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Emerging and Practical Concepts and Controversies in Leukemias

16 May 2021

Virtual Breakout: Pediatric Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Patrick Brown

APTITUDE HEALTH

Meet the Faculty

Patrick A. Brown, MD
Johns Hopkins University
School of Medicine, USA

JPAC Faculty

> **Michael Osborn, MBBS**
Royal Adelaide Hospital Cancer Centre, Australia

> **Bhavna Padhye, MD**
The Children's Hospital at Westmead, Australia

Objectives of the Program

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

Virtual Breakout – Pediatric ALL Patients (Day 2)

Chair: Patrick Brown

TIME (UTC +9)	TITLE	SPEAKER
11.00 – 11.15	Session open • Educational ARS questions for the audience	Patrick Brown
11.15 – 11.35	First-line treatment of pediatric ALL • Presentation (15 min) • Q&A (5 min)	Bhavna Padhye
11.35 – 11.55	Current treatment options for relapsed ALL in children including HSCT; COVID-19 considerations and vaccinations • Presentation (15 min) • Q&A (5 min)	Michael Osborn
11.55 – 12.15	Bispecifics for pediatric ALL, focus on frontline therapy • Presentation (15 min) • Q&A (5 min)	Patrick Brown
12.15 – 12.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: All faculty	Case 1: Bhavna Padhye (10 min) Case 2: Michael Osborn (10 min) Discussion (10 min)
12.45 – 13.30	Interactive Q&A and session close • Educational ARS questions for the audience	Patrick Brown

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Educational ARS Questions

Patrick Brown

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Q

Educational Questions Pediatric ALL

Question 1: Which of the following subsets of 1st relapse ALL patients can be considered at very high risk?

a) All patients with B-ALL relapsing within 18 months from diagnosis
b) All patients with MLL-rearranged leukemia
c) All patients with hypodiploidy
d) Each of the 3 previous subsets

Q

Educational Questions Pediatric ALL

Question 2: Which assertion is correct for children with B-ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment
b) Inotuzumab dosage is 3 mg/m^2
c) TBI-based conditioning regimen should be preferentially used in children above the age of 4 years
d) None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

Q

Educational Questions Pediatric ALL

Question 3: For children and adolescents with high risk of first relapse of B-ALL, what regimen offers the best chance of survival?

a) Reinduction chemotherapy followed by HSCT
b) Reinduction chemotherapy followed by consolidation chemotherapy followed by HSCT
c) Reinduction chemotherapy followed by blinatumomab followed by HSCT
d) Reinduction chemotherapy followed by consolidation chemotherapy followed by continuation/maintenance chemotherapy
e) Reinduction chemotherapy followed by blinatumomab followed by continuation/maintenance chemotherapy

Global Leukemia Academy

First-line treatment of pediatric ALL

Bhavna Padhye

APTITUDE HEALTH

First-Line Treatment of Pediatric ALL

Dr Bhavna Padhye

MBBS, FRACP, MClinTRes, PhD

Cancer Centre for Children

The Children's Hospital at Westmead, Sydney, Australia

First-Line Treatment of Pediatric ALL

- **Ph-negative or Ph-like B-ALL**
- **Ph-positive B-ALL**
- **T-ALL**
- **Infant ALL**

First-Line Treatment of Pediatric ALL

- **Ph-negative or Ph-like B-ALL**
- Ph-positive B-ALL
- T-ALL
- Infant ALL

AALL0031

original reports

Outcome in Children With Standard-Risk B-Cel Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0331

Kelly W. Maloney, MD[1,2]; Meenakshi Devidas, PhD[3]; Cindy Wang, MS[4]; Leonard A. Mattano, MD[3]; Alison M. Friedmann, MSc, MD[5]; Patrick Buckley, MD, PhD[3]; Michael J. Borowitz, MD, PhD[6]; Andrew J. Carroll, PhD[3]; Julie M. Gastier-Foster, PhD[10-12]; Nyla A. Heerema, PhD[13]; Nina Kadan-Lottick, MSPH, MD[14]; Mignon L. Loh, MD[15,16]; Yousif H. Matloub, MD[17]; David T. Marshall, MS, MD[18]; Linda C. Stork, MD[19]; Elizabeth A. Raetz, MD[20,21]; Brent Wood, MD, PhD[22,23]; Stephen P. Hunger, MD[24-26]; William L. Carroll, MD[20,21]; and Naomi J. Winick, MD[27,28]

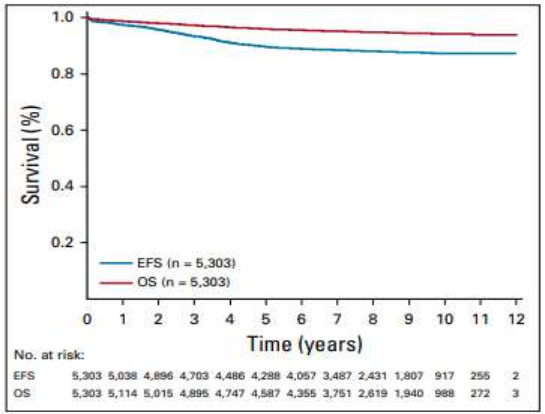


FIG 2. Event-free survival (EFS) and overall survival (OS; 6-year EFS, 88.96% ± 0.46%; 6-year OS, 95.54% ± 0.31%).

AALL0331 enrolled 5,377 patients

All patients received a 3-drug induction with dexamethasone, vincristine, and pegaspargase (PEG) and were then classified as SR low, SR average, or SR high on the basis of genetic features and response

At the EOI, patients were randomized to receive standard consolidation (6-MP, vincristine, and intrathecal methotrexate) vs intensified consolidation (cyclophosphamide, cytarabine, 6-MP, vincristine, pegaspargase, and intrathecal methotrexate)

Maloney KW, et al. *J Clin Oncol.* 2020;38:602-612.

COG AALL0331

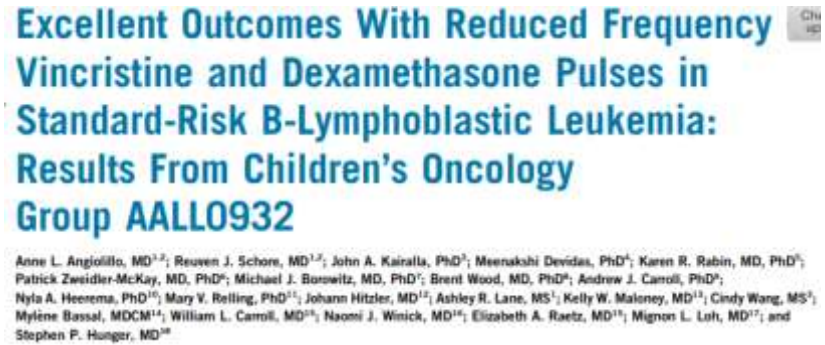
For **standard-risk low patients** (blasts positive for triple trisomies of chromosomes 4, 10, and 17 or positive for *ETV6-RUNX1* plus day 8 [or day 15] M1 bone marrow and day 29 MRD <0.1%), the 5-year EFS and OS rates were 95% and 99%, respectively

Standard-risk high patients (day 15 bone marrow >5% blasts and/or day 29 MRD >0.1%) were nonrandomized to intensified consolidation and 2 intensified IM and DI phases, resulting in 5-year EFS and OS rates of 85% an 94%, respectively

The 5-year EFS and OS for **all evaluable patients** with standard-risk disease was 89% and 96%, respectively, and intensified consolidation did not significantly improve outcomes for **standard-risk average patients**

Maloney KW, et al. *J Clin Oncol.* 2020;38:602-612.

COG AALL0932



Excellent Outcomes With Reduced Frequency Vincristine and Dexamethasone Pulses in Standard-Risk B-Lymphoblastic Leukemia: Results From Children's Oncology Group AALL0932

Anne L. Angiolillo, MD[1,2]; Reuven J. Schore, MD[1,2]; John A. Kairalla, PhD[3]; Meenakshi Devidas, PhD[4]; Karen R. Rabin, MD, PhD[5]; Patrick Zweidler-McKay, MD, PhD[6]; Michael J. Borowitz, MD, PhD[7]; Brent Wood, MD, PhD[8]; Andrew J. Carroll, PhD[9]; Nyla A. Heerema, PhD[10]; Mary V. Relling, PhD[11]; Johann Hitzler, MD[12]; Ashley R. Lane, MS[1]; Kelly W. Maloney, MD[13]; Cindy Wang, MS[1]; Mylène Bassal, MDCM[14]; William L. Carroll, MD[15]; Naomi J. Winick, MD[16]; Elizabeth A. Raetz, MD[15]; Mignon L. Loh, MD[17]; and Stephen P. Hunger, MD[18]

AALL0932 enrolled 9,229 patients with B-ALL

2,364 average-risk (AR) patients were randomly assigned (2 × 2 factorial design) at the start of maintenance therapy

Vincristine-dexamethasone pulses every 4 **(VCR-DEX4)** or every 12 **(VCR-DEX12)** weeks, and a starting dose of once-weekly oral methotrexate of 20 mg/m^2 **(MTX20)** or 40 mg/m^2 **(MTX40)**

Angiolillo AL, et al. *J Clin Oncol*. 2021;39:1437-1447.

COG AALL0932

The 5-year DFS and OS for patients randomly assigned to receive **VCR-DEX4 vs VCR-DEX12** were 94.1% and 98.3% vs 95.1% and 98.6%

The 5-year DFS and OS for AR patients randomly assigned to receive **MTX20 vs MTX40** were 95.1% and 98.8% vs 94.2% and 98.1%

The NCI-SR AR B-ALL who received VCR-DEX12 had outstanding outcomes despite receiving one-third of the vincristine-dexamethasone pulses previously used as standard of care on COG trials

The higher starting dose of MTX of 40 mg/m^2 once weekly did not improve outcomes when compared with 20 mg/m^2 once weekly

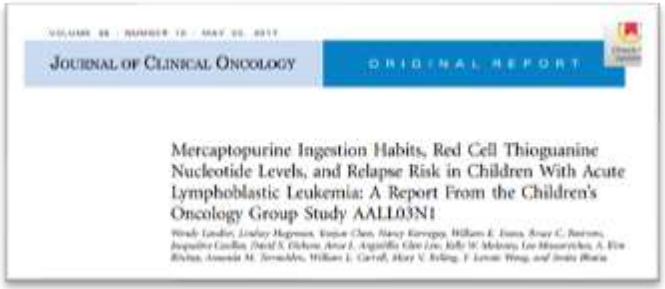
Angiolillo AL, et al. *J Clin Oncol*. 2021;39:1437-1447.

Duration of Maintenance Therapy Different for Boys and Girls?

Optimizing therapy in the modern age: differences in length of maintenance therapy in acute lymphoblastic leukemia

David T. Teachey,[1] Stephen P. Hunger,[1] and Mignon L. Loh[2]

Teachy DT, et al. *Blood*. 2021;137:168-177.



JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Mercaptopurine Ingestion Habits, Red Cell Thioguanine Nucleotide Levels, and Relapse Risk in Children With Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group Study AALL03N1

CLINICAL TRIALS AND OBSERVATIONS

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

Published in final edited form as:
JAMA Oncol. 2015 June 1; 1(3): 287–295. doi:10.1001/jamaoncol.2015.0245.

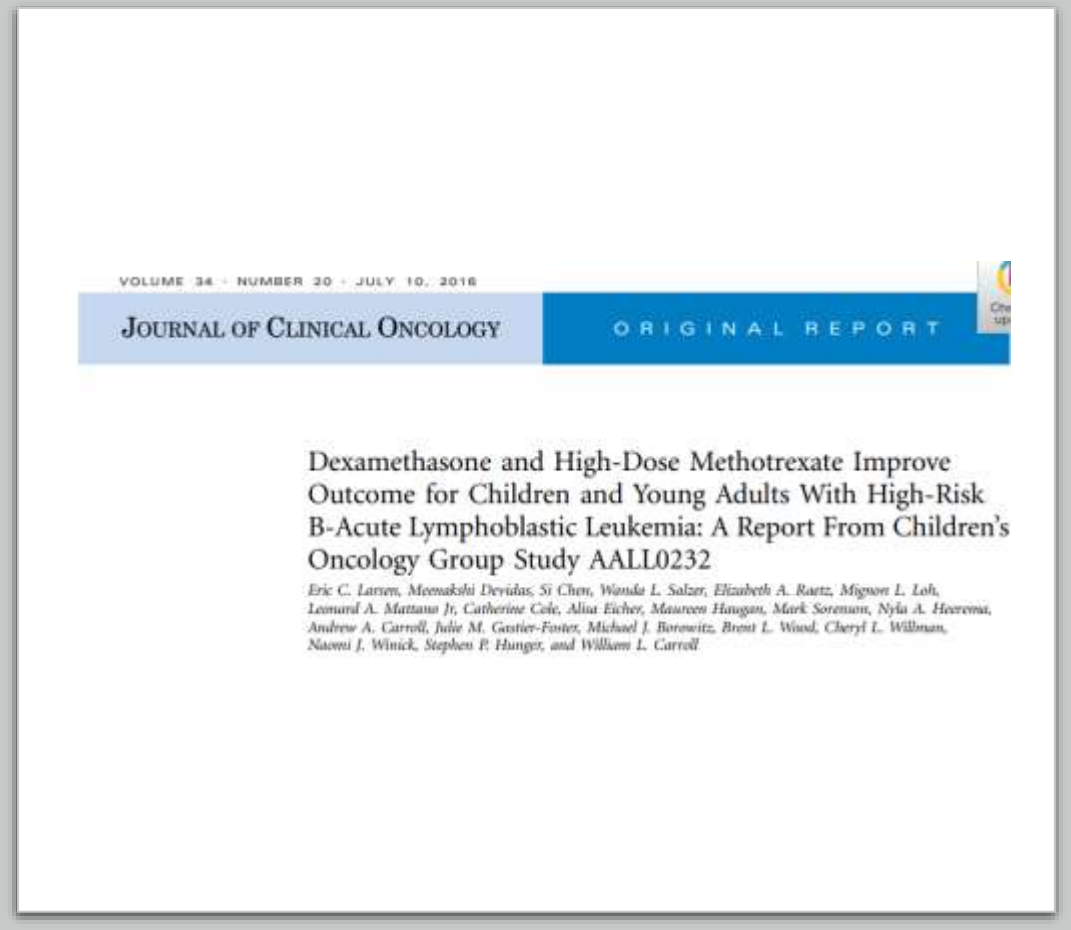
Systemic Exposure to Thiopurines and Risk of Relapse in Children with Acute Lymphoblastic Leukemia: A Children's Oncology Group Study

Smita Bhatia, MD, MPH[1,12], Wendy Landier, PhD, RN[1,12], Lindsey Hageman, MPH[1], Yanjun Chen, MS[1], Heeyoung Kim, MPH[1], Can-Lan Sun, PhD[1], Nancy Kornegay, MS[2], William E Evans, PharmD[2], Anne L Angiolillo, MD[3], Bruce Bostrom, MD[4], Jacqueline Casillas, MD, MSHS[5], Glen Lew, MD[6], Kelly W Maloney, MD[7], Leo Mascarenhas, MD, MS[8], A. Kim Ritchey, MD[9], Amanda M Termuhlen, MD[10], William L Carroll, MD[11], F Lennie Wong, PhD[1], and Mary V Relling, PharmD[2]

Compliance: Maintenance Chemotherapy

COG AALL0232

- AALL0232 enrolled 3,154 participants 1 to 30 years old with newly diagnosed high-risk B-acute lymphoblastic leukemia
- By using a 2 × 2 factorial design, 2,914 participants were randomly assigned to receive **dexamethasone** (14 days) vs **prednisone** (28 days) during induction and **high-dose methotrexate vs Capizzi escalating-dose methotrexate** plus pegaspargase during interim maintenance 1


VOLUME 34 · NUMBER 20 · JULY 10, 2016
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232

Eric C. Larsen, Meenakshi Devidas, Si Chen, Wanda L. Salzer, Elizabeth A. Raetz, Mignon L. Loh, Leonard A. Mattano Jr, Catherine Cole, Alisa Eicher, Maureen Haugan, Mark Sorenson, Nyla A. Heerema, Andrew A. Carroll, Julie M. Gastier-Foster, Michael J. Borowitz, Brent L. Wood, Cheryl L. Willman, Naomi J. Winick, Stephen P. Hunger, and William L. Carroll

Larsen EC, et al. *J Clin Oncol*. 2016;34:2380-2388.

AALL0232

5-year EFS rates of 79.6% for high-dose methotrexate and 75.2% for Capizzi methotrexate (*P* = .008)

High-dose methotrexate decreased both marrow and CNS recurrences. No difference in mucositis, CNS toxicity, osteonecrosis

Patients 1 to 9 years old who received dexamethasone and high-dose methotrexate had a superior outcome compared with those who received the other 3 regimens (5-year EFS, 91.2% vs 83.2%, 80.8%, and 82.1%; *P* = .015)

Older participants derived no benefit from dexamethasone during induction and experienced excess rates of osteonecrosis

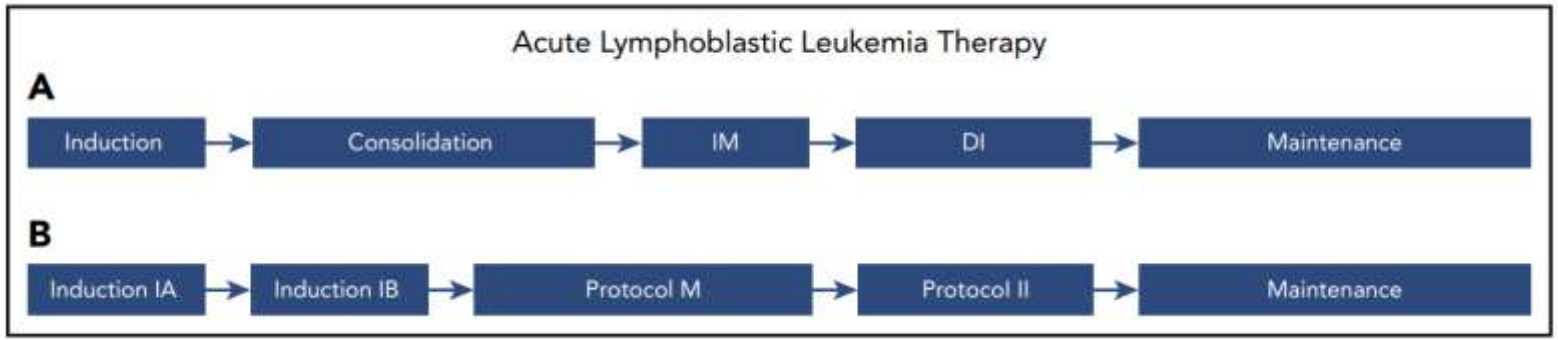
Larsen EC, et al. *J Clin Oncol*. 2016;34:2380-2388.

COG AALL1131

- For HR-BCP ALL
- 4-drug induction
- **VHR B-ALL** received modified Berlin-Frankfurt-Munster therapy after induction and were randomized to following arms during the second half of consolidation and delayed intensification
    - CPM, cytarabine, mercaptopurine, vincristine (VCR), and pegaspargase (control arm)
    - CPM, ETOP, VCR, and pegaspargase (experimental arm 1)
    - CPM, ETOP, CLOF (30 mg/m^2/d 3 5), VCR, and pegaspargase (experimental arm 2)
- Triple IT vs IT MTX for HR patients

Salzer WL, et al. *Cancer.* 2018;124:1150-1159; Burke MJ, et al. *Haematologica*. 2019;104:986-992; Salzer WL, et al. *J Clin Oncol*. 2020;38:2628-2638.

AIEOP-BFM 2000/2009



AIEOP-BFM 2000/2009

- 4-drug induction for all patients
- Prednisolone
- Dexamethasone for PGR T-ALL
- Cyclophosphamide on day 10 for PPR for T-ALL
- Day 15 FCM MRD >10% is high-risk feature
- High prognostic value of PCR MRD at day 33 and day 79
- *IKZF1* deletions co-occurring with deletions in *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1* in the absence of *ERG* deletion conferred the worst outcome and were grouped as *IKZF1*^{plus}

Basso G, et al. 2009; Conter et al. 2010; Schrappe et al. 2011.

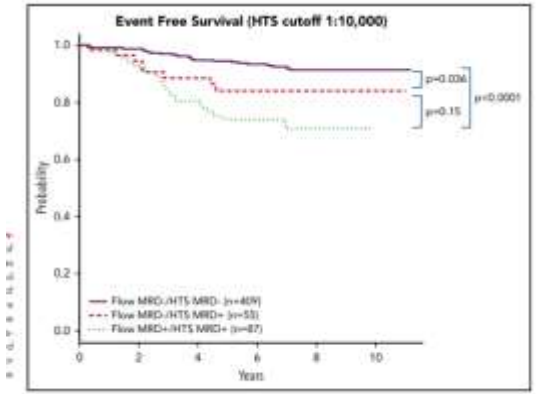
How Do We Further Improve Outcomes?

- More sophisticated risk stratification
  - HTS MRD
- Further intensification of cytotoxic therapy
  - Long-term side effects
- Incorporation of immunotherapy upfront
  - Blinatumomab/inotuzumab/CAR T cells
- Incorporation of targeted precision small-molecular agents
  - Bortezomib/TKI/ruxolitinib

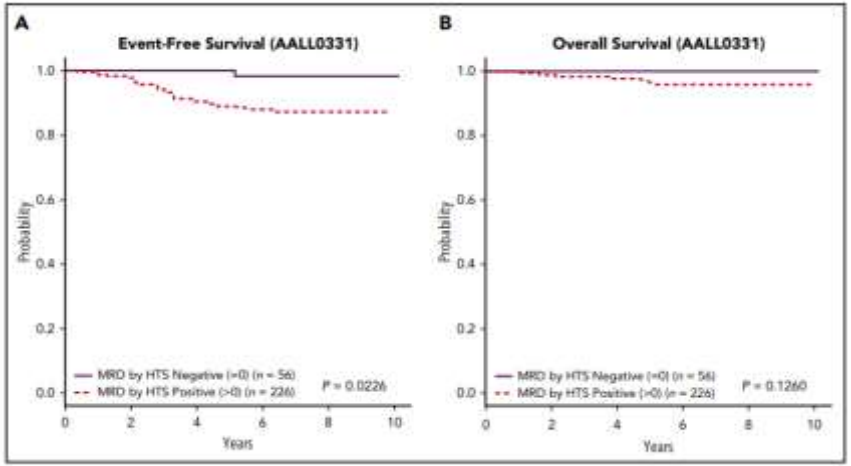
LYMPHOID NEOPLASIA

Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL

Brent Wood,[1,*] David Wu,[1,*] Beryl Crossley,[2] Yunfeng Dai,[3] David Williamson,[2] Charles Gawad,[4] Michael J. Borowitz,[4] Meenakshi Devidas,[3] Kelly W. Maloney,[5] Eric Larsen,[6] Naomi Winick,[7] Elizabeth Raetz,[8] William L. Carroll,[9] Stephen P. Hunger,[10] Mignon L. Loh,[11] Harlan Robins,[2,12,†] and Ilan Kirsch[2,†]



- HTS identifies MRD at the conventional clinical cutoff in more patients than FC, and these patients have worse outcomes
- A subset of B-ALL patients essentially cured using current chemotherapy is identified at end of induction by HTS



Wood et al. *Blood*. 2018.

AIEOP-BFM-2017

Randomization R-eHR: Early High-risk (early HR) pB-ALL defined by genetics and/or inadequate treatment response over the course of induction: Can the pEFS from time of randomization be improved by additional therapy with the proteasome inhibitor Bortezomib during an extended consolidation treatment phase compared with standard extended consolidation?

Randomization R-HR: High-risk (HR) pB-ALL defined by genetics and/or inadequate treatment response by the end of consolidation: Can the pEFS from time of randomization be improved by a treatment concept including two cycles of post-consolidation immunotherapy with Blinatumomab (15 µg/m²/d for 28 days per cycle) plus 4 doses intrathecal Methotrexate replacing two conventional highly intensive chemotherapy courses?

Randomization R-MR: Intermediate risk (MR) pB-ALL defined by genetics and intermediate MRD response: Can the probability of disease-free survival (pDFS) from time of randomization be improved by additional therapy with one cycle of post-reintensification immunotherapy with Blinatomomab (15 µg/m²/d for 28 days)?

COG/Incorporation of Immunotherapy Upfront

- AALL1731/SR ALL: blinatumomab
- AALL1732/HR ALL: inotuzumab
- AALL1721/VHR ALL (high MRD EOC): CAR T cell

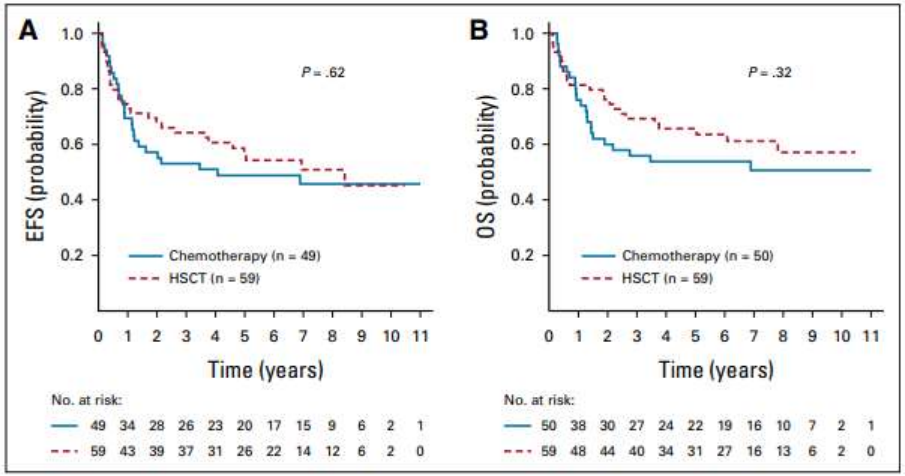
Winters et al. *Haematology.* 2019.

Hypodiploid ALL

original report

Hematopoietic Stem-Cell Transplantation Does Not Improve the Poor Outcome of Children With Hypodiploid Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group

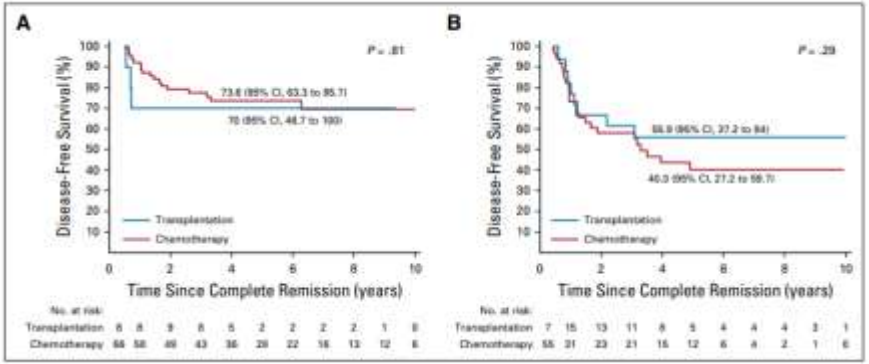
Jennifer L. McNeer, MD[1]; Meenakshi Devidas, PhD[2]; Yunfeng Dai, MSc[2]; Andrew J. Carroll, PhD[3]; Nyla A. Heerema, PhD[4]; Julie M. Gastier-Foster, PhD[5]; Samir B. Kahwash, MD[6]; Michael J. Borowitz, MD, PhD[7]; Brent L. Wood, MD, PhD[7]; Eric Larsen, MD[8]; Kelly W. Maloney, MD[9]; Leonard Mattano, MD[10]; Naomi J. Winick, MD[11]; Kirk R. Schultz, MD[12]; Stephen P. Hunger, MD[13];



original report

Outcome of Children With Hypodiploid Acute Lymphoblastic Leukemia: A Retrospective Multinational Study

Ching-Hon Pui, MD[1]; Paola Rebora, PhD[2]; Martin Schrappe, MD, PhD[3]; Andishe Attarbaschi, MD[4]; Andre Baruchel, MD[5]; Giuseppe Basso, MD[6]; Hélène Cavé, MD, PharmD, PhD[7]; Sarah Elitzur, MD[7]; Katsuyoshi Koh, MD[8]; Hsi-Che Liu, MD[9]; Kajsa Paulsson, PhD[10]; Rob Pieters, MD, PhD[11]; Lewis B. Silverman, MD[12]; Jan Stary, MD[13]; Ajay Vora, MBBS[14]; Allen Yeoh, MBBS[15]; Christine J. Harrison, PhD[16]; and Maria Grazia Valsecchi[2] on behalf of the Ponte di Legno Childhood ALL Working Group



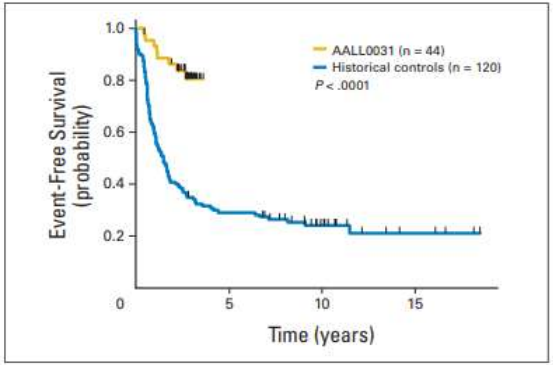
First-Line Treatment of Pediatric ALL

- Ph-negative or Ph-like ALL
- **Ph-positive B-ALL**
- T-ALL
- Infant ALL

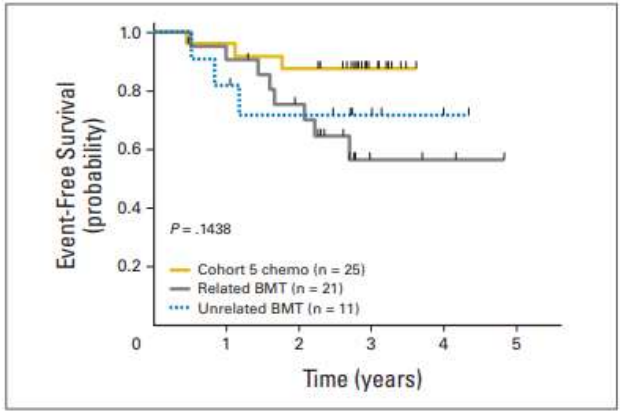
COG AALL0031

Improved Early Event-Free Survival With Imatinib in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Children's Oncology Group Study

Kirk R. Schultz, W. Paul Bowman, Alexander Aledo, William B. Slayton, Harland Sather, Meenakshi Devidas, Chenguang Wang, Stella M. Davies, Paul S. Gaynon, Michael Trigg, Robert Rutledge, Laura Burden, Dean Jorstad, Andrew Carroll, Nyla A. Heerema, Naomi Winick, Michael J. Borowitz, Stephen P. Hunger, William L. Carroll, and Bruce Camitta



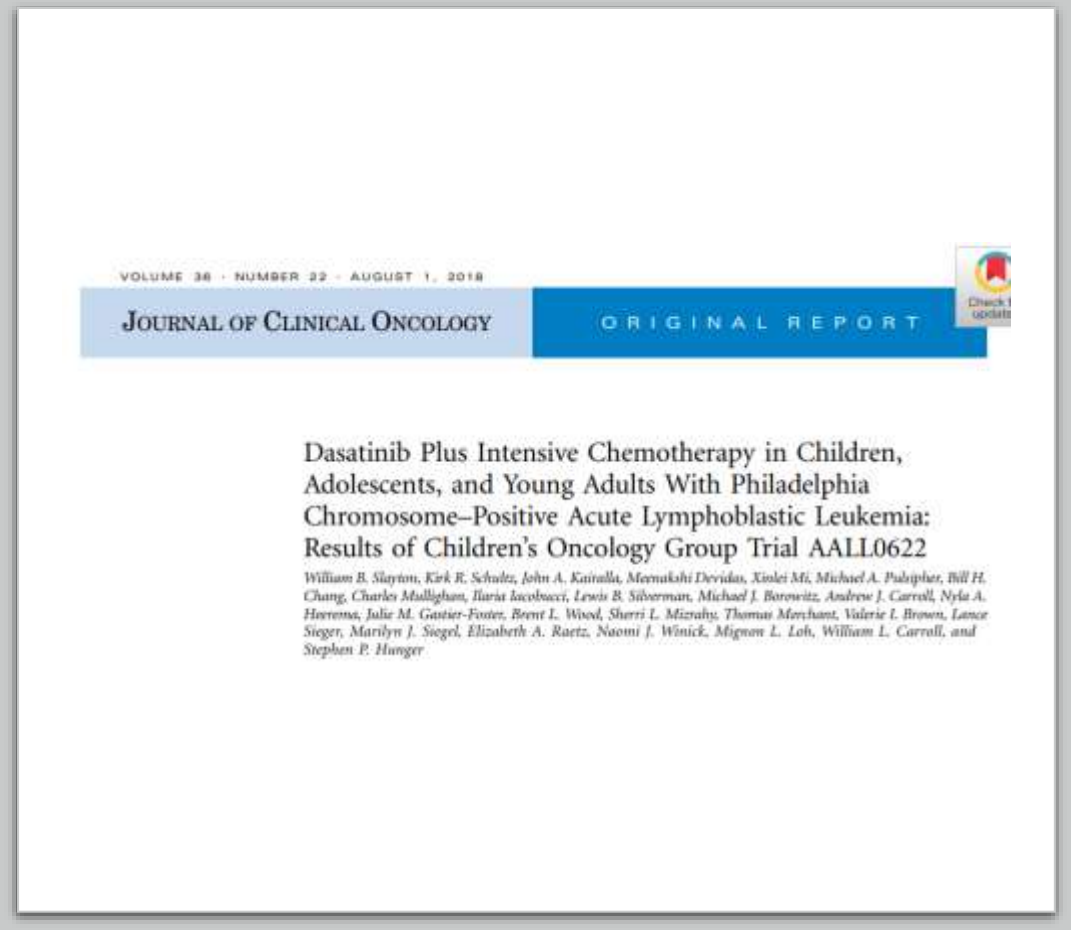
Therapy	Cons 1 (3 wk)	Cons 2 (3 wk)	Reind 1 (3 wk)	Intens 1 (9 wk)	Reind 2 (3 wk)	Intens 2 (9 wk)	Maint 1-4 (8-wk cycles)	Maint 5-12 (8-wk cycles)
Cohort 1				Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 2		Imatinib × 3 wk	Imatinib × 3 wk		Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 3	Imatinib × 3 wk →				Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 4	Imatinib × 3 wk →							Imatinib × 2 wk every 4 wk
Cohort 5	Continuous dosing of imatinib							Imatinib × 2 wk every 4 wk



Schultz et al. *J Clin Oncol.* 2009.

COG AALL0622

- In a phase II single-arm trial (COG AALL0622) of children and young adults with Ph-positive ALL (n = 60; aged 1–30 years), imatinib was replaced with dasatinib on induction day 15 and combined with the same chemotherapy used in COG AALL0031
- The 5-year OS and EFS rates were 86% and 60%, respectively, and outcomes were similar to those observed in COG AALL0031



VOLUME 36 · NUMBER 22 · AUGUST 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

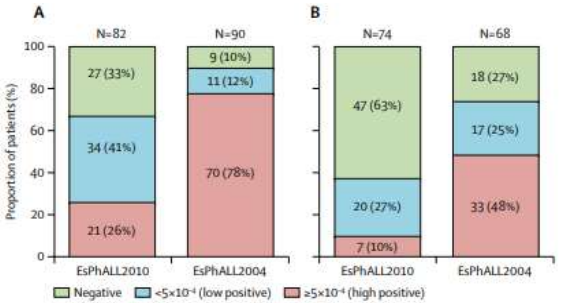
Dasatinib Plus Intensive Chemotherapy in Children, Adolescents, and Young Adults With Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0622

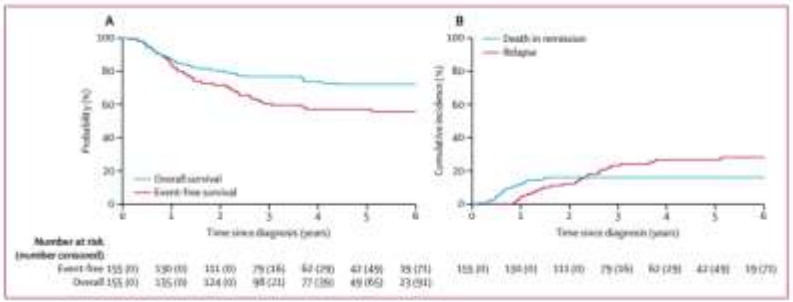
William B. Slayton, Kirk R. Schultz, John A. Kairalla, Meenakshi Devidas, Xiolei Mi, Michael A. Pulsipher, Bill H. Chang, Charles Mullighan, Ilaria Iacobucci, Lewis B. Silverman, Michael J. Borowitz, Andrew J. Carroll, Nyla A. Heerema, Julie M. Gastier-Foster, Brent L. Wood, Sherri L. Mizrahy, Thomas Merchant, Valerie I. Brown, Lance Sieger, Marilyn J. Siegel, Elizabeth A. Raetz, Naomi J. Winick, Mignon L. Loh, William L. Carroll, and Stephen P. Hunger

EsPhALL 2010

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

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





Biondi et al. *Lancet.* 2018.

AALL1631
(combined EsPhALL and COG study)

Continuous imatinib from day 15

Standard-risk patients (MRD negative) randomized to EsPhALL backbone vs experimental COG backbone

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HR patients: 3 blocks of consolidation followed by BMT

First-Line Treatment of Pediatric ALL

- Ph-negative or Ph-like ALL
- Ph-positive B-ALL
- **T-ALL**
- Infant ALL

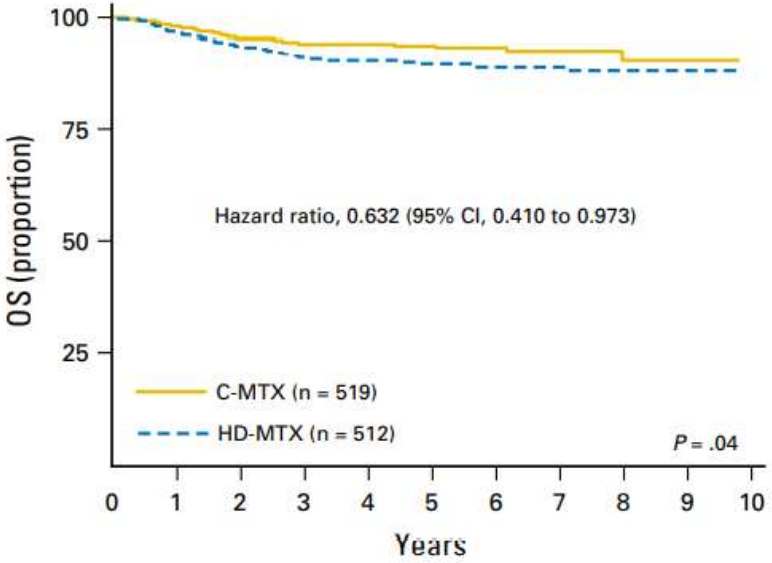
Nelarabine/AALL0434

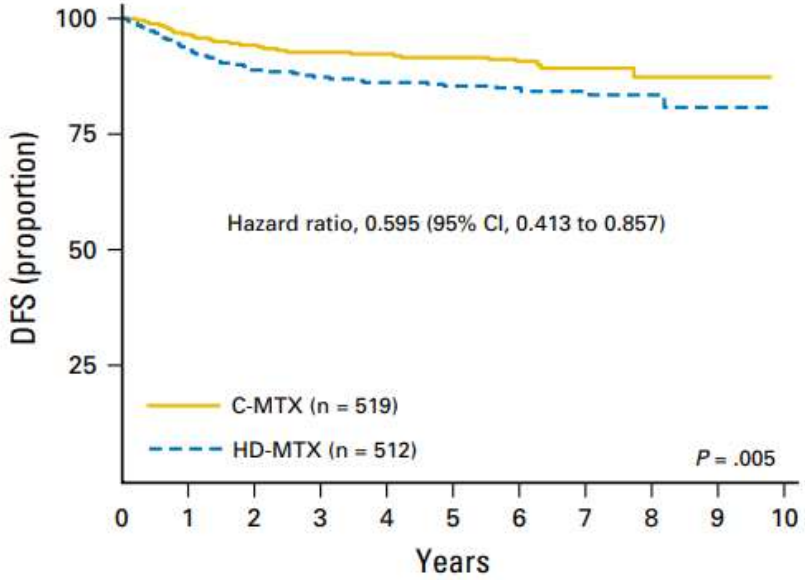
- 2 × 2 randomization
- Capizzi MTX vs HD MTX
- Nelarabine vs no nelarabine
- Prednisolone

- All HR and IR patients had prophylactic CRT

Winter SS, et al. *J Clin Oncol*. 2018;36:2926-2934; Dunsmore KP, et al. *J Clin Oncol*. 2020;38:3282-3293.

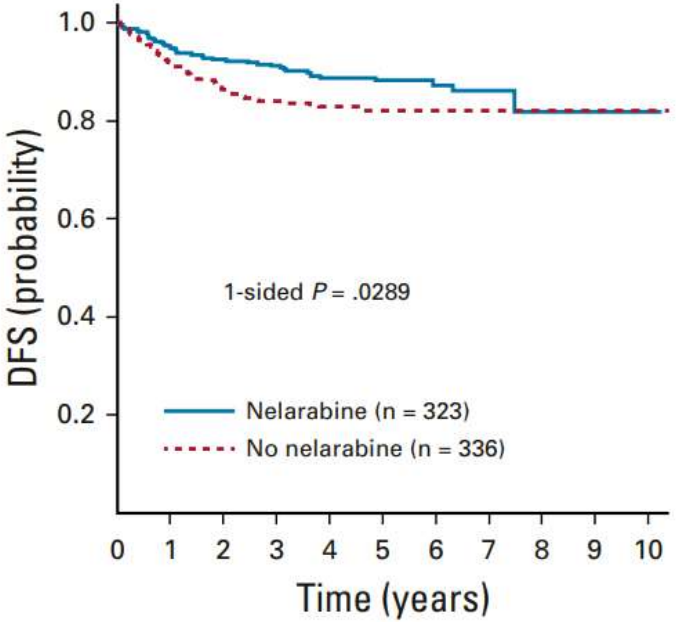
HD MTX vs Capizzi MTX

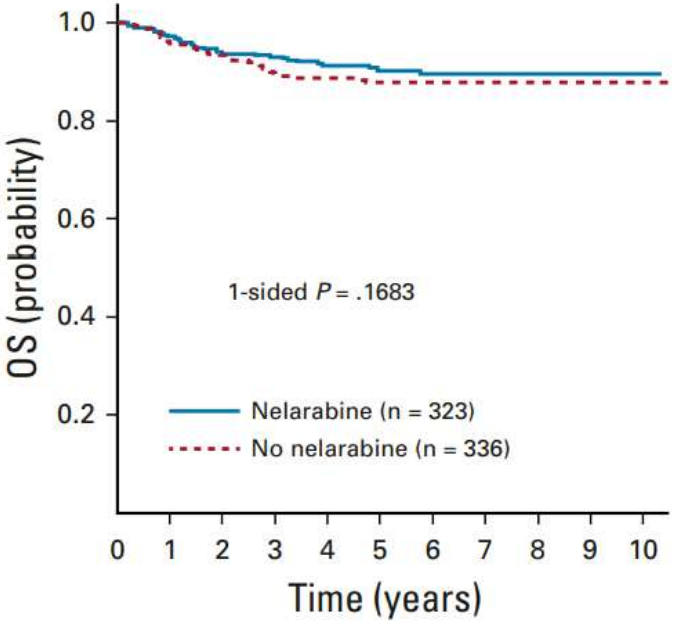




Winter SS, et al. *J Clin Oncol*. 2018;36:2926-2934.

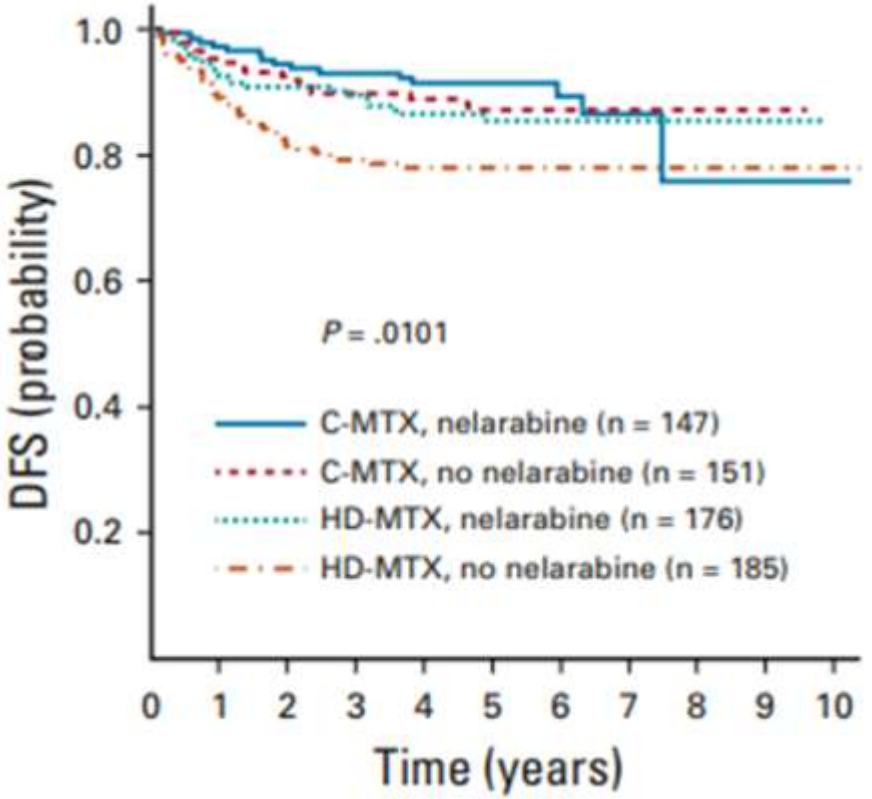
Nelarabine vs No Nelarabine





Dunsmore KP, et al. *J Clin Oncol*. 2020;38:3282-3293.

Nelarabine and Capizzi MTX



Dunsmore KP, et al. *J Clin Oncol*. 2020;38:3282-3293.

COG AALL1232

- COG phase III clinical trial that randomized children and young adults (age 1-30 years) to a modified augmented BFM (aBFM) backbone +/- the proteasome inhibitor bortezomib during induction and delayed intensification (DI) (1.3 mg/m^2 × 4 doses per block
- Dexamethasone/extra PEG-asparaginase
- CNS RT in selected group
- The 3-year EFS for Arm A (no bortezomib) vs Arm B (bortezomib) was 81.7 ± 2.4% and 85.1 ± 2.2% (HR = 0.782; *P* = .074)
- SR and IR pts, who account for 95% of pts, had significantly improved EFS on Arm B compared with Arm A
- CNS relapse rates were higher in these pts on AALL1231 (4.5%) as compared with AALL0434 (1.7%), but overall relapse rates were the same (6.5% vs 6.4%)

Teachy et al. ASH 2020. Abstract.

BFM 2000: MRD at TP1 and TP2

- Negativity of MRD at TP1 was the most favorable prognostic factor
- An excellent outcome was also obtained in patients turning MRD negative only at TP2, indicating that early (TP1) MRD levels were irrelevant if MRD at TP2 was negative
- MRD >10^{-3} at TP2 constitutes the most important predictive factor for relapse in childhood T-ALL

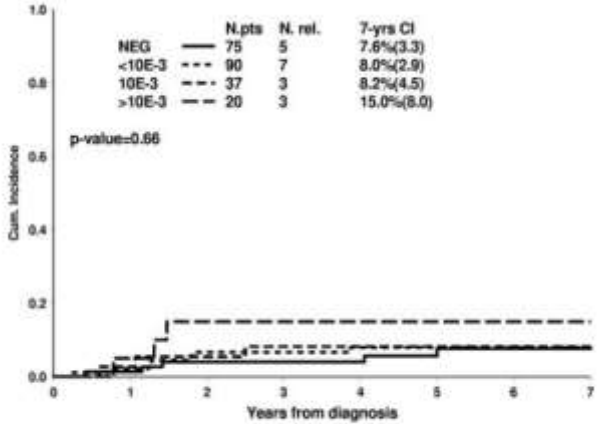


Figure 4. Cumulative incidence of relapse in 222 T-ALL patients with negative MRD at TP2 according to MRD results at TP1.

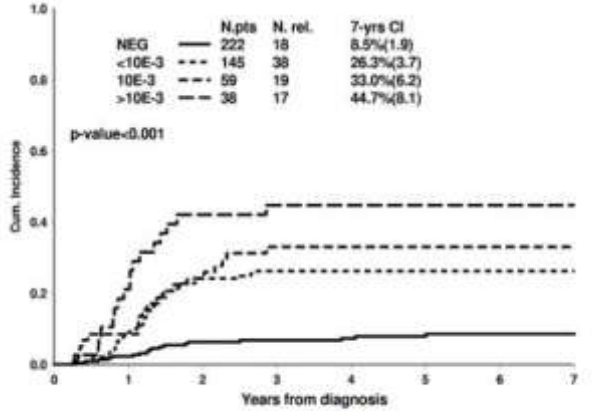


Figure 5. Cumulative incidence of relapse in 464 T-ALL patients by MRD levels at TP2.

Schrappe M, et al. *Blood*. 2011;118:2077-2084.

EFS and CI of Relapse According to Risk Groups

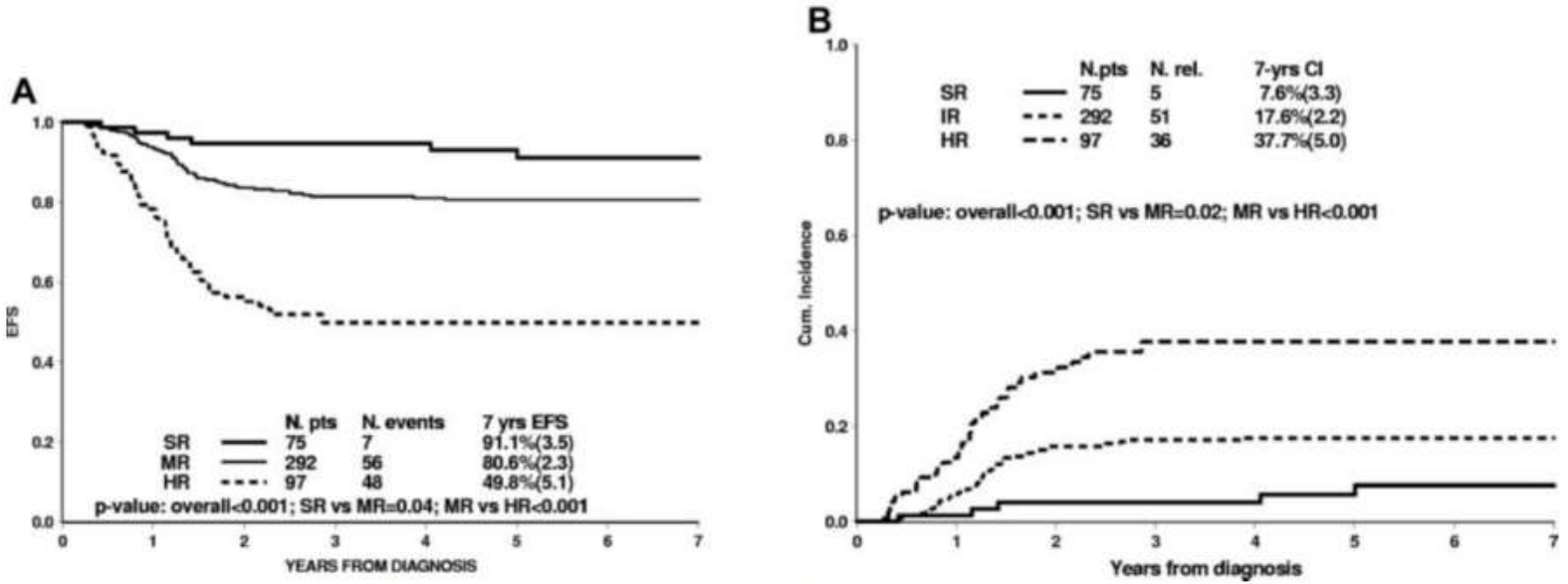


Figure 2. Treatment outcome in risk groups. EFS (A) and cumulative incidence of relapse (B) according to PCR-based MRD classification in 464 patients.

Schrappe M, et al. *Blood*. 2011;118:2077-2084.

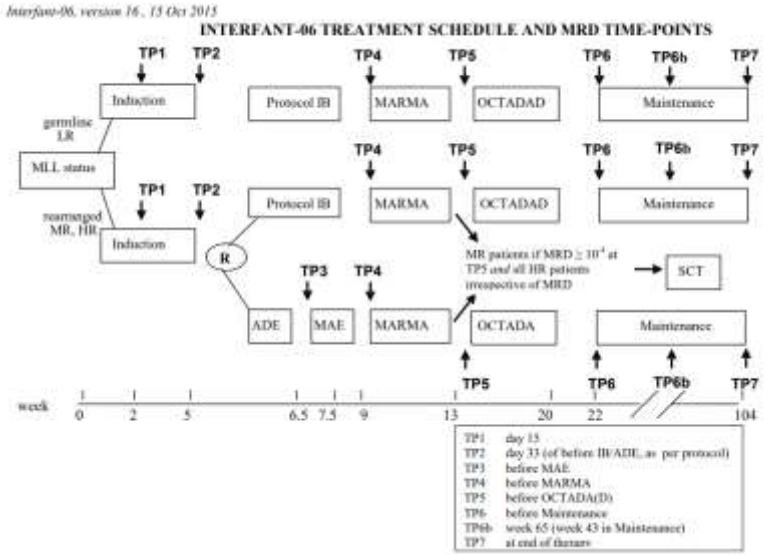
AIEOP-BFM-2017

Randomization R-T: Early non-standard risk (early non-SR) T-ALL patients defined by treatment response over the course of induction: Can the pEFS from time of randomization be improved by the extension of the standard of care consolidation phase by 14 days with an increase of the consolidation cumulative doses of Cyclophosphamide, Cytarabine and 6-Mercaptopurine by 50%?

First-Line Treatment of Pediatric ALL

- Ph-negative or Ph-like ALL
- Ph-positive B-ALL
- T-ALL
- **Infant ALL**

Interfant -06



4. RISK GROUP STRATIFICATION AND RANDOMISATION

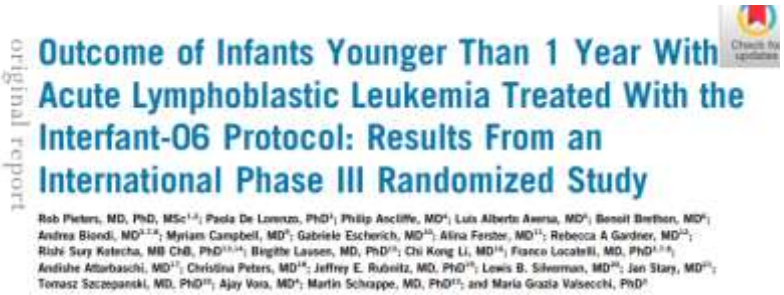
Low risk (LR): MLL germline

High risk (HR): MLL rearranged AND
Age at diagnosis < 6 months (i.e. <183 days) AND
WBC ≥ 300 x $10^6$9/L and/or prednisone poor response

Medium risk (MR): all other cases so including those with:

- MLL status unknown (see Section 9.1 point 3.3) OR
- MLL rearranged AND age > 6 months OR
- MLL rearranged AND age < 6 months AND WBC < 300 x $10^6$9/L AND prednisone good response

Interfant-06: Results



original report

Outcome of Infants Younger Than 1 Year With Acute Lymphoblastic Leukemia Treated With the Interfant-06 Protocol: Results From an International Phase III Randomized Study

Rob Pieters, MD, PhD, MSc[1,2]; Paola De Lorenzo, PhD[3]; Philip Ancliffe, MD[4]; Luis Alberto Aversa, MD[5]; Benoit Brethon, MD[6]; Andrea Biondi, MD[7,8]; Myriam Campbell, MD[9]; Gabriele Escherich, MD[10]; Alina Ferster, MD[11]; Rebecca A Gardner, MD[12]; Rishi Sury Kotecha, MB ChB, PhD[13,14]; Birgitte Lausen, MD, PhD[15]; Chi Kong Li, MD[16]; Franco Locatelli, MD, PhD[1,17]; Andishe Attarbaschi, MD[17]; Christina Peters, MD[18]; Jeffrey E. Rubnitz, MD, PhD[19]; Lewis B. Silverman, MD[20]; Jan Stary, MD[21]; Tomasz Szczepanski, MD, PhD[22]; Ajay Vora, MD[4]; Martin Schrappe, MD, PhD[23]; and Maria Grazia Valsecchi, PhD[3]

- A total of 651 infants were included, with 6-year event-free survival (EFS) and overall survival of 46.1% and 58.2%
- The 6-year probability of disease-free survival was comparable for the randomized arms (ADE/MAE 39.3% vs IB 36.8%)
- The 6-year EFS rate of patients in the HR group was 20.9% with the intention to undergo SCT; only 46% of them received SCT, because many had early events
- *KMT2A* rearrangement was the strongest prognostic factor for EFS, followed by age, WBC count, and prednisone response

Pieters et al. *J Clin Oncol.* 2019.

Interfant-06: MRD and Type of Consolidation Therapy

original reports

Clinical Implications of Minimal Residual Disease Detection in Infants With *KMT2A*-Rearranged Acute Lymphoblastic Leukemia Treated on the Interfant-06 Protocol

Janine Stutterheim, MD, PhD[1]; Inge M. van der Sluis, MD, PhD[2]; Paola de Lorenzo, PhD[2,3]; Julia Alten, MD[4]; Philip Ancliffe, MD[4]; Andishe Attarbaschi, MD[5]; Benoit Brethon, MD[6]; Andrea Biondi, MD[7]; Myriam Campbell, MD[8]; Giovanni Cazzaniga, PhD[9]; Gabriele Escherich, MD[10]; Alina Fenster, MD[11]; Rishi S. Kotecha, MBChB, PhD[12,13]; Birgitte Lausen, MD, PhD[14]; Chi Kong Li, MD[15]; Luca Lo Nigro, MD, PhD[16]; Franco Locatelli, MD, PhD[17]; Rolf Marschalek, PhD[18]; Claus Meyer, PhD[18]; Martin Schrappe, MD, PhD[19]; Jan Stary, MD, PhD[20]; Ajay Vora, MD[21]; Jan Zuna, MD, PhD[22]; Vincent H. J. van der Velden, PhD[2]; Tomasz Szczepanski, MD, PhD[23]; Maria Grazia Valsecchi, PhD[9]; and Rob Pieters, MD, PhD, MSc[1,24]

- This study investigated the clinical relevance of MRD in 249 infants with *KMT2A*-rearranged ALL treated according to the Interfant-06 protocol
- This study showed that MRD is of significant prognostic value for infants with *KMT2A*-rearranged ALL
- Most important, the data show that patients with high MRD at the end of induction (EOI) have better outcome when treated with myeloid-like consolidation therapy, whereas patients with low MRD have better outcome when treated with lymphoid-type consolidation therapy
- Patients with positive MRD at the end of consolidation (EOC) have dismal outcome

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

AALL0631

Leukemia (2021) 35:1279–1290
https://doi.org/10.1038/s41375-021-01177-6

ARTICLE

Acute lymphoblastic leukemia

FLT3 inhibitor lestaurtinib plus chemotherapy for newly diagnosed KMT2A-rearranged infant acute lymphoblastic leukemia: Children's Oncology Group trial AALL0631

Patrick A. Brown[1] · John A. Kairalla[2] · Joanne M. Hilden[3] · ZoAnn E. Dreyer[4] · Andrew J. Carroll[5] · Nyla A. Heerema[6] · Cindy Wang[2] · Meenakshi Devidas[7] · Lia Gore[3] · Wanda L. Salzer[4] · Naomi J. Winick[8] · William L. Carroll[10] · Elizabeth A. Raetz[10] · Michael J. Borowitz[11] · Donald Small[5] · Mignon L. Loh[12] · Stephen P. Hunger[13]

- AALL0631 tested whether adding lestaurtinib to postinduction chemotherapy improved EFS
- Correlative assays included FLT3i plasma pharmacodynamics (PD), which categorized patients as inhibited or uninhibited, and FLT3i ex vivo sensitivity (EVS), which categorized leukemic blasts as sensitive or resistant
- There was no difference in 3-year EFS between patients treated with chemotherapy plus lestaurtinib
- However, for the lestaurtinib-treated patients, FLT3i PD and FLT3i EVS significantly correlated with EFS

Brown et al. *Leukemia.* 2021.

Conclusions

- More precise risk stratification
- HTS MRD to identify population of patients with outstanding outcomes
- Further intensification of cytotoxic therapy is unlikely to be beneficial
- Best way of incorporating immunotherapy in frontline trials

Questions?

Global Leukemia Academy

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

Michael Osborn

APTITUDE HEALTH

Relapsed Paediatric ALL

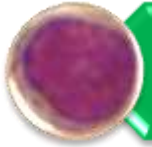
Current and Emerging Treatment Options

Dr Michael Osborn

Haematologist/Paediatric, Adolescent, and Young Adult Oncologist

Women's and Children's Hospital and Royal Adelaide Hospital

Risk stratification for relapsed ALL



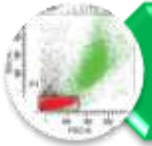
1st vs subsequent relapse

Time from diagnosis to relapse

- Earlier is worse

Site of relapse

- Marrow worse than isolated extramedullary



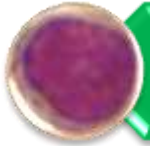
Immunophenotype

- T worse than B

MRD response

Risk status	Definition
COG, North America[17]	
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 relapse, any site and timing
BFM Group, Western Europe[14]	
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 (regardless of timing)
Cancer Research UK Children's Cancer Group, United Kingdom[15]	
Standard	Late IEM relapse
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 elapse B-ALL very-early marrow or combined relapse T-ALL marrow or combined relapse, any timing

Risk stratification for relapsed ALL



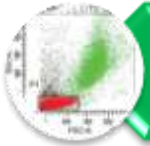
1st vs subsequent relapse

Time from diagnosis to relapse

- Earlier is worse

Site of relapse

- Marrow worse than isolated extramedullary



Immunophenotype

- T worse than B

MRD response

Which **induction** regimen?

Whom to **transplant**?

How to get to transplant?

Post-induction therapy and new agents

First bone marrow relapse of B-ALL

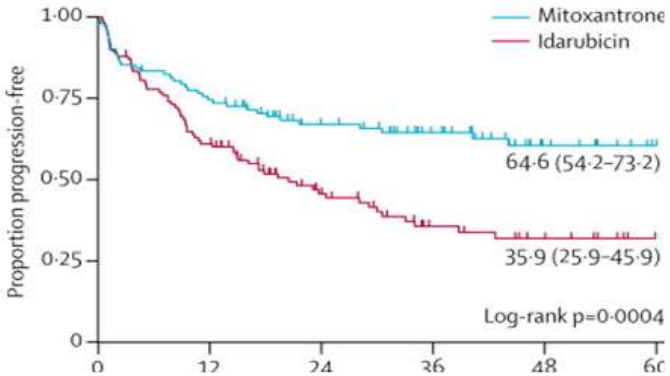
Which induction regimen?

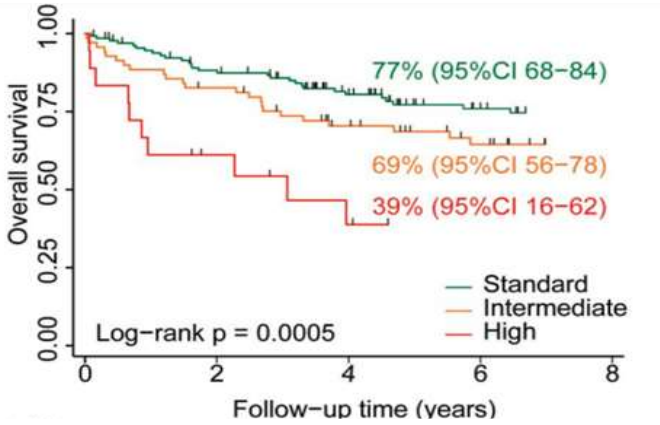
UKALL R3

4-drug induction

- Dex/Vinc/**Mitox vs Ifos**/PEG-Asp + IT

- IR and HR with MRD ≥10^{-4} had HSCT after block 3 cf SR and IR with MRD <10^{-4} did not





Parker et al. *Lancet*. 2010;376: 2009-2017.

First bone marrow relapse of B-ALL

Which induction regimen?

UKALL R3

4-drug induction

- Dex/Vinc/**Mitox vs Ifos**/PEG-Asp + IT
- **Mitoxantrone improved PFS and OS**
- IR and HR with MRD ≥10^{-4} had HSCT after block 3 cf SR and IR with MRD <10^{-4} did not
- **MRD <10^{-4} identified IR patients who did not need HSCT**
- **Survival remained suboptimal in HR group**

Whom to transplant?

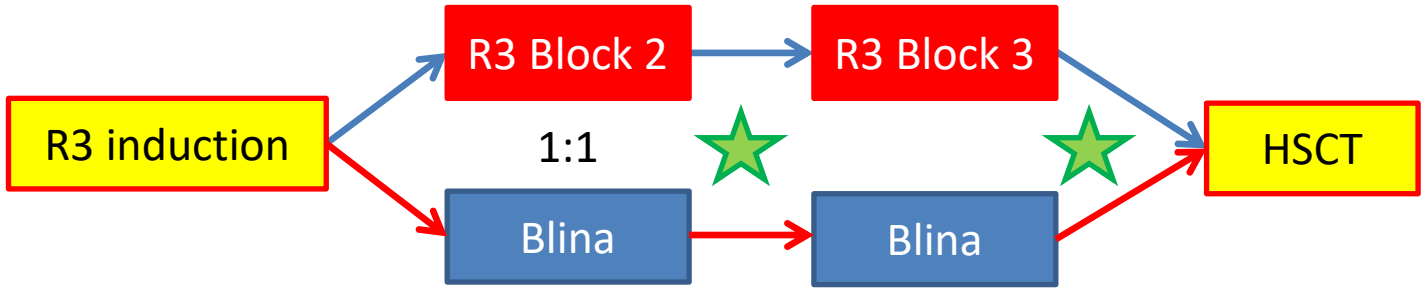
- Early BM relapse
  - COG: <36 mo from diagnosis
  - UK/BFM: <6 mo after end of Rx if isolated or <18 mo from diagnosis if combined
- Late BM relapse with high MRD
  - COG: ≥0.1% at end of induction
  - UKALLR3: ≥0.01%
  - REZ-BFM: ≥0.1%

Parker et al. *Lancet*. 2010;376: 2009-2017.

First bone marrow relapse of B-ALL

Optimal consolidation strategy pre-HSCT?

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-AraC/Erwinia (wk 1, 2); ID MTX/Erwinia (wk 4); IT MTX or ITT

Arm B: Blinatumomab

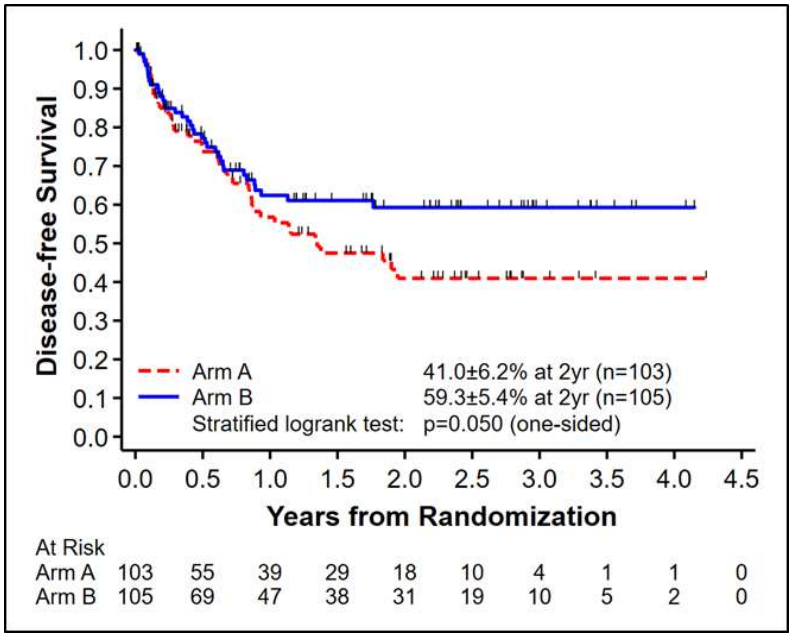
Cycle 1 and 2: 15 µg/m^2/day × 28 days, then 7 days off

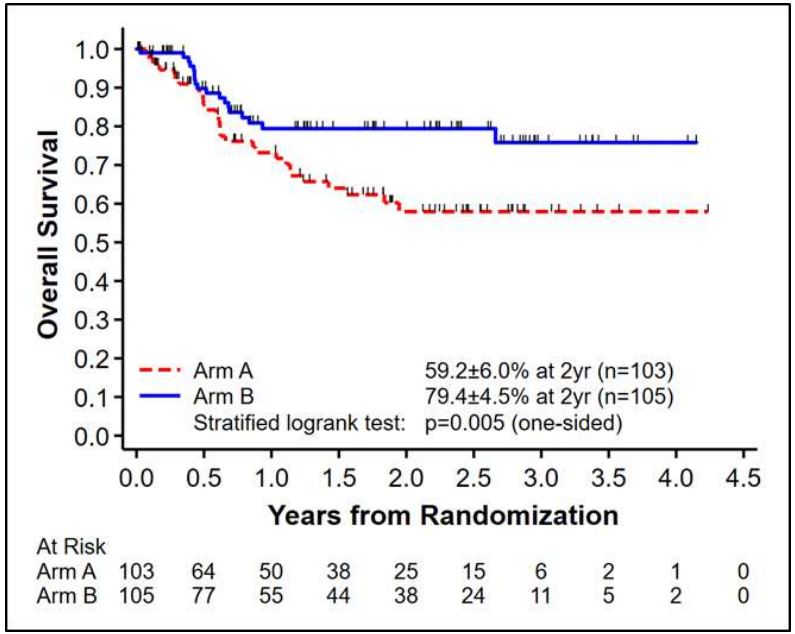
Brown et al. *JAMA*. 2021;325(9):833-842.

First bone marrow relapse of B-ALL

Optimal consolidation strategy pre-HSCT?

COG AALL1331: HR/IR



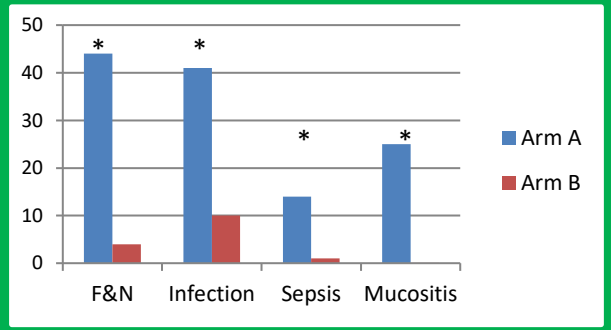


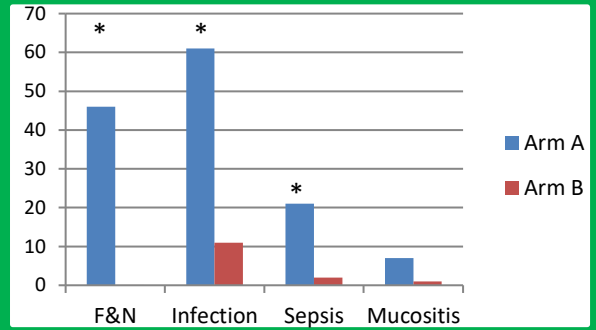
Brown et al. *JAMA*. 2021;325(9):833-842.

First bone marrow relapse of B-ALL

Optimal consolidation strategy pre-HSCT?

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





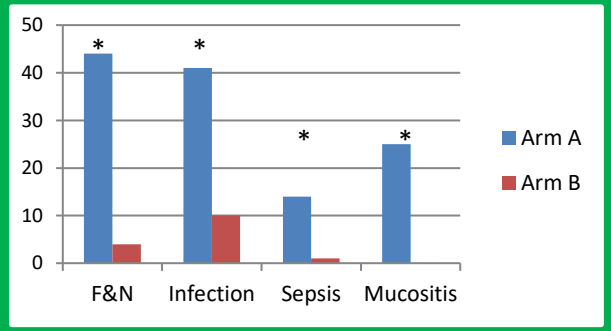
Blinatumomab AEs	Cycle 1		Cycle 2	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Cytokine release syndrome	22%	11%	1%	0%
Neurotoxicity	18%	3%	11%	2%
Seizure	4%	1%	0%	0%
Other (encephalopathy)	14%	2%	11%	2%

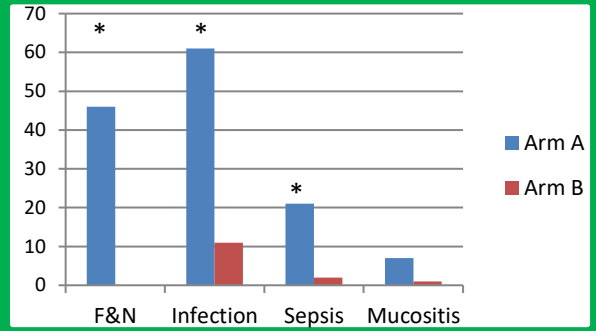
Brown et al. *JAMA*. 2021;325(9):833-842.

First bone marrow relapse of B-ALL

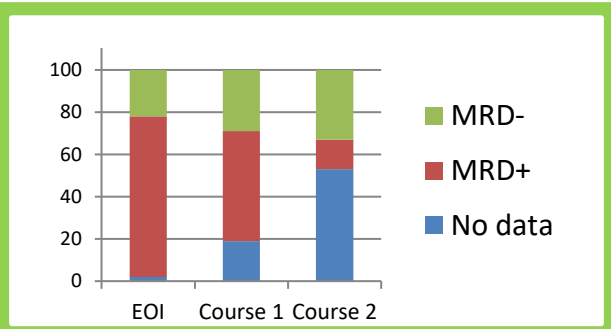
Optimal consolidation strategy pre-HSCT?

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

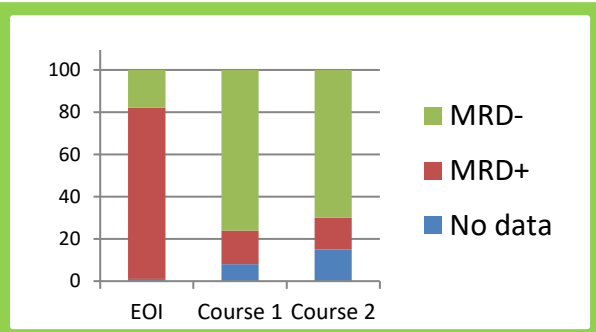




Blinatumomab **cleared MRD** better



Arm A: Chemo



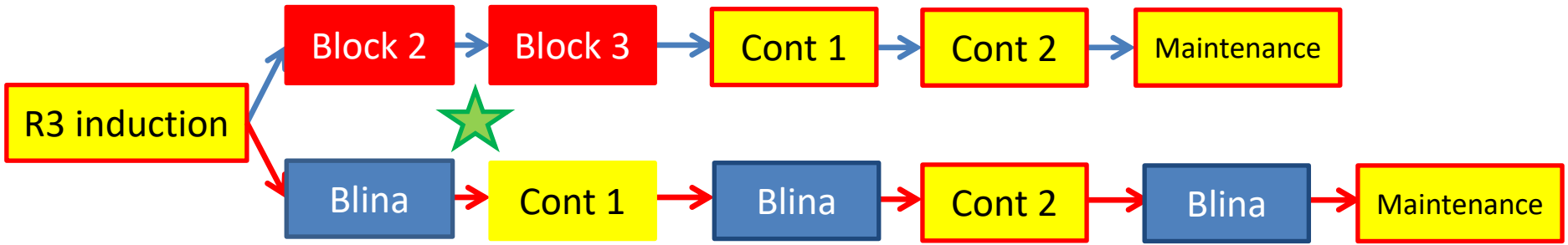
Arm B: Blinatumomab

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

First bone marrow relapse of B-ALL

Optimal consolidation strategy pre-HSCT?

COG AALL1331: **Standard Risk**



Standard-Risk Relapse:

- Isolated extramedullary relapse
- Late isolated or combined BM relapse (>36 mo from relapse) + MRD <0.1% after induction

Awaiting results

62nd ASH® Annual Meeting and Exposition
DECEMBER 5-8, 2020

Cytogenetic Subgroups Drive Risk Stratification and Response to Chemotherapy and Blinatumomab in Children and Young Adults with Relapsed B-ALL

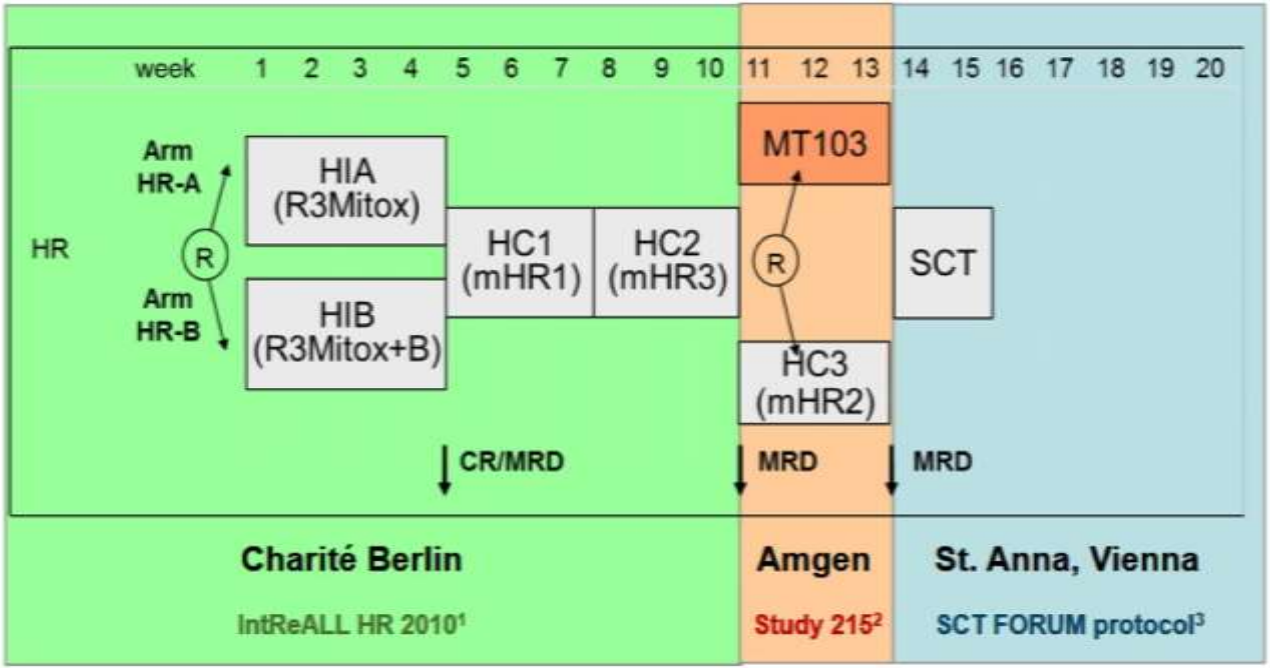
Bhatla T, Hogan L, Xu X, et al

- Cytogenetics at relapse cf diagnosis
  - Unfavourable CG were more common (17 vs 7%; *P* <.001)
  - Favourable CG were less common (22 vs 42%; *P* <.001)
- Patients with favourable CG relapse later and more likely to achieve EOI MRD $<10^{-4}$
- All CG subgroups demonstrated a better MRD response to blina than chemo
  - But this only translated to a better DFS/OS in the favourable-CG subgroup (DFS 44 vs 77%; OS 52 vs 93%)
- Influence of CG subgroups on DFS/OS may differ depending on whether blina or chemo is used as post-induction consolidation

First bone marrow relapse of B-ALL

Optimal consolidation strategy pre-HSCT?

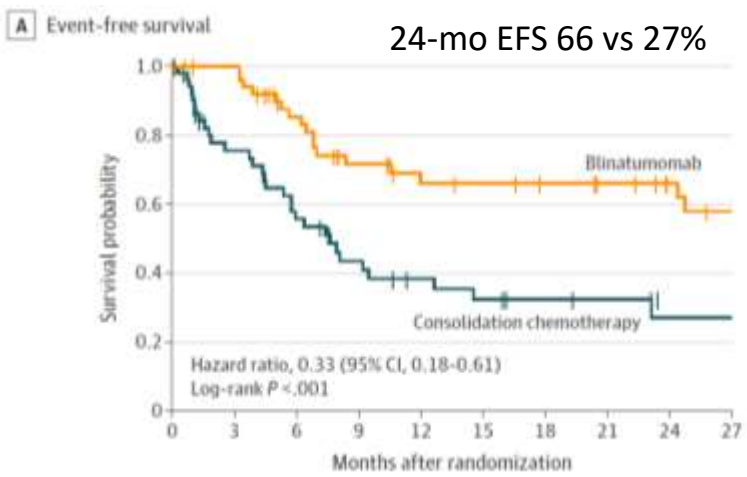
IntReALL HR 2010

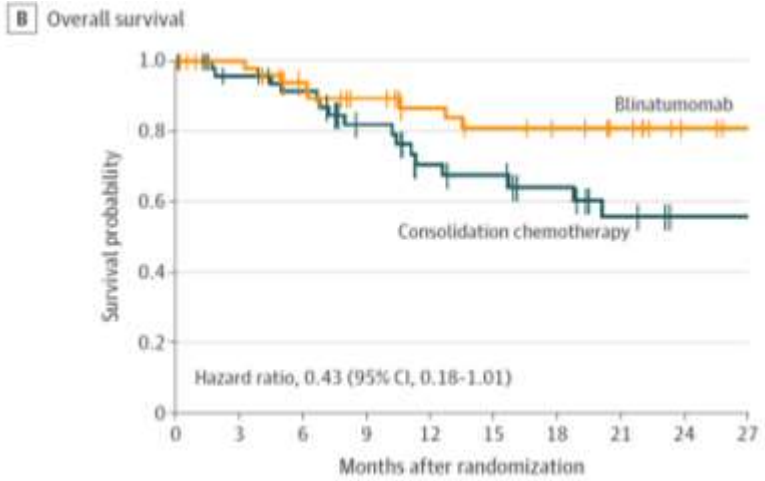


First bone marrow relapse of B-ALL

Optimal consolidation strategy pre-HSCT?

IntReALL HR 2010





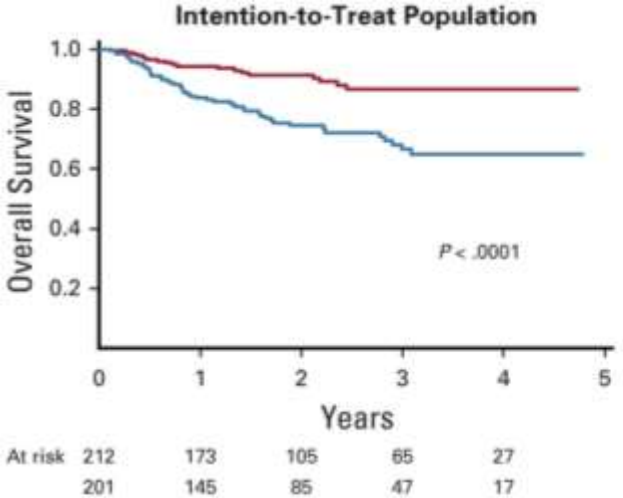
Better MRD response ($<10^{-4}$) with blinatumomab: 90 vs 54%
Subgroup with MRD $>10^{-4}$ at baseline converting to MRD $<10^{-4}$: 93 vs 24%
Fewer SAEs with blinatumomab: 24 vs 43%

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

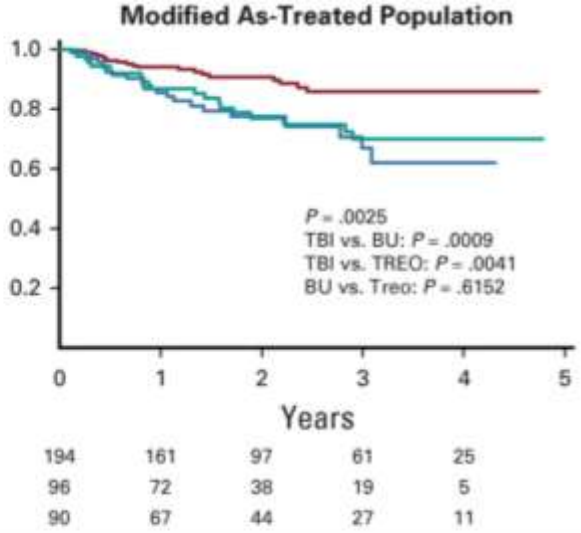
HSCT for relapsed ALL

FORUM study

TBI/etoposide vs Flu/Thiotepa/Bu or Treo



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



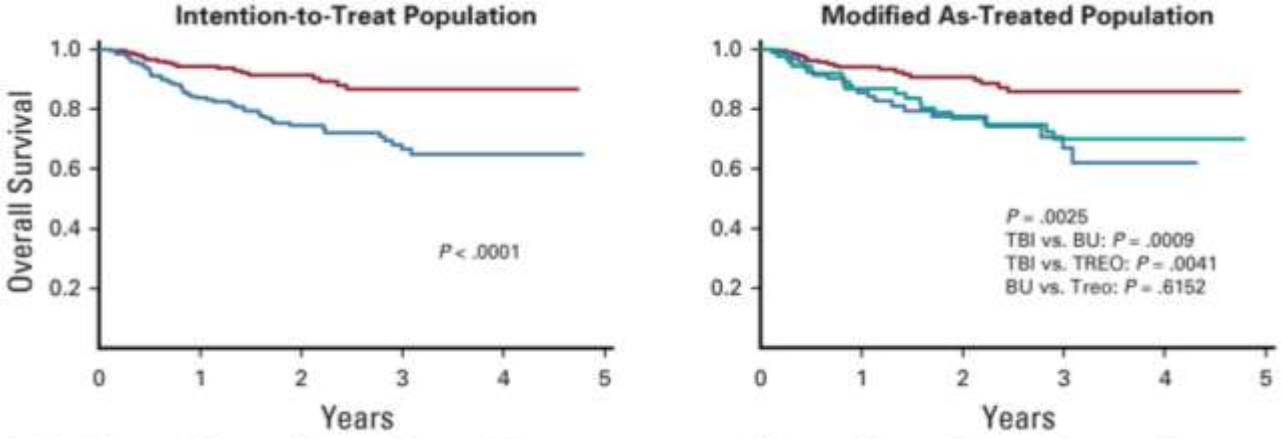
	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

Peters et al. *J Clin Oncol*. 2021;39:295-307.

HSCT for relapsed ALL

FORUM study

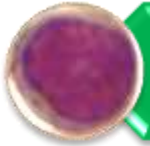
TBI/etoposide vs Flu/Thiotepa/Bu or Treo



Total Body Irradiation + Etoposide recommended for children aged >4 years undergoing HSCT for high-risk ALL

Peters et al. *J Clin Oncol*. 2021;39:295-307.

Other relapsed ALL scenarios

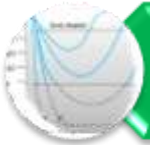


1st vs subsequent relapse

Time from diagnosis to relapse
- Earlier is worse

Site of relapse
- Marrow worse than isolated extramedullary

Immunophenotype
- T worse than B



MRD response

Isolated Extramedullary Relapse

Relapse post-HSCT

T-ALL

Isolated extramedullary relapse

- Outcome better than BM/combined relapse unless very early:

Late IEM relapse (>18 mo post-diagnosis)	EFS 75–80%
Very early IEM (<18 mo post-diagnosis)	EFS 41%

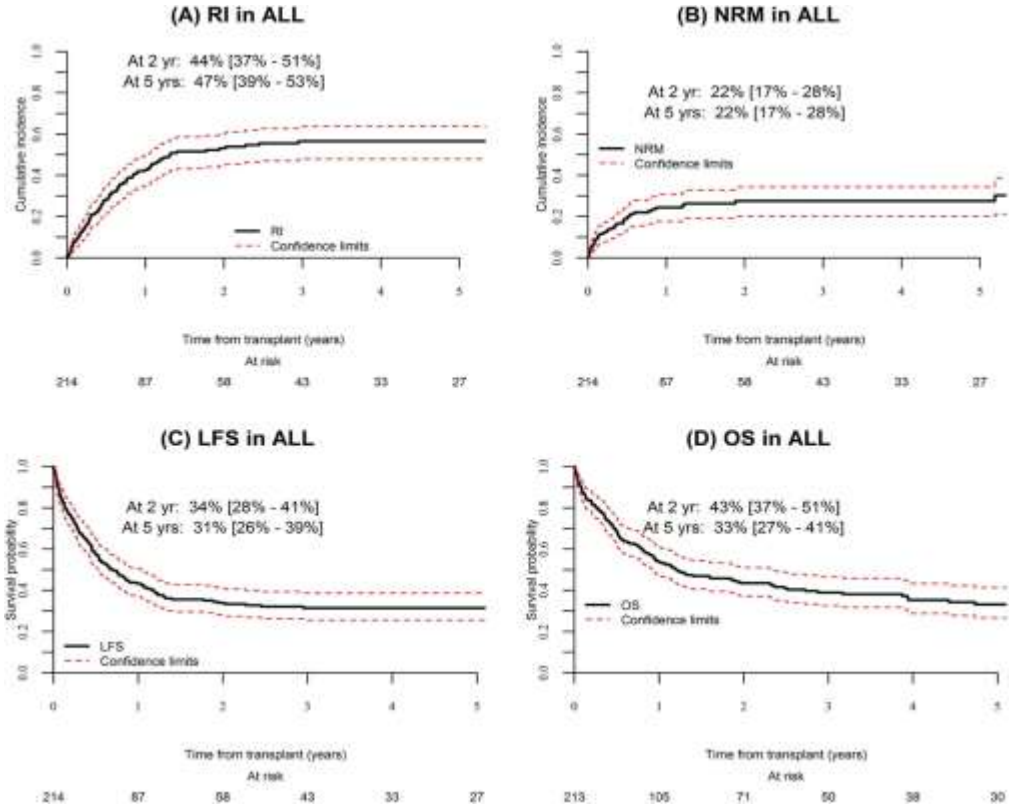
HSCT

- Intensive reinduction strategy + CNS-directed therapy (cranial irradiation)
  - Because IEM relapse is often a harbinger of BM relapse
- Triple intrathecal therapy

- **Very early IEM:** UKALL R3 blocks 1-3 + ITT, then HSCT with TBI-based conditioning
- **Late IEM:** UKALL R3 + ITT (2 years) + cranial irradiation (1800 cGy)
  - Provided MRD <0.01

Relapse after HSCT

2nd transplant: 25%–30% survival *if* remission achieved



Yaniv et al. *Biol Blood Marrow Transplant*. 2018;24:1629-1642.

How CAR-T Therapy Works

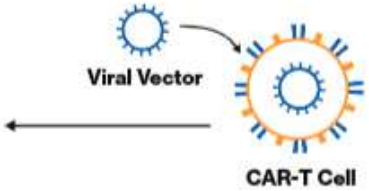
1. Leukapheresis

A patient's white blood cells, including T cells, are extracted through a specialized blood filtration process (leukapheresis). The T cells are then cryopreserved and sent to our manufacturing facility for reprogramming

Manufacturing Facility

2. Reprogrammed cells

Using an inactive virus (viral vector), T cells are genetically encoded to recognize cancer cells and other cells expressing a specific antigen



3. Expansion

Newly created CAR-T cells undergo expansion

4. Quality Check

Strict quality testing occurs prior to the release and shipment of the CAR-T cells back to the patient

5. Lymphodepleting chemotherapy

Lymphodepleting chemotherapy is given to the patient to reduce the level of white blood cells and help the body accept the reprogrammed CAR-T cells

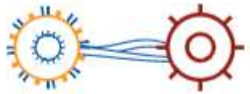
6. Cell Infusion

Deliver reprogrammed CAR-T cells into the patient's blood

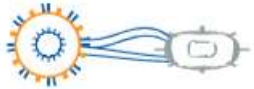
7. Cell Death

Within the patient's body, the CAR-T cells have the potential to recognize the patient's cancer cells and other cells expressing a specific antigen and attach to them, which may initiate direct cell death

CAR-T cells attach to cancer cells

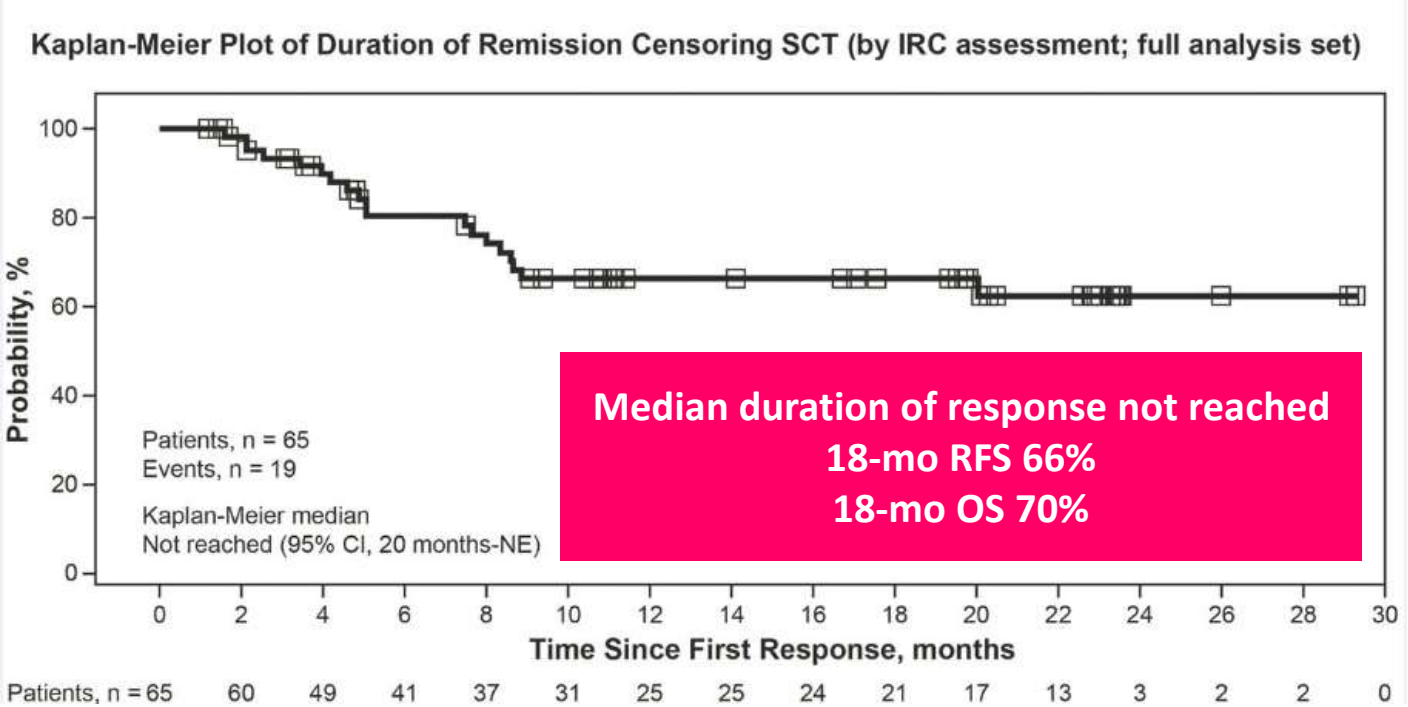


Cell death is initiated



ELIANA: Updated Analysis of the Efficacy and Safety of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed/Refractory (r/r) Acute Lymphoblastic Leukemia

S. Grupp, S. Maude, et al; ASH 2018



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

Current limitations of CAR T cells

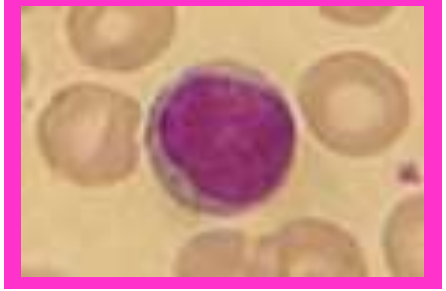
CAR failure

- Fail to harvest enough T cells
- Fail to expand (in vitro or in vivo)
- Limited persistence in vivo

Time from harvest to infusion

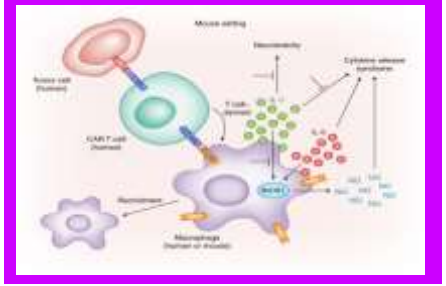
Antigen modulation

- Antigen loss or downregulation
- Lineage switch



CAR T-cell toxicities

- Severe CRS
- Neurotoxicity

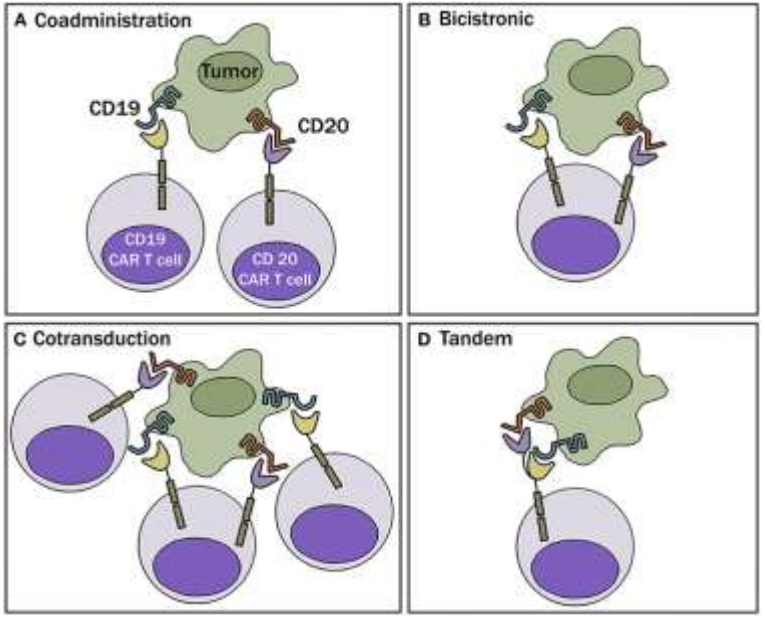


$ Cost and Age Restriction

New CARs

- **New designs**
  - Humanised CART19: CTL119
    (Maude, ASH 2017)
  - CD22 CAR T cell
    (Fry, Nat Med 2018)
  - Dual targeting: CD19/22
    (Amrolia, ASH 2018)
  - Allo universal CAR
    (Zhang, ASH 2018)

- **Improved functionality**
  - PD-1 blockade combination
  - PD-1 knockout
  - Modular/switch design



Dual targeting CAR T cells

New CARs

- **New designs**
  - Humanised CART19: CT
    (Maude, ASH 2017)
  - CD22 CAR T c
    (Fry, Nat Me
  - Dua

Need for HSCT after CAR T cells?

HSCT indicated if:

1. **Any MRD recurrence**
2. **B-cell recovery in first 6 months**

Relapsed T-ALL

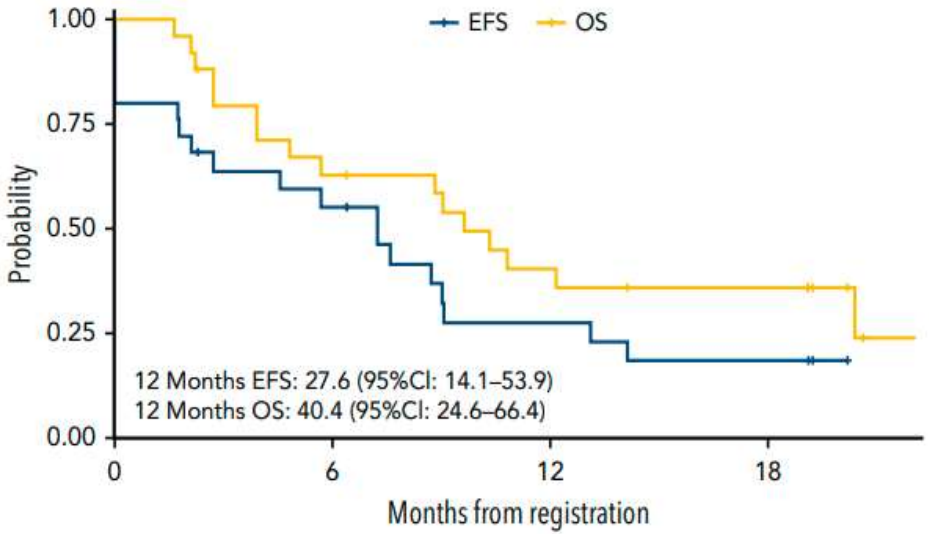
- Occurs earlier than B-ALL
- Survival poor: OS <25%
- HSCT regardless of timing or site of relapse as soon as MRD– remission obtained
- No standard reinduction approach

UKALL R3 Mitoxantrone arm	**3-yr PFS 65%**
COG AALL07P1 Bortezomib + 4-drug induction	CR2 68%
NECTAR Nelarabine, cyclophosphamide, etoposide	CR2 44%

A phase 1 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 multiply R/R ALL
- CR in 80%
  - 75% with 1.4 mg/m^2
  - 85% with 1.8 mg/m^2
- 84% of responders MRD–
- 12-mo OS 40%



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

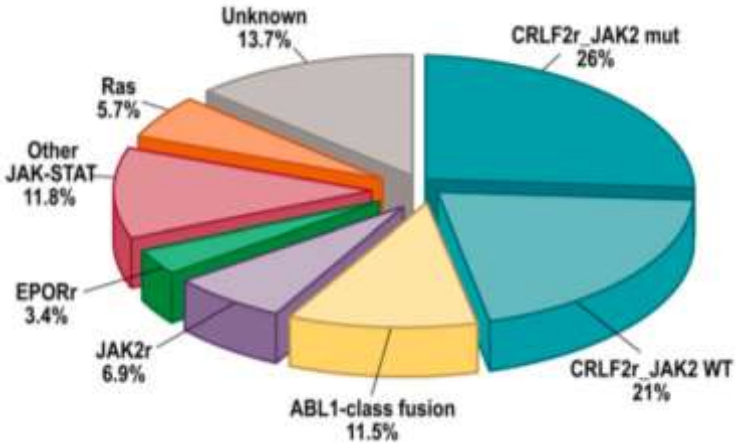
A phase 1 study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia

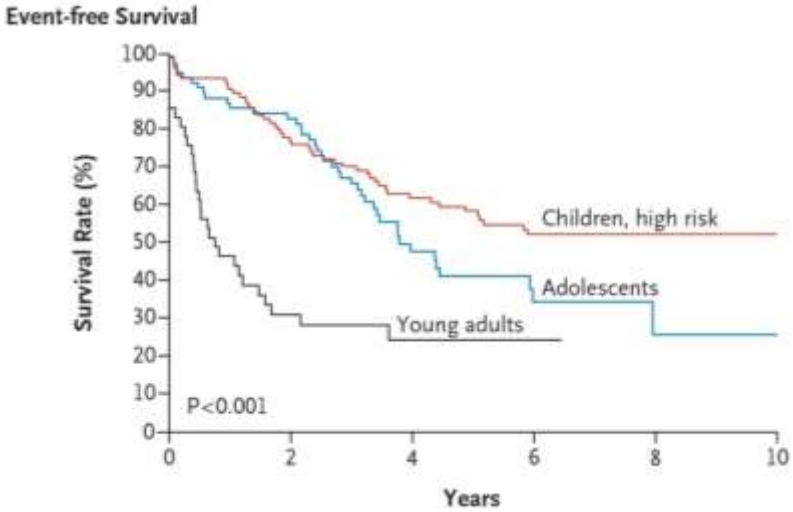
ITCC-059: Brivio E, Locatelli F, Lopez-Yurda M, et al

- No SOS during treatment but 2 episodes after multiagent chemo
  - Bhojwani 2019: 11/21 (53%) had SOS during subsequent HSCT
  - AALL1621: 4/13 (30.7%) had SOS during subsequent HSCT
  - Ursodeoxycholic acid prophylaxis and consider defibrotide
- Seems better tolerated than relapse chemotherapy
  - Fever 64%, ↓plts 60%, ↓neutrophils 56%, anaemia 44%
  - Hepatic (grade 3-4): ↑ bilirubin 12%, transaminitis ~20%

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

Small molecules for “Ph-like” ALL





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

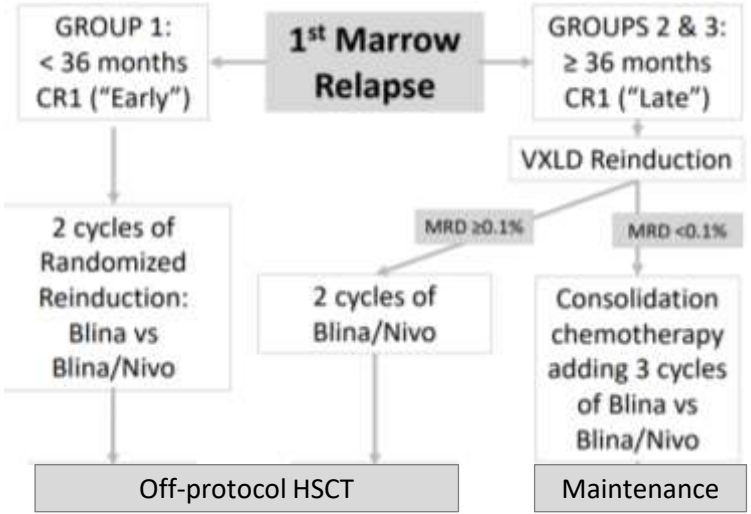
Roberts et al. *N Engl J Med.* 2014; Weston et al. *J Clin Oncol.* 2014.

AALL1821

Blinatumomab in combination with nivolumab for 1st relapse of B-ALL

Goals

1. For 1st BM relapse, does a blinatumomab induction increase efficacy and decrease toxicity?
2. After induction, does a checkpoint inhibitor augment the efficacy of blinatumomab?
    - Blina resistance often due to endogenous T-cell factors (eg CD8+ T-cell exhaustion)



Early phase clinical trials

- **Proteasome inhibitors**
  - Bortezomib, carfilzomib, ixazomib
- **CDK4/6 inhibitors**
  - Palbociclib, ribociclib
- **BCL2 inhibitors**
  - Venetoclax ± navitoclax
- **mTOR inhibitors**
  - Temsirolimus, everolimus
- **Anti-CD38 monoclonal antibody**
  - Daratumumab
- **CAR T cells**

Global Leukemia Academy

Bispecifics for pediatric ALL, focus on frontline therapy

Patrick Brown

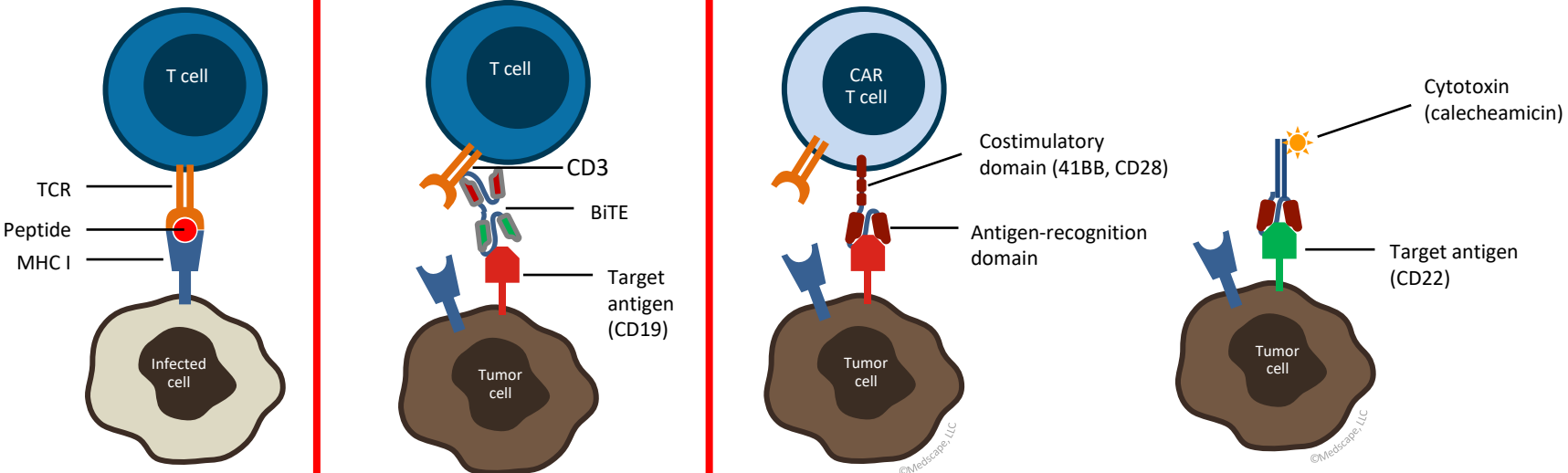
APTITUDE HEALTH

Bispecifics for Pediatric ALL: Focus on Frontline Therapy

Patrick Brown, MD

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

Mechanism: Normal vs BiTE vs CAR vs ADC



- Off the shelf
- Continuous IV infusion

- Complicated and prolonged process
- Single infusion

- Off the shelf
- Weekly short IV infusions

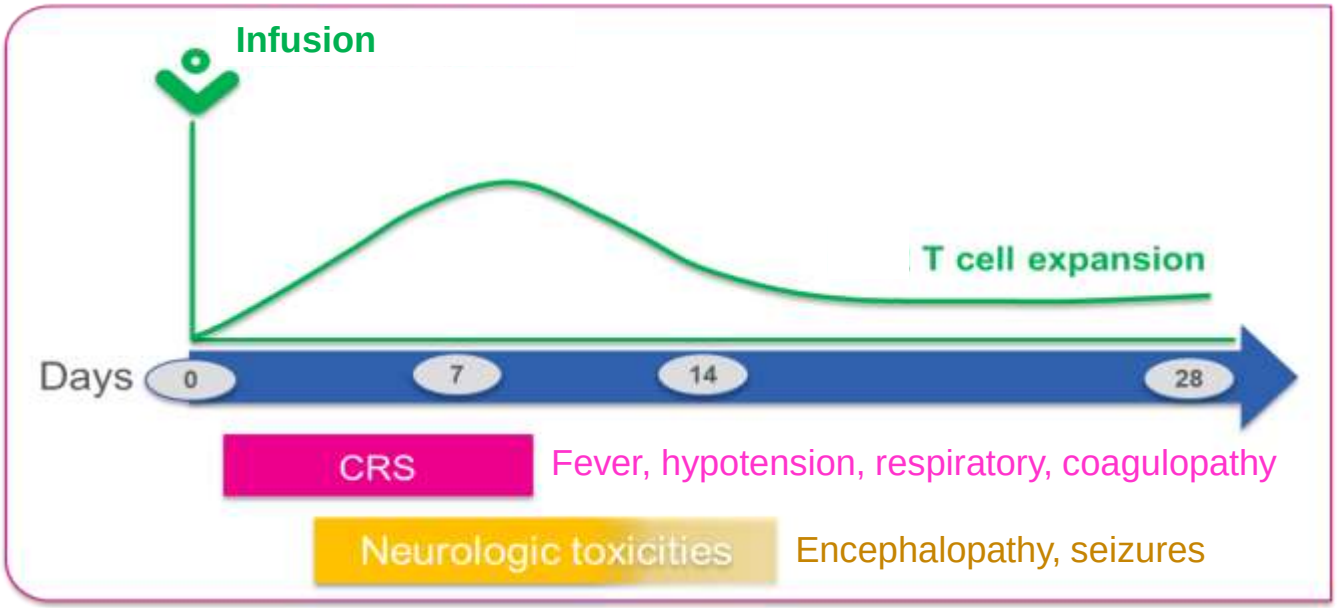
Adapted from: Hinrichs CS, et al. *Nat Biotechnol.* 2013;31:999-1008.

Adverse Events in Relapsed/Refractory B-ALL

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

1. Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847; 2. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; 3. Maude SL, et al. *N Engl J Med.* 2018;378:439-448.

AEs After Blinatumomab and CAR T Cells



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

MRD+

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

Adapted from/courtesy of Novartis.

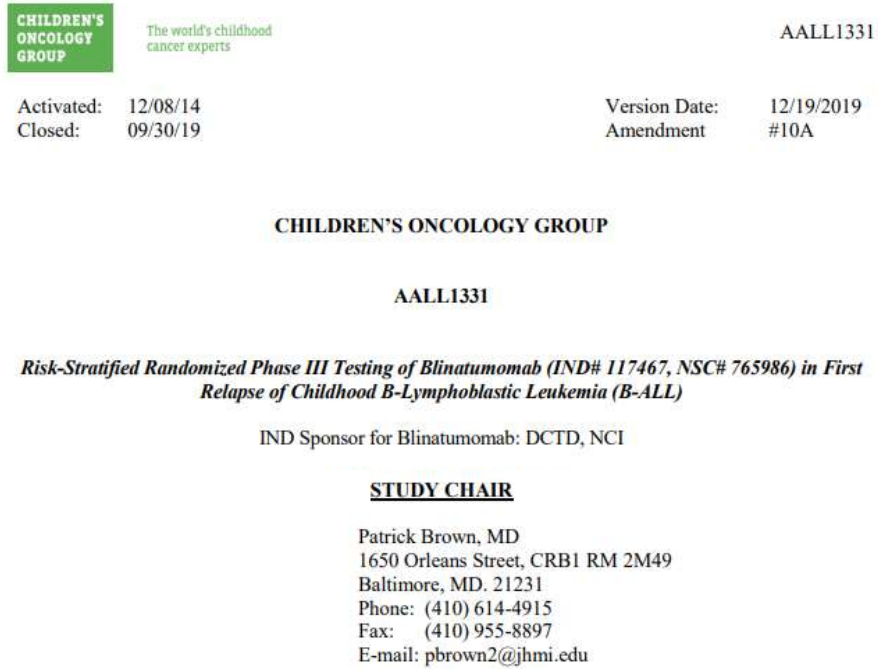
Blinatumomab (CD19 BiTE)

- In multiple relapsed/refractory setting (peds and adults)
  - CR 40%–45%
  - MRD-negative CR 20%–35%
  - Early survival benefit (adults)

von Stackelberg et al. *J Clin Oncol.* 2016;34:4381-4389
Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847

- In MRD+ setting (adults)
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

Gokbuget et al. *Blood.* 2018;131:1522-1531



CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts

AALL1331

Activated: 12/08/14
Closed: 09/30/19

Version Date: 12/19/2019
Amendment #10A

CHILDREN'S ONCOLOGY GROUP

AALL1331

Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC# 765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

IND Sponsor for Blinatumomab: DCTD, NCI

STUDY CHAIR

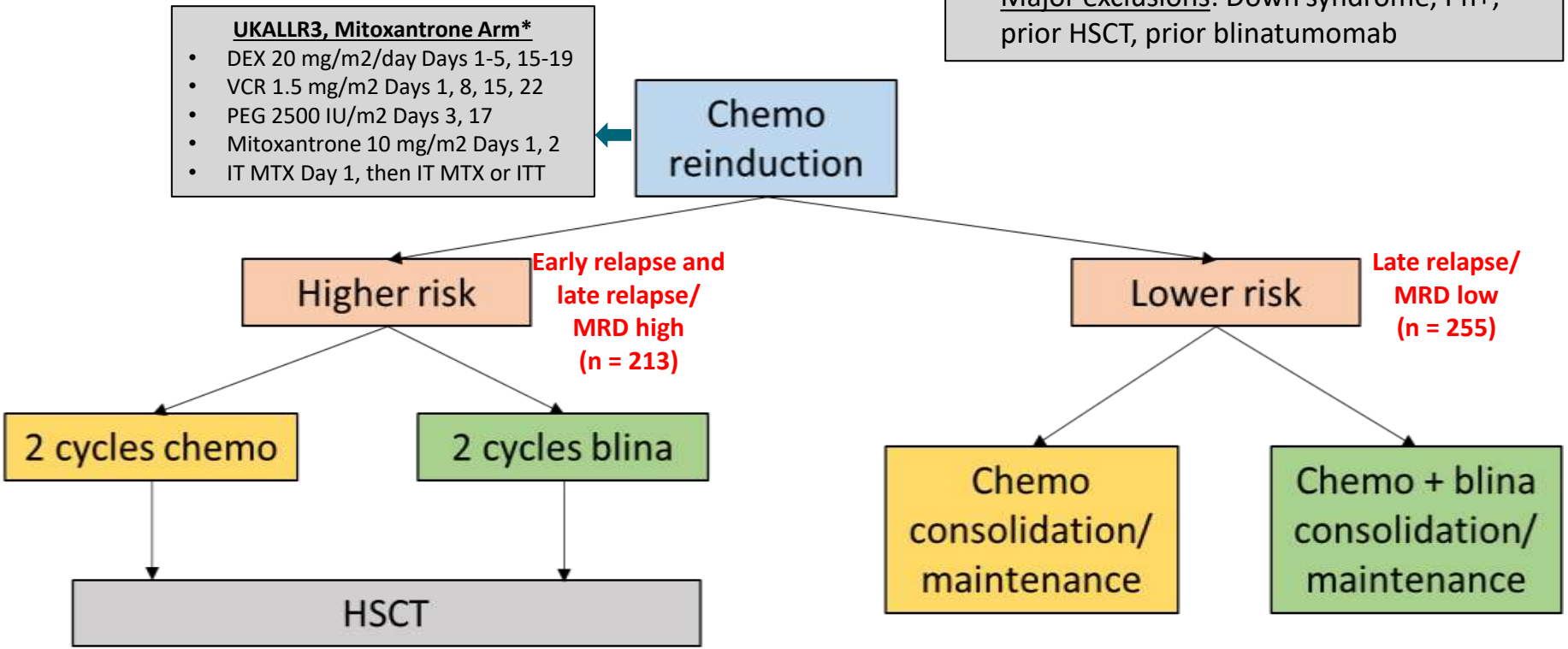
Patrick Brown, MD
1650 Orleans Street, CRB1 RM 2M49
Baltimore, MD. 21231
Phone: (410) 614-4915
Fax: (410) 955-8897
E-mail: pbrown2@jhmi.edu

CHILDREN'S ONCOLOGY GROUP

Overall objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in 1st relapse of childhood/AYA B-ALL

AALL1331: "Big Picture"

- All first relapse (any CR1 duration, any site)
- Ages 1-30
- Major exclusions: Down syndrome, Ph+, prior HSCT, prior blinatumomab



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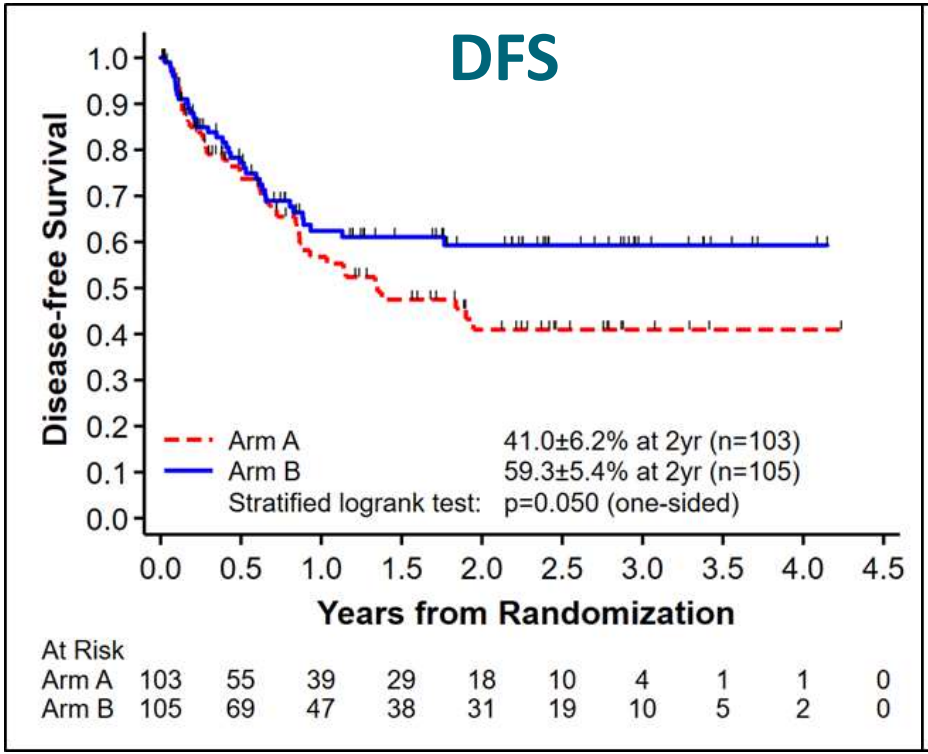
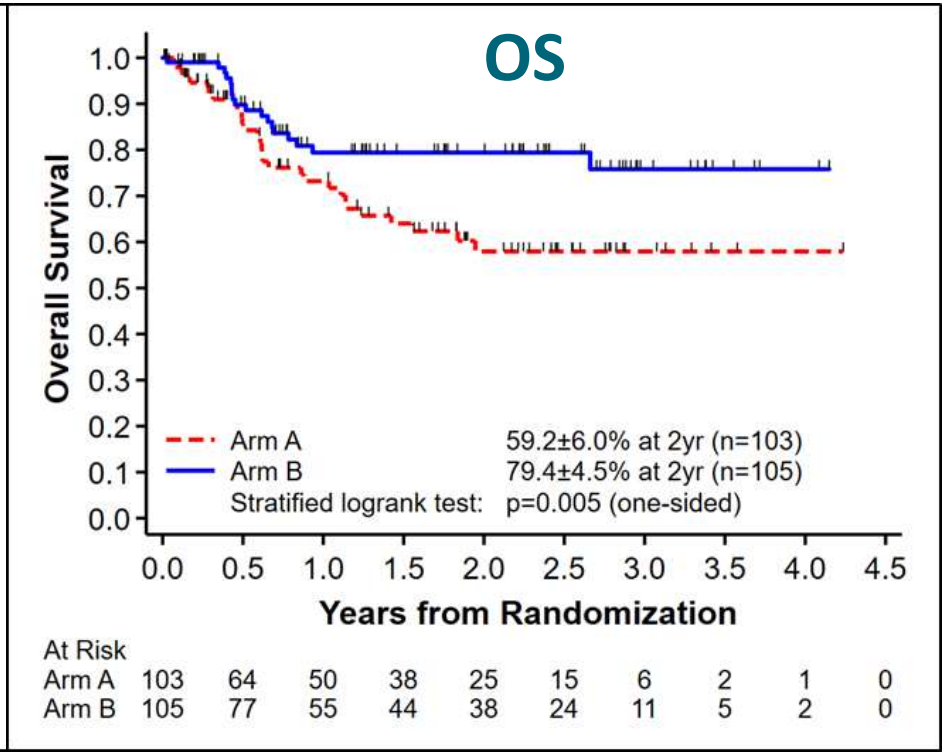
*UKALLR3 reference: *Parker, et al. Lancet. 2010;376:2009-2017.*

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



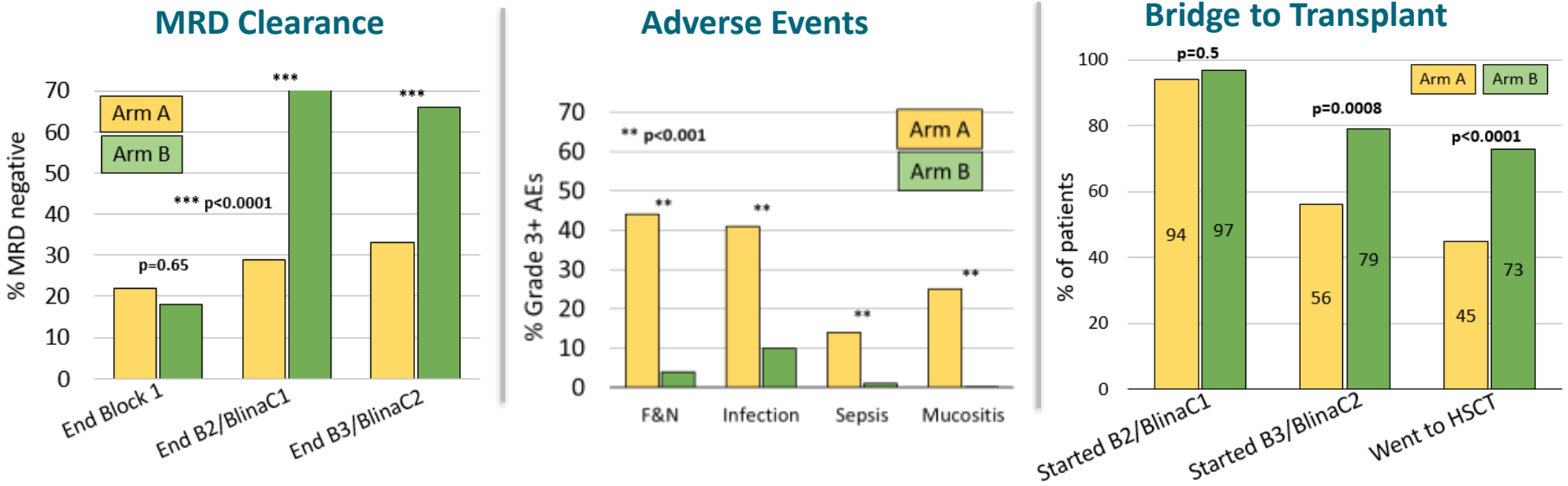


CHILDREN'S ONCOLOGY GROUP

Median follow-up 2.9 years

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

Other Endpoints: MRD, AEs, HSCT Bridging



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

CHILDREN'S ONCOLOGY GROUP

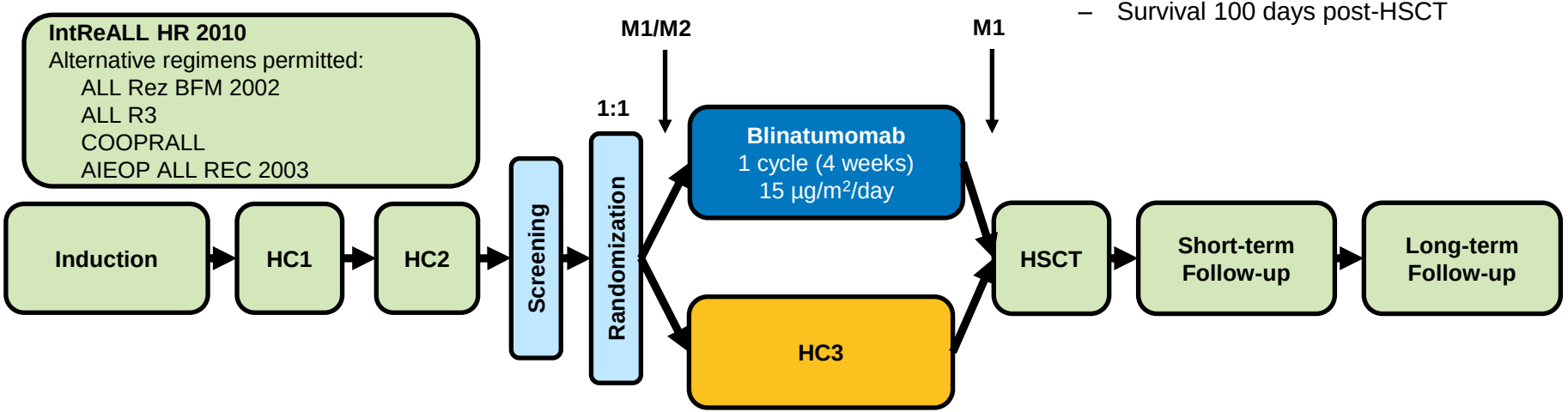
Brown P, et al. *JAMA*. 2021;325(9):833-842.

Amgen 20120215: Open-Label, Randomized, Phase 3 Trial – 47 Centers, 13 Countries

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

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

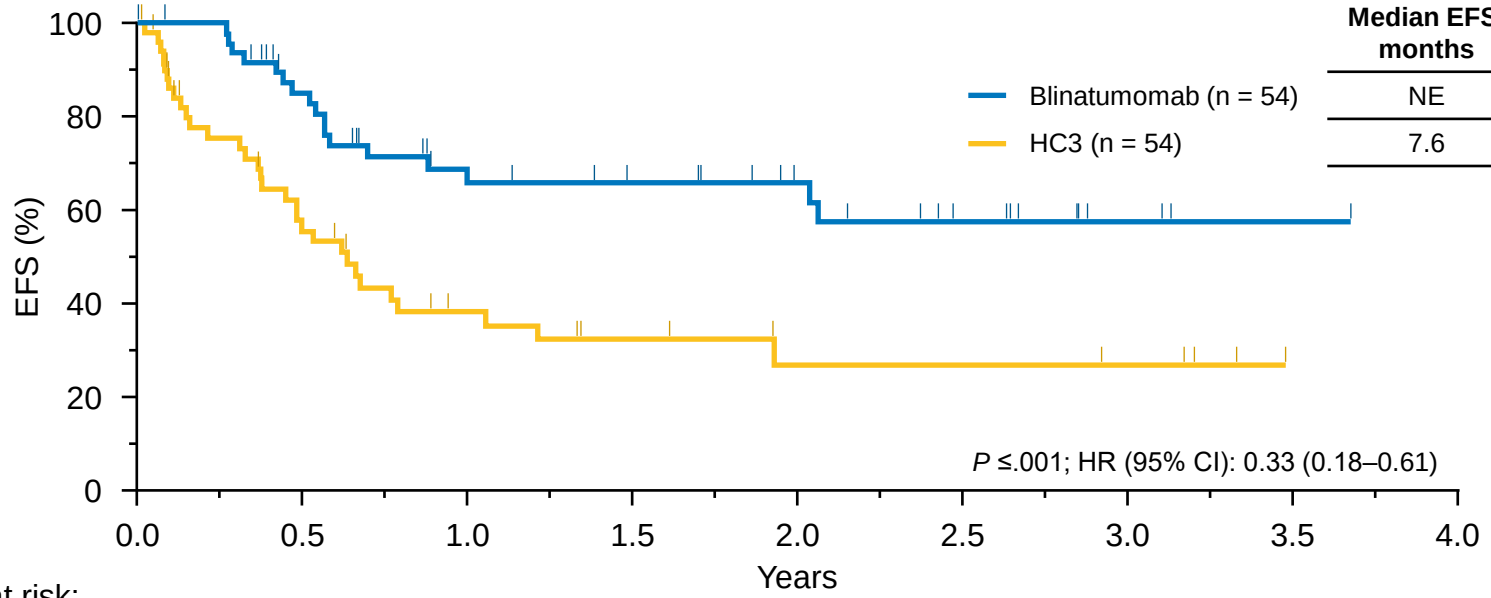
Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post-HSCT



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

BCP, B-cell precursor; EFS, event-free survival; HC, high-risk consolidation.

Superior EFS in the Blinatumomab Arm



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

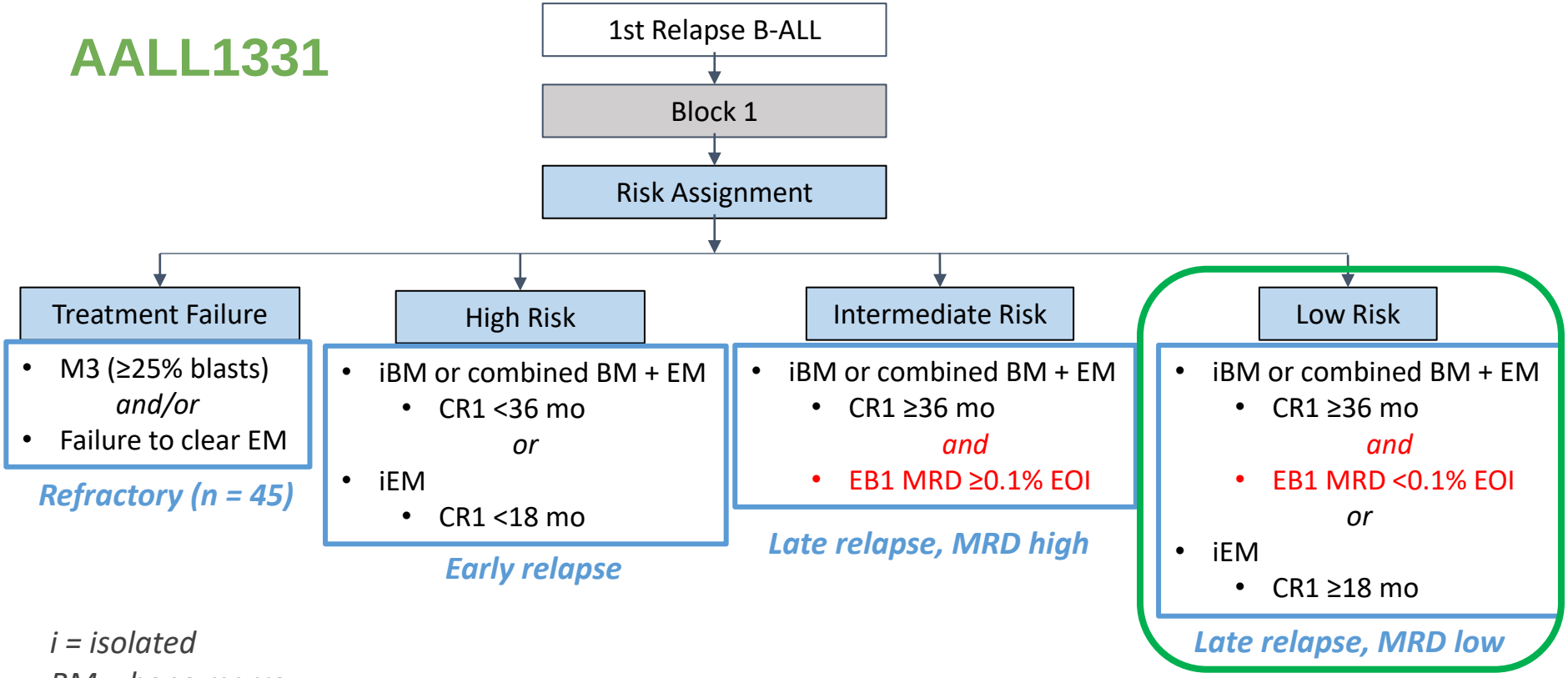
Patients at risk:

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

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

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

AALL1331



i = isolated
BM = bone marrow
EM = extramedullary (CNS, testes)
CR1 = duration of first remission
EB1 = end-Block 1

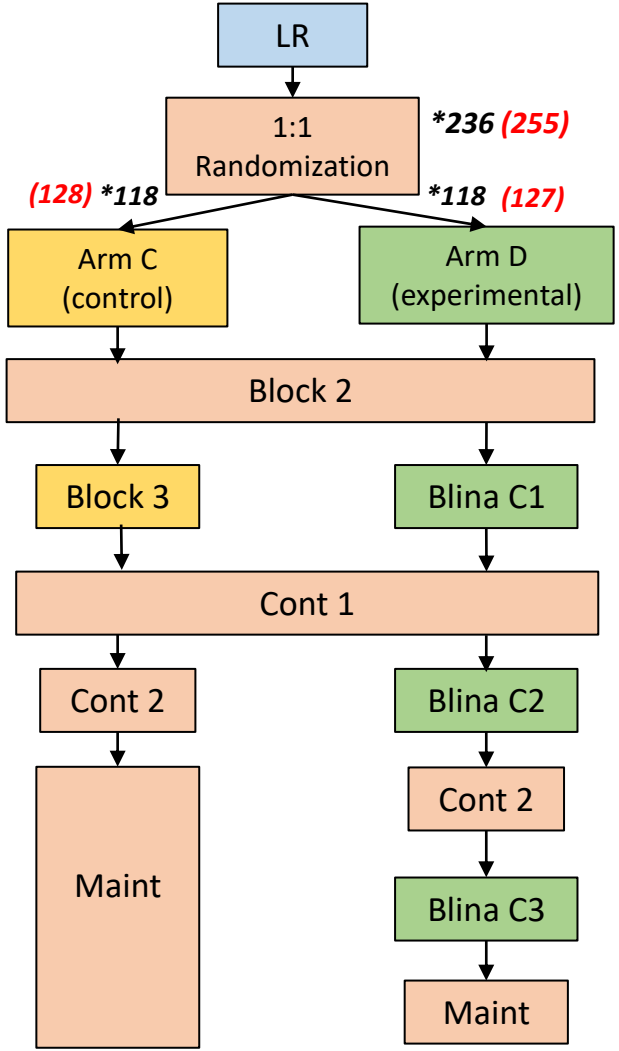
*UKALLR3 reference: *Parker, et al. Lancet. 2010;376:2009-2017.*

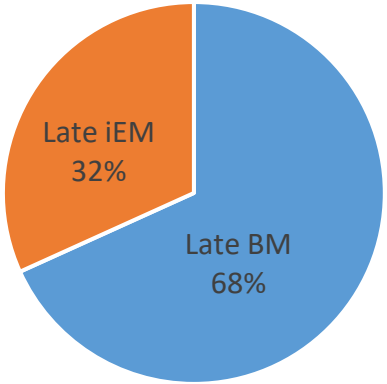
AALL1331

UKALLR3, Block 2*
- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

UKALLR3, Block 3*
- VCR, DEX week 1
- HD ARAC, Erwinia Weeks 1-2
- ID MTX, Erwinia Week 4
- IT MTX or ITT

UKALLR3, Continuation 1/2*
- VCR, DEX week 1
- 6MP week 1-6
- PO MTX week 2, 3, 5, 6
- ddMTX (CNS1/2) or ID MTX (CNS3) week 4
- CPM/ETOP/TG/ARAC week 7, 8
- IT MTX or ITT

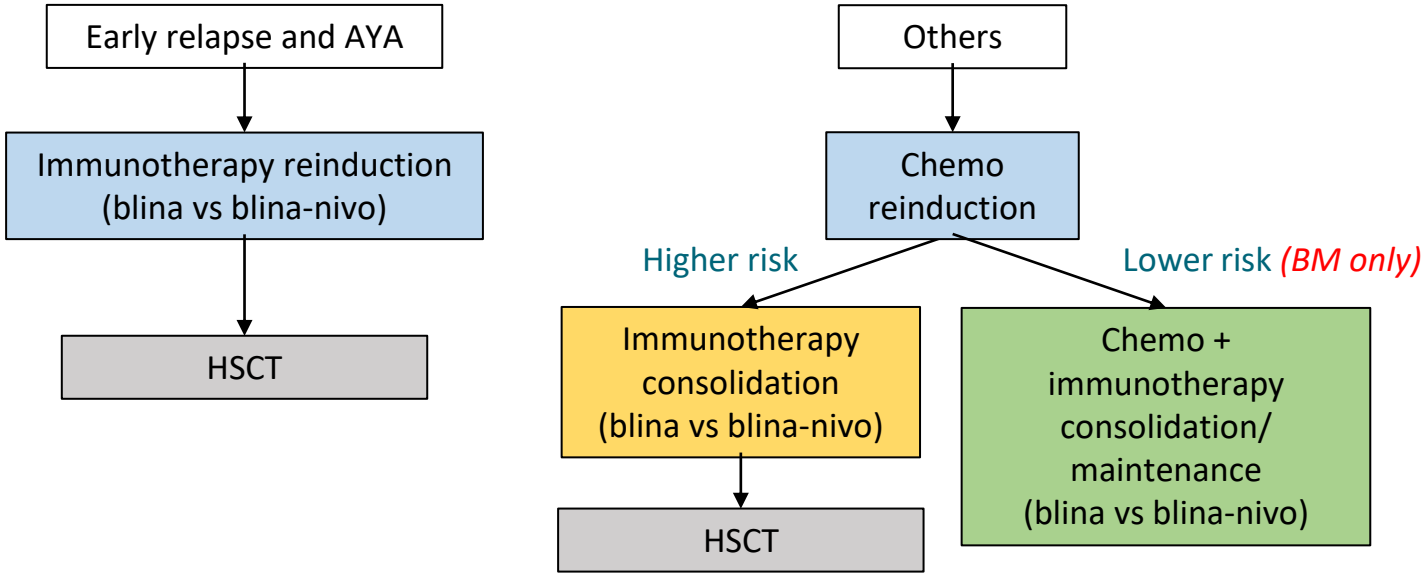




Blina C1, C2, C3
- Blinatumomab 15 ug/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed (C1 only)

- ***First patient randomized Jan 2015***
- ***Last patient randomized Sep 2019***

AALL1821: Blinatumomab + Nivolumab



COG: B-ALL Initial Risk-Stratification

Standard Risk

- WBC <50K *and*
- Age <10 *and*
- CNS1/2 *and*
- No testicular *and*
- No steroid pretreatment

High Risk

- WBC ≥50K *or*
- Age ≥10 *or*
- CNS3 *or*
- Testicular *or*
- Steroid pretreatment

Remission induction: 4 weeks

- IT chemo (AraC, then MTX)
- Steroids
  - NCI SR: 28 days DEX
  - NCI HR (≥10 y.o.): 28 days PRED
  - NCI HR (<10 y.o.): 14 days DEX
- Weekly IV VCR
- IV PEG × 1
- Weekly IV DAUNO (pre-induction HR only)

CHILDREN'S ONCOLOGY GROUP

COG: B-ALL Postinduction Risk-Stratification

	AALL1731						AALL1732		AALL1721
Risk Group	**SR-Fav**	**SR-Avg**		**SR-High**			**HR-Fav**	**High**	Very High
5-yr EFS	>95%	90-95%		70-90%			>94%	65-90%	40%
NCI Risk Group	SR	SR	SR	SR	SR	SR	HR <10 yr	HR	HR
Genetics	Fav	Fav	Neut	Neut	Any	Unfav	Fav	Any	Any
CNS	1/2	1/2	1	2	1/2	1/2	1	Any	Any
MRD d8 (PB)	<1	≥1	Any	Any	Any	Any	-	-	-
MRD d29 (BM)	<0.01	<0.01	<0.01	Any	≥0.01	Any	<0.01	Any	EOC BM MRD ≥0.01%
Distribution:	**33%**	**22%**		**10%**			**2%**	**27%**	**2%**

CHILDREN'S ONCOLOGY GROUP

Genetics:

Favorable	Unfavorable
• Hyperdiploidy (incl. +4, +10) • ETV6-RUNX1 – t(12;21)	• Hypodiploidy (<44) • KMT2A-r - 11q23 • TCF3-HLF - t(17;19) • iAMP21

Clinical Trial Questions in COG: Molecularly/Immunologically Targeted Therapy in B-ALL

	Risk Group	Projected 5-yr DFS	Therapeutic Question	
33%	SR-Favorable	>95%	Standard therapy with 2-year duration of maintenance therapy for boys and girls	AALL1731
2%	HR-Favorable	>94%		AALL1732
32%	SR-Avg & High	~89%	Blinatumomab } Randomized	AALL1731
27%	High Risk	~80%	Inotuzumab } Randomized	AALL1732
2%	Very High Risk	<50%	CAR T-cell therapy	AALL1721
5%	Ph+, Ph-like	60-85%	Molecularly targeted therapy	AALL1631 & 1521

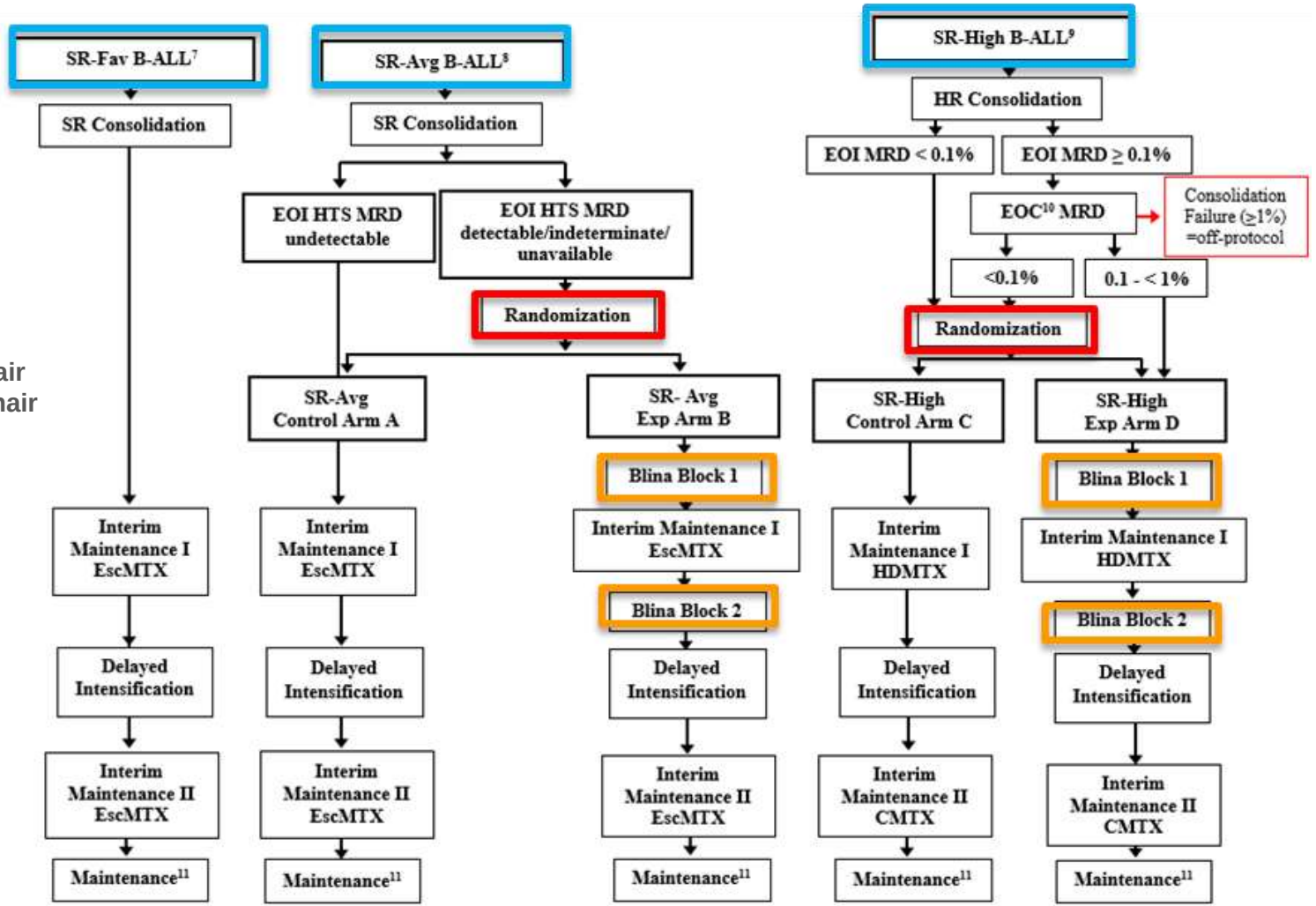
- **All patients on AALL1731 and AALL1732 will receive q12week pulses of VCR/steroid**
- **All boys and girls on AALL1731 and AALL1732 will receive therapy for 2 years from the phase that starts after consolidation**

CHILDREN'S ONCOLOGY GROUP

AALL1731:
Postinduction

Rachel Rau, Study Co-chair
Sumit Gupta, Study Co-chair

Opened June 2019
Accrued ~1800 of ~6400

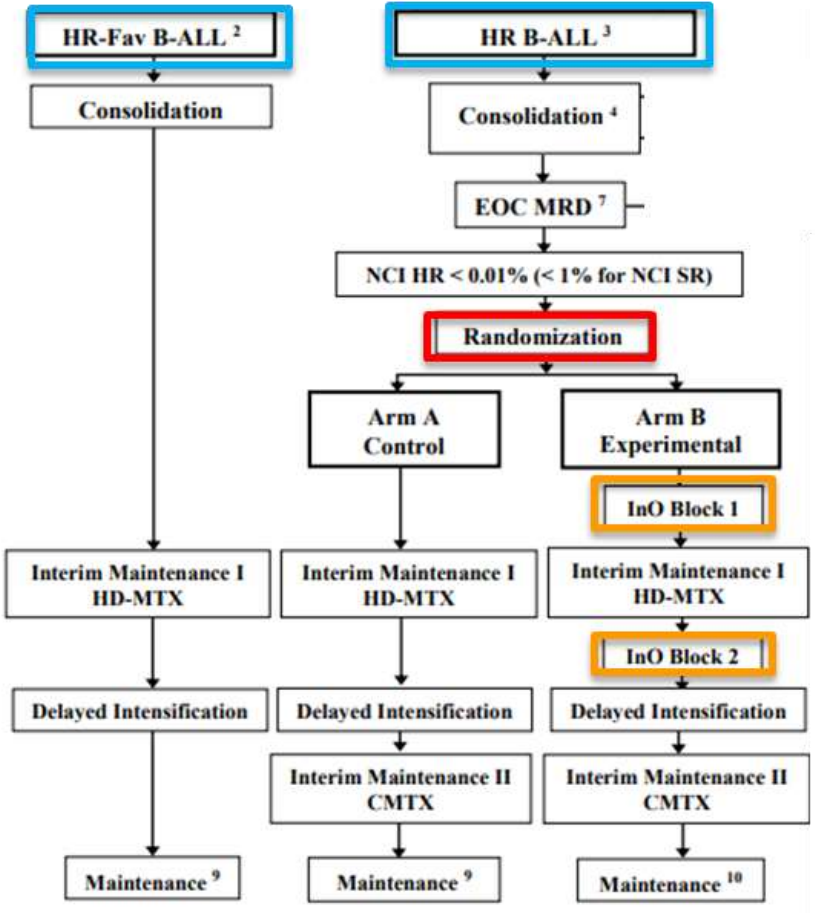


CHILDREN'S ONCOLOGY GROUP

AALL1732:
Postinduction

Maureen O'Brien, Study Co-chair
Jennifer McNeer, Study Co-chair

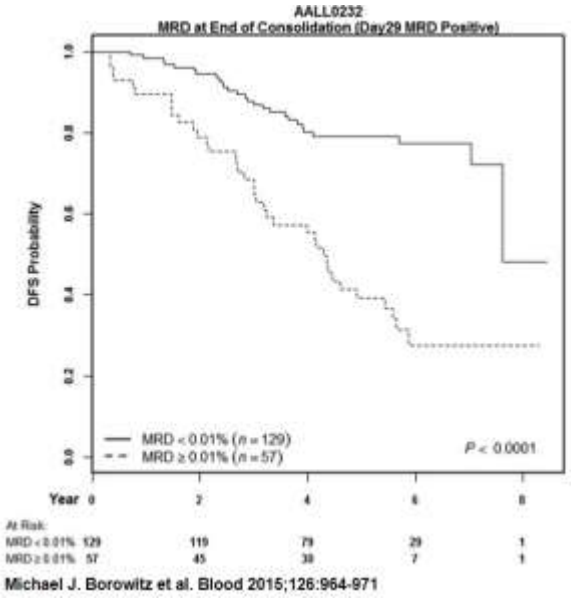
Opened October 2019
Accrued ~1000 of ~2500



CHILDREN'S ONCOLOGY GROUP

AALL1721: CAR T Cells for Late MRD+ B-ALL

Sponsor: Novartis; COG lead Shannon Maude



Michael J. Borowitz et al. Blood 2015;126:964-971

Patients with HR B-ALL treated on AALL0232

MRD determined by multi-parameter flow cytometry

Day 29 MRD >0.1%

5-year DFS by EOC MRD
MRD <0.01%: 79% ± 5%
MRD ≥0.01%: 39% ± 7%

blood

***de novo* NCI HR B-ALL**

HR Induction

MRD ≥1%

Leukapheresis

HR Consolidation

MRD ≥0.01%

Continue protocol Chemotherapy Proceed to CTL019 infusion when available

Screen and Enroll

CTL019 Manufacture

Infusion

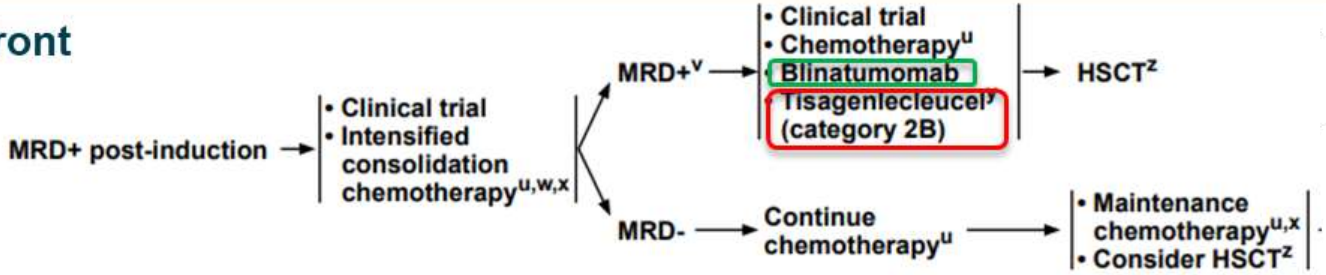
CHILDREN'S ONCOLOGY GROUP

Immunologically Targeted Therapy for Upfront B-ALL

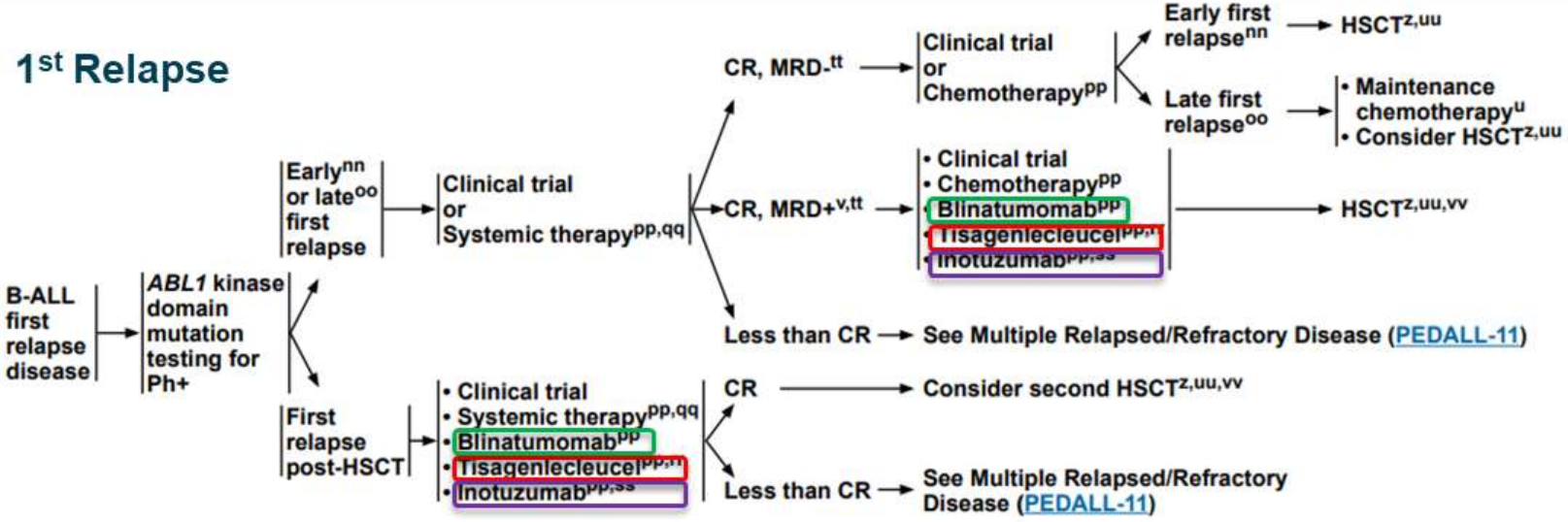
	Risk Group	Projected 5-yr DFS	Therapeutic Question	
33%	SR-Favorable	>95%	Standard therapy with 2-year duration of maintenance therapy for boys and girls	
2%	HR-Favorable	>94%		
32%	SR-Avg & High	~89%	**Blinatumomab** } **Randomized**	**60%**
27%	High Risk	~80%	Inotuzumab }	
2%	Very High Risk	<50%	CAR T-cell therapy	
5%	Ph-like	60-85%	Molecularly targeted therapy	

CHILDREN'S ONCOLOGY GROUP

Upfront



1st Relapse



Q

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

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

Q

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

a. True
b. False

Global Leukemia Academy

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

Bhavna Padhye

APTITUDE HEALTH

Patient case

- 14 y/o male
- Diagnosed with T-ALL/CNS-1
- Treatment according to AIEOP-BFM ALL 2009 protocol
- Dexamethasone in induction (starts after day 8, 10 mg/m^2/day for 21 days)
- Complicated by invasive pulmonary aspergillosis

Patient: Progress

- Responded well
  - Prednisolone good responder
  - PCR MRD at the end of induction: 5×10^{-4}
  - PCR MRD at the end of consolidation: negative

- Standard-risk T-ALL
  - Protocol M (4 × high-dose MTX)
  - Protocol II/reinduction (continuous dexamethasone)
  - Maintenance (no steroid pulses)

Patient: Progress

- Five months into treatment
- Presented with intermittent lower-limb pains
- MRI hips and knees
  - Hips: normal
  - Femur and tibia: early changes of osteonecrosis
- Referred to orthopedics

- What is the best management of early osteonecrosis?

- How is further steroid therapy managed?

Background

- Survival rates for ALL >85%

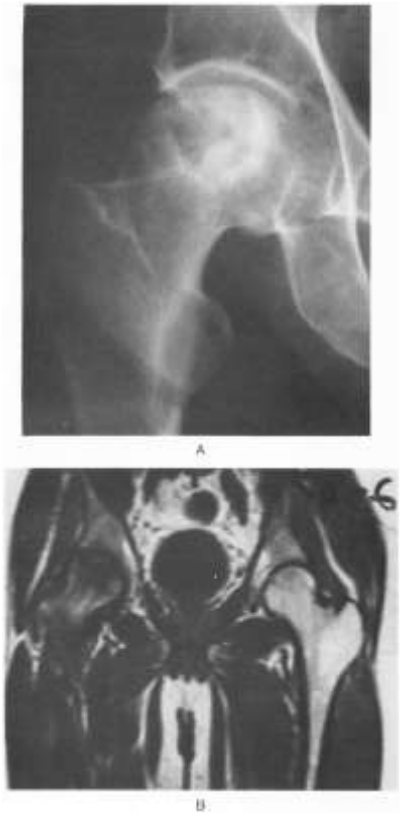
- Significant long-term side effects
- Skeletal morbidity in the form of osteonecrosis, osteopenia, osteoporosis, and fractures is common during treatment of ALL
- Osteonecrosis: involves weight-bearing joints/multiple joints
- ON has significant impact on long-term quality of life: pain, activity restriction, joint replacement, and need for revision surgery

Relative risk (as compared to siblings) of major joint replacement surgery in cancer survivors (not as part of cancer therapy) is 54 (7.6-386.3)[1]

1. Oeffinger KC, Mertens AC, Sklar CA, et al. *N Engl J Med*. 2006;355:1572-1582.

Pathogenesis of steroid/chemotherapy-induced osteonecrosis

- Direct effects of steroid on the bone
- Damage to vascular endothelium (methotrexate)
- Hypercoagulability (asparaginase)
- Adipocyte hypertrophy
- Increased intracortical pressure
- Compromise of blood flow causes infarction and necrosis of the bone
- Repair process: revascularization of dead bone, osteoclastic bone resorption with osteoblastic bone formation
- Next phase of repair process is uncontrolled and damages integrity of bone mass, can cause stress fractures, cartilage disintegration, and deformity
- This later phase varies in its time of onset, extent, and duration, which contributes to variations in presentation and clinical course



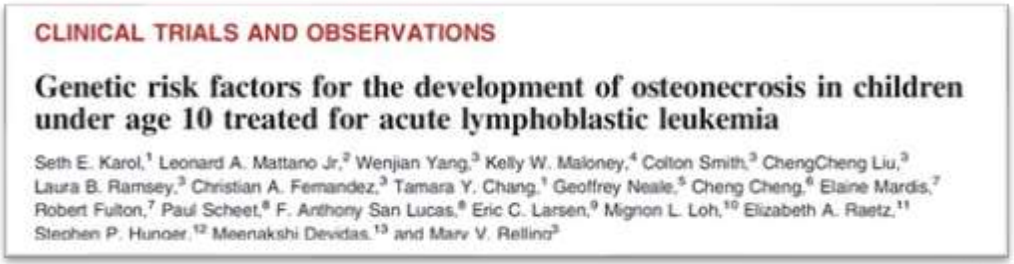
Risk factors

- Demographic: **age (>10 years),** gender, White race, higher BMI
- Treatment related: type of steroid (prednisolone vs dexamethasone), schedule of administration (continuous vs interrupted), other drugs asparaginase, methotrexate
- Hyperlipidemia, hypoalbuminemia, hypercoagulability
- Genetic: *SERPINE1, VDR, CYP3A4, PAI-1, ACP1,* glutamate receptor *GRIN3A, GRIK1*

CLINICAL TRIALS AND OBSERVATIONS

Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia

Seth E. Karol,[1,*] Wenjian Yang,[2,*] Sara L. Van Driest,[3] Tamara Y. Chang,[1] Sue Kaste,[4,5] Erica Bowton,[6] Melissa Basford,[6] Lisa Bastarache,[7] Dan M. Roden,[6,8] Joshua C. Denny,[7,9] Eric Larsen,[10] Naomi Winick,[11] William L. Carroll,[12] Cheng Cheng,[13] Deqing Pei,[13] Christian A. Fernandez,[2] Chengcheng Liu,[2] Colton Smith,[2] Mignon L. Loh,[14] Elizabeth A. Raetz,[15] Stephen P. Hunger,[16] Paul Scheet,[17] Sima Jeha,[1] Ching-Hon Pui,[1] William E. Evans,[2] Meenakshi Devidas,[18] Leonard A. Mattano Jr,[19] and Mary V. Relling[2]



CLINICAL TRIALS AND OBSERVATIONS

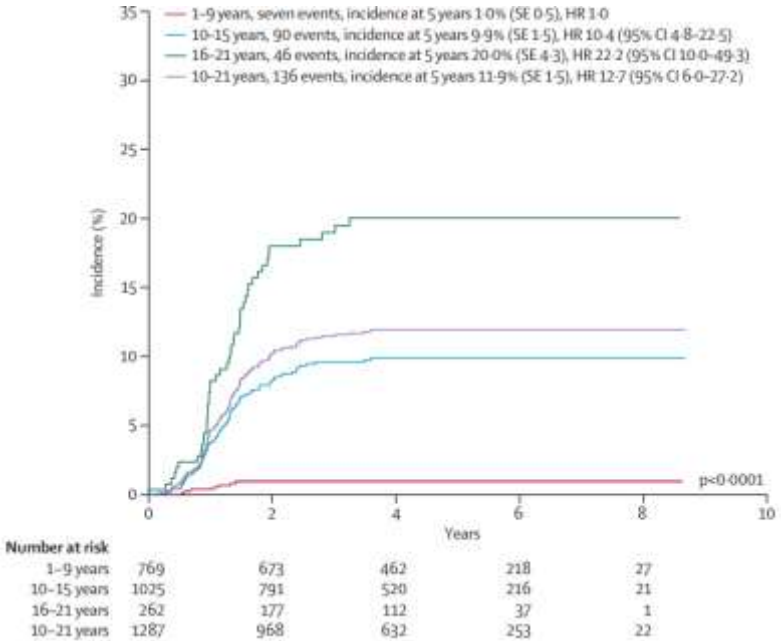
Genetic risk factors for the development of osteonecrosis in children under age 10 treated for acute lymphoblastic leukemia

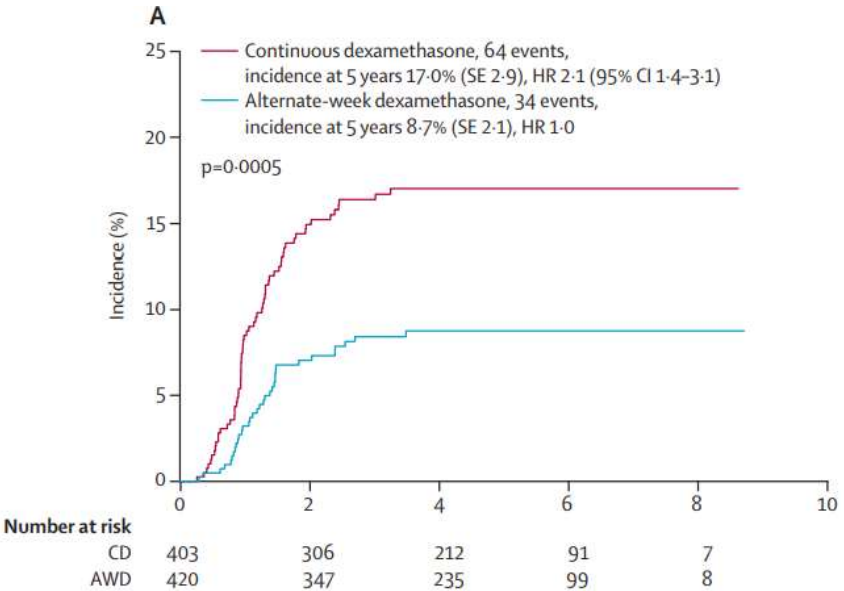
Seth E. Karol,[1] Leonard A. Mattano Jr,[2] Wenjian Yang,[3] Kelly W. Maloney,[4] Colton Smith,[3] ChengCheng Liu,[3] Laura B. Ramsey,[3] Christian A. Fernandez,[3] Tamara Y. Chang,[1] Geoffrey Neale,[5] Cheng Cheng,[6] Elaine Mardis,[7] Robert Fulton,[7] Paul Scheet,[8] F. Anthony San Lucas,[8] Eric C. Larsen,[9] Mignon L. Loh,[10] Elizabeth A. Raetz,[11] Stephen P. Hunger,[12] Meenakshi Devidas,[13] and Mary V. Relling[3]

Karol SE, et al. *Blood*. 2015;126:1770-1776; Karol SE, et al. *Blood*. 2016;127:558-564.

CCG 1961

Incidence of ON by age and steroid administration schedule





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

Incidence of ON (retrospective)

Study protocol	Incidence of ON
CCG 1882	9.3% **>10 years: 14.2%,** <10 years: 0.9%
CCG 1961	7.7% **10-15 years: 9.9% ≥16 years: 20%,** 1-9 years: 1%
COG AALL 0232	10.4% **>10 years: 15.2%** and <10 years: 2.6%
COG AALL 0331	2.7% 1-2 years: 0.8%, 3-4 years: 2.0%, 5-6 years: 3.3%, **7-9 years: 7.8%**
COG AALL 0434	8% **>10 years: 14.6%** and <10 years: 2.6%
DFCI 87-01 and 91-01	7% **>9 years: 21%** and <9 years: 4%
DFCI 00-01	6% **>10 years: 14%** and <10 years: 3.5%
CCOG ALL-9	6% Age
BFM 95	1.8% **>10 years: 8.9%** and <10 years: 0.2%
BFM 2000	3.6% **>10 years: girls 18.4%, boys 7.6%,** <10 years: girls 0.8%, boys 0.7%
AIEOP ALL 95	1.6% **>10 years: 7.4%,** 0-5 years: 0.3%, and 6-9 years: 0.7%
UKALL 2003	4% **>16 years: 16%, 10-15 years: 13%,** and <10 years: 1%

Kunstreich M, et al. *Haematologica*. 2016:101:1295-1305.

<u>Prospective data</u> St. Jude Total XV study[1] (screening MRIs at regular intervals irrespective of symptoms): cumulative incidence of any vs symptomatic osteonecrosis was 71.8% vs 17.6%

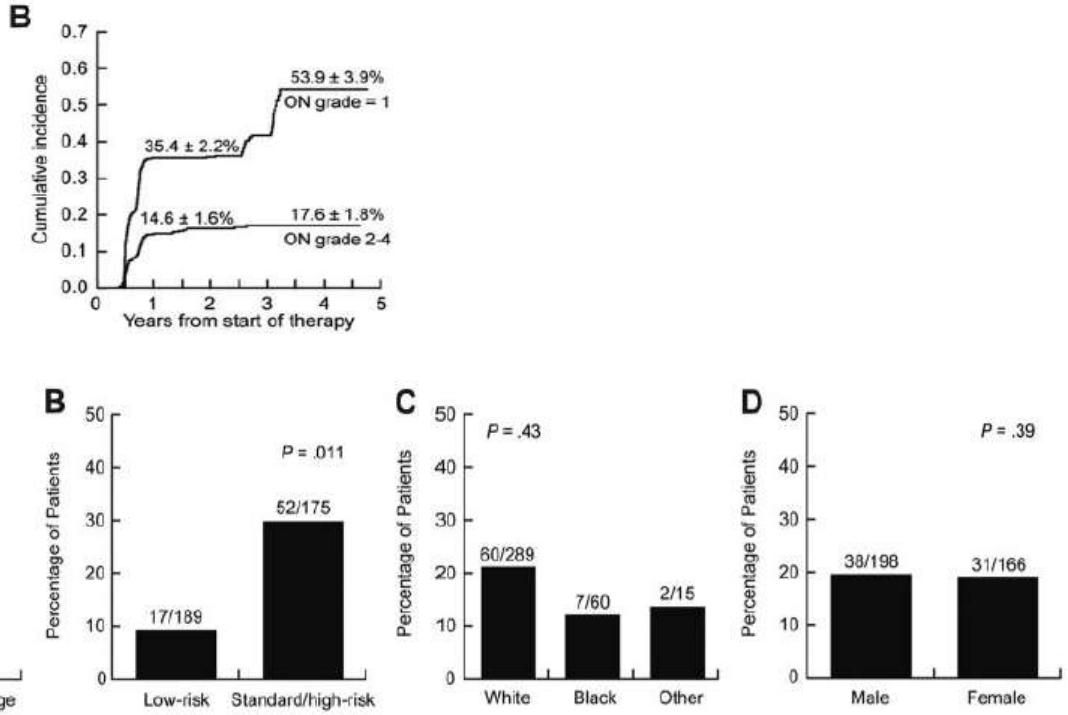


Figure 2. Age and treatment arm were associated with symptomatic osteonecrosis. Percentage of patients who developed grade 2 to 4 osteonecrosis by (A) age, (B) treatment arms, (C) race, and (D) sex.

1. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. Blood 2011;117:2340–2347.

- Should patients be screened for osteonecrosis?
  - Which patients (age)?
  - How do we screen?
  - What are the radiologic features that predict the joint outcome?
  - What do we do if we find early/asymptomatic changes of ON?
- Can natural history of osteonecrosis be modified?

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Utility of Early Screening Magnetic Resonance Imaging for Extensive Hip Osteonecrosis in Pediatric Patients Treated With Glucocorticoids

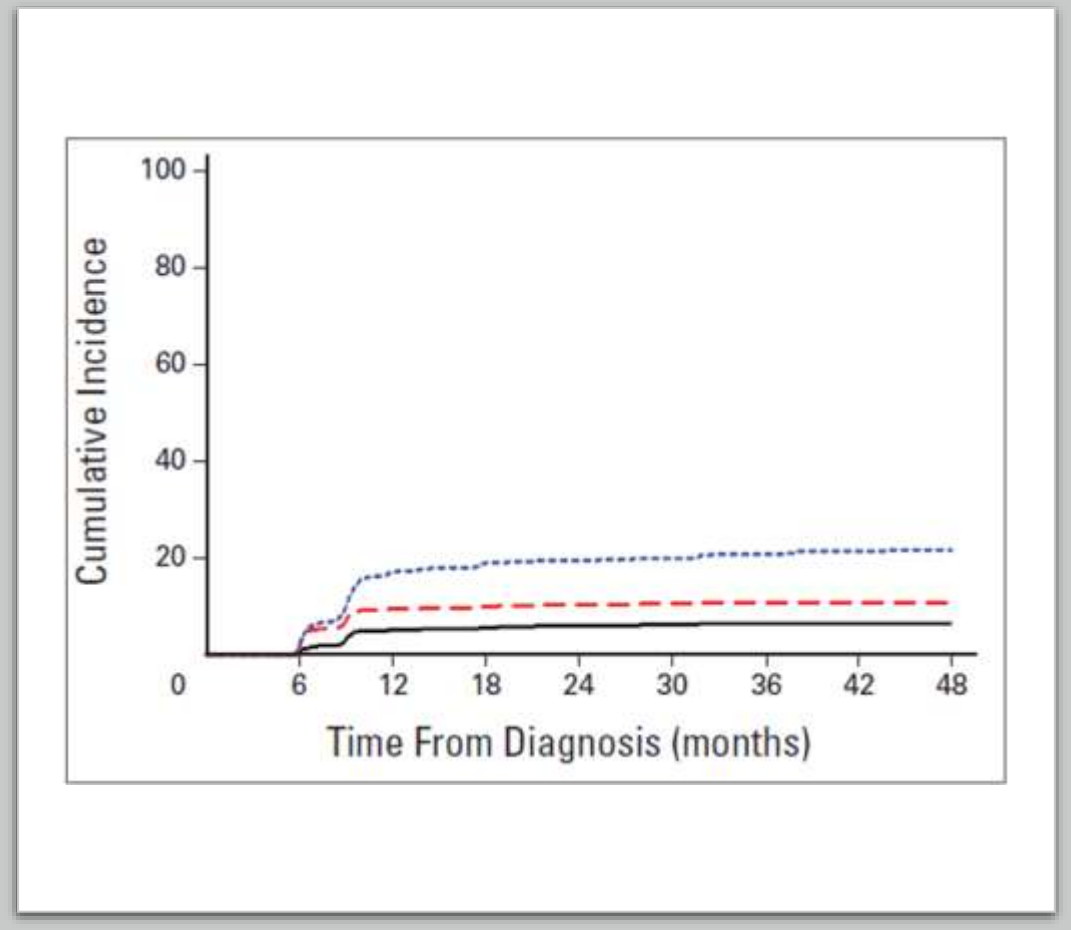
Sue C. Kaste, Deqing Pei, Cheng Cheng, Michael D. Neel, W. Paul Bowman, Raul C. Ribeiro, Monika L. Metzger, Deepa Bhojwani, Hiroto Inaba, Patrick Campbell, Jeffrey E. Rubnitz, Sima Jeha, John T. Sandlund, James R. Downing, Mary V. Relling, Ching-Hon Pui, and Scott C. Howard

- 462 patients underwent screening MRI (hip at 6.5/9/end of therapy)
- Screening sensitivity was 84.1% and specificity was 99.4%
- Number needed to screen

	Patients	Joints
Overall	17	20.1
>10 yr	3.8	4.4
<10 yr	149	198

Kaste SC, et al. *J Clin Oncol*. 2015;33:610-615.

- Patients with extensive ON (>30% of femoral head involvement) are at significantly higher risk of joint collapse
- About 80% of patients who would ultimately develop ON did so within 1 year of diagnosis
- Yield of screening is low beyond 1 year even in patients older than 10 years



Kaste SC, et al. *J Clin Oncol*. 2015;33:610-615.

Treatment of osteonecrosis

- Analgesia
- No weight bearing
- Surgical procedures: core decompression
- Joint replacement
- Nonsurgical treatments: prostaglandins, hyperbaric oxygen, nifedipine, bisphosphonates
- **NO preventive treatment**

Coming back to the patient . . .

- What is the current management of osteonecrosis?
  - Non-weight bearing
  - Pharmacologic agents
  - Surgical management

- Can further steroids be administered?
  - If yes: is dose reduction required?
  - If no: what is dexamethasone replaced with?

- He received zoledronic acid
- Pain improved
- He received dexamethasone in reinduction
- But the hip joints progressed, requiring bilateral hip joint replacements

- Screening
  - Imaging
  - Genetics
- Known risk factors
  - Age >10 = significant risk factor
  - Steroid type and timing may be more important than cumulative dose
- Early detection
- Orthopedic intervention
- Medication changes

Global Leukemia Academy

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

Michael Osborn

APTITUDE HEALTH

Case Presentation: Miss J

COLT 2017

SAHMRI

Miss J: diagnosed with Ph+ ALL

- Diagnosed 13/10/2009: CNS negative
- Treated according to COG AALL0622 with imatinib rather than dasatinib, and several other modifications due to toxicity
- Cranial irradiation: 12 Gy in 8 fractions
- Completed maintenance chemotherapy 23/2/12, but continued on imatinib (compassionate supply)

- End of induction BMB (12/11/09) showed morphological remission but 23/30 cells were Ph+
- MRD negative (CCIA), but BCR-ABL *never* negative on imatinib

- **Was this Ph+ ALL or CML in lymphoid blast crisis? What to do?**

Switched to dasatinib April 2014

- Did not tolerate imatinib well – myalgia and gastrointestinal toxicity
- BMB on imatinib in July 2013 showed loss of CCR: 1/32 Ph+
  - No significant blast population
- Following switch
  - Peripheral blood BCR-ABL fell to undetectable by 3 months (July 2014)
  - Sept 2014: Re-appeared at low levels, ranging from 0.008 to 0.061 until mid-2015
- February 2015 mutation analysis? V299L

August 2015: Florid relapse of Ph+ ALL

- June 2015: BCR-ABL undetectable on 4 June
- July 2015: Rose to 0.16
- Aug 2015: Rose to 3.5

- BMB (19/8/15): 60% blasts, BM BCR-ABL 79%
  - Almost 6 years after original diagnosis
  - No mutation detected
- Treated according to UKALLR3 SR 2010 + ponatinib then MUD HSCT
- Subsequent relapse
  - Brief response to inotuzumab
  - Succumbed to infection with evidence of relapsing disease at the time

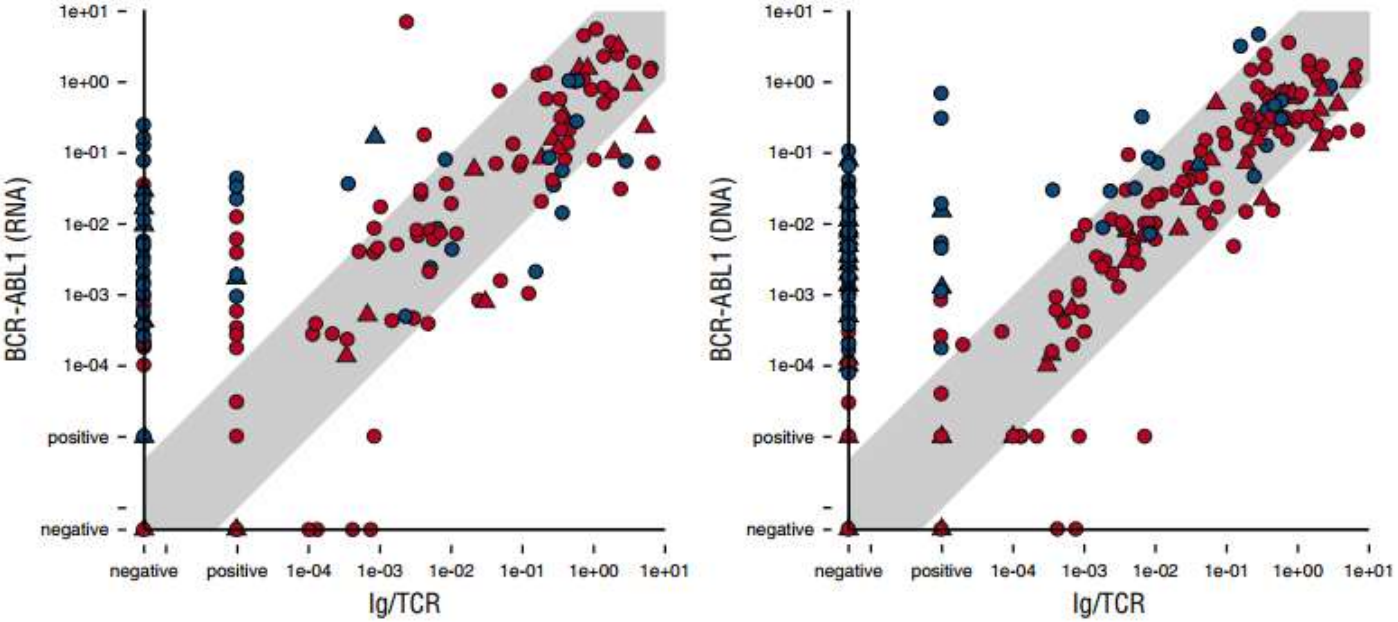
Regular Article

blood

LYMPHOID NEOPLASIA

Monitoring of childhood ALL using *BCR-ABL1* genomic breakpoints identifies a subgroup with CML-like biology

Lenka Hovorkova,[1,2] Marketa Zaliova,[1-3] Nicola C. Venn,[4] Kirsten Bleckmann,[5] Marie Trkova,[6] Eliska Potuckova,[1,2] Martina Vaskova,[1,2] Jana Linhartova,[7] Katerina Machova Polakova,[7] Eva Fronkova,[1,2] Walter Muskovic,[4] Jodie E. Giles,[4] Peter J. Shaw,[8] Gunnar Cario,[5] Rosemary Sutton,[4,9] Jan Stary,[2,3] Jan Trka,[1-3] and Jan Zuna[1-3]



Regular Article blood

LYMPHOID NEOPLASIA

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- Cell sorting
  - BCR-ABL1 (but not Ig/TCR rearrangement) in
    - 15%–83% of non-ALL B lymphocytes
    - 12%–21% of T cells
    - 15%–80% of myeloid cells
- Suggests multipotent haematopoietic progenitor affected by BCR-ABL1 fusion

Regular Article blood

LYMPHOID NEOPLASIA

Monitoring of childhood ALL using *BCR-ABL1* genomic breakpoints identifies a subgroup with CML-like biology

Lenka Hovorkova,[1,2] Marketa Zaliova,[1-3] Nicola C. Venn,[4] Kirsten Bleckmann,[5] Marie Trkova,[6] Eliska Potuckova,[1,2] Martina Vaskova,[1,2] Jana Linhartova,[7] Katerina Machova Polakova,[7] Eva Fronkova,[1,2] Walter Muskovic,[4] Jodie E. Giles,[4] Peter J. Shaw,[8] Gunnar Cario,[5] Rosemary Sutton,[4,9] Jan Stary,[2,3] Jan Trka,[1-3] and Jan Zuna[1-3]

- "CML-like BCR-ABL1-positive ALL"
- Impact on
  - Optimal treatment: early HSCT vs long-term TKI
  - MRD testing

Global Leukemia Academy

Interactive Q&A

Patrick Brown

APTITUDE HEALTH

Global Leukemia Academy

Educational ARS Questions

Patrick Brown

APTITUDE HEALTH

Q

Educational Questions Pediatric ALL

Question 1: Which of the following subsets of 1st relapse ALL patients can be considered at very high risk?

a) All patients with B-ALL relapsing within 18 months from diagnosis
b) All patients with MLL-rearranged leukemia
c) All patients with hypodiploidy
d) Each of the 3 previous subsets

Q

Educational Questions Pediatric ALL

Question 2: Which assertion is correct for children with B-ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment
b) Inotuzumab dosage is 3 mg/m^2
c) TBI-based conditioning regimen should be preferentially used in children above the age of 4 years
d) None of the patients relapsing later than 6 months after treatment discontinuation should be transplanted

Q

Educational Questions Pediatric ALL

Question 3: For children and adolescents with high risk of first relapse of B-ALL, what regimen offers the best chance of survival?

a) Reinduction chemotherapy followed by HSCT
b) Reinduction chemotherapy followed by consolidation chemotherapy followed by HSCT
c) Reinduction chemotherapy followed by blinatumomab followed by HSCT
d) Reinduction chemotherapy followed by consolidation chemotherapy followed by continuation/maintenance chemotherapy
e) Reinduction chemotherapy followed by blinatumomab followed by continuation/maintenance chemotherapy

Global Leukemia Academy

Closing Remarks

Patrick Brown

APTITUDE HEALTH

Thank You!

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

THANK YOU!

AMGEN

abbvie

Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

16 May 2021

Virtual Breakout: Pediatric Leukemia Patients

APTITUDE HEALTH