1 or 2 recommendations
- 14% received matched targeted therapy

- Preventing the emergence of drug-resistant clones



Pikman Y, et al. *Cancer Discov.* 2021;11(6):1424-1439.

Mullighan CG, et al. *Science.* 2008;322(5906):1377-1380.

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Future Directions in Immunotherapy

- Optimize dose, schedule, combinations, and eligible populations
- Address resistance/relapse due to low antigen expression and/or loss
  - Multiantigen targeting
  - Combination therapy to increase antigen expression
- Reduce CAR T-cell manufacturing failures
- Address CAR T-cell loss due to rejection, T-cell exhaustion
  - Constructs: humanized, co-stimulatory molecules
  - Checkpoint inhibitors, epigenetic modifiers, antigen vaccines
- Unique toxicities
  - Prevention, treatment strategies

Conclusions

- Despite the success in treating childhood ALL, less than half of patients overall with marrow relapse survive long-term
- MRD response is an important prognostic variable and treatment options are needed for patients in CR with detectable MRD
- The intensity of prior therapy does not appear to change relapse outcomes, suggesting that intrinsic chemoresistance may be present in a subpopulation of cells at diagnosis
- Poor salvage rates underscore the need to develop new frontline treatment strategies to reduce the risk for treatment failure
- Genome-wide initiatives to identify targets/pathways at relapse may offer promise for prioritizing new agents and developing new treatment options

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Acknowledgments

COG ALL Committee

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Karen Rabin
Mini Devidas
John Kairalla

Michael Borowitz
Brent Wood
Karen Rabin
Julie Gastier-Foster
Nyla Heerema
Andrew Carroll
Mary Relling
Jun Yang
Charles Mullighan
Lingyun Ji

Sarah Tasian
Anne Angiolillo
Susan Rheingold
Patrick Brown
Jennifer McNeer
Maureen O'Brien
Sumit Gupta
Rachel Rau
Shannon Maude
John Kairalla

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Global Leukemia Academy

Case 3: Relapsed/ Refractory Setting

Miri Tukana

APTITUDE HEALTH

Our center

Fiji

- Population ~900,000
- Upper middle income
- We do have a dedicated pediatric oncology unit
- 20–30 oncology patients per year, with an age range of 0–15 years
- 2 doctors working with children with cancer
- 6 nurses working with children with cancer
- Do not have a patient registry
  - Excel sheet in Fiji and NZ

Challenges

- Skilled nurses moving to NZ and Australia
- Unavailability of chemotherapy
- Lab services: no basic tests, immunochemistry
- Radiology services: lack expertise, a lot of down time
- Many competing priorities

Patient

- ES: 25 months old, female
- Cough and fever for 1 month
- Multiple presentations to health centers and several courses of antibiotics
- Child becoming increasing pale with submandibular swelling; presented to ED and FBC done
- Hb 4.1 g/dL, WCC 43.7, Plt 30,000

Patient: On examination

- Young female infant, non-dysmorphic, very pale but not in obvious distress. Well nourished
- BP: Sys 97-124; Dys 54-66; MAP 67-85; Temp: 36-37°C
- HR: 110–120; RR: 20s; CBG: 5–7 mmol/L; Sats: 99% RA
- Pupils 2 mm bil/reactive
- Multiple pea-sized nodes over cervical region. Matted nodes over Lt submandibular region. Also has matted nodes over Lt inguinal region
- Resp: Clear lung fields with good air entry bilaterally
- CVS: normal heart sounds/no murmur
- Abd: soft
- Liver-extends down to umbilicus
- (+) Splenomegaly grade 4
- Ext: warm, CR <2 sec, pale, resolved skin lesions

Summary

25-month-old female with hepatosplenomegaly, bicytopenia, and leukocytosis

Patient

Investigation

Blood film

- RBC: mostly normochromic cells noted. Few elliptocytes and microcytic hypochromic cells seen
- WBC: neutropenia and increased lymphoblast noted at 91%, a few of which show cerebriform nuclear pattern. Most of the blasts have agranular cytoplasm and intermediate nuclear size. Few blasts show granular cytoplasm
- Platelets: decreased platelet population seen with few large and giant forms
- The features are suggestive of **ACUTE LYMPHOBLASTIC LEUKEMIA. ALL, L2**

Progress

- PICU admission
- Hyperhydration with allopurinol
- BMA and IT methotrexate and sent CSF for cytology
- Platelets prior, during, and after BMA
- Packed cells; tachycardic (HR 160s)
- Facial puffiness → dec fluids to 100 mL/m^2/hr; UO >3 mL/kg/hr
- Started prephase with prednisone and transferred to oncology unit

Treatment

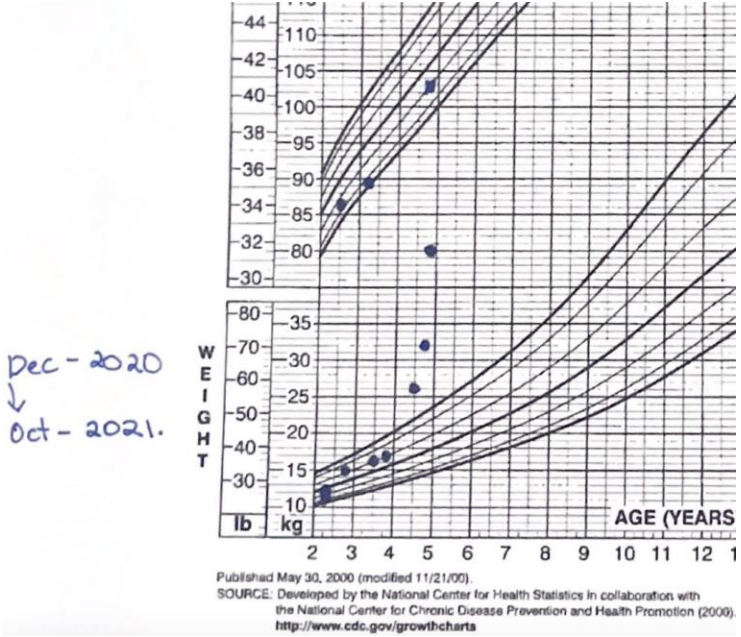
Phase	Drugs
Prephase + Induction	• Prednisone (40 mg/m^2/d • Methotrexate 10 mg IT days 1, 15, 29 • L-asparaginase (6000 U/m^2) (9 doses) • Vincristine (1.5 mg/m^2) 1.16 mg IV day 1, 8, 15, 22
Consolidation	• Methotrexate 12 mg IT day 1, 8, 15 • 6-mercaptopurine (60 mg/m^2/day) day 1-28 • Cyclophosphamide (1000 mg/m^2) IV day 1, 22 • Ara-C (75 mg/m^2/day) SC days 1-4, 8-11, and 15-18, 22-25
Interim Maintenance	• Methotrexate age related 10 mg IT day 29 • Vincristine (1.5 mg/m^2) IV days 1, 29 • Dexamethasone (6 mg/m^2/day) PO BD days 1-5, 29-33 • 6-mercaptopurine (75 mg/m^2/day) days 1-56 • Methotrexate (20 mg/m^2/week) PO days 1, 8, 15, 22, 36, 43, 50 (omit day 29 as IT given)
Delayed Intensification	• Vincristine (1.5 mg/m^2) day 1, 8, 15 • Doxorubicin (25 mg/m^2) day 1, 8, 15 • *E. coli* L-asparaginase (6000 U/m^2) × 6 doses M, W, F, from D3 • Dexamethasone (10 mg/m^2/day) 1-7, 15-21 • Methotrexate age related 12 mg day 1, 29, 36 • 6-mercaptopurine (60 mg/m^2/day) day 29-43 • Cyclophosphamide (1000 mg/m^2) IV infuse × 1 hr day 29 • Ara-C (75 mg/m^2/day) SC day 29-32, 36-39
Maintenance	• Methotrexate 12 mg IT • Vincristine (1.5 mg/m^2) IV days 1, 29 • Dexamethasone (6 mg/m^2/day) days 1-5, 29-33 • 6-mercaptopurine (75 mg/m^2/day) 1-56 • Methotrexate 20 mg/m^2/week days 1, 8, 15 etc (*omit if IT given)

Progress

Last month of maintenance

- ES: 4 yr 8 mo had lower limb weakness acutely but overnight was well and mobilizing again; neuro exam was normal
- Hyperphagia and mood changes
- Markedly obese past 3 months; diet and exercise

Growth chart



Progress

Last month of maintenance

- ES: 4 yr 9 mo presents to ED with seizures
- Apparently well the day of admission
- She was weak, unable to get out of bed, and sleepy
- Noted up-rolling of eyes and jerky movements of the whole body
- Lasted less than 5 min
- Screened and started antibiotics

RELAPSE: CNS

- Treatment
- Palliative care
- Fitted and became comatose
- Parents opted to take home due to strict COVID restrictions in hospital
- Passed away at home 2 days later

Relapse

Evid Based Complement Alternat Med. 2022; 2022: 7783823.
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PMCID: PMC8959945
PMID: 35356245

Evid Based Complement Alternat Med

Obesity as a Prognostic Factor of Central Nervous System Relapse in Children with Acute Lymphoblastic Leukemia: A Single-Centre Study and Literature Review

Guo-qian He, [1,2] Yi-ling Dai, [1,2] Ming-yan Jiang, [1,2] Ju Gao, [1,2] and Xia Guo [1,2]

Associated Data

▸ **Data Availability Statement**

Abstract

Go to: ▸

Points for discussion

- Middle-income country; worth to invest in treatment of ALL relapse

Global Leukemia Academy

ALL Case-Based Panel Discussion

Moderators: Michael Osborn and Elizabeth Raetz

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Global Leukemia Academy

Session Close

Elizabeth Raetz

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Repeat Question 2

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

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

Repeat Question 3

Which assertion is correct for children with B-ALL?

A. Inotuzumab is approved for induction treatment of relapsed B-ALL in childhood

B. Inotuzumab dosage is 3 mg/m^2

C. Blinatumomab is approved for consolidation treatment before HSCT in children with B-ALL

D. None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

Thank You!

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