AMGEN Adaptive biotechnologies®

Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

8–9 July 2020

APTITUDE HEALTH®

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour and Fatih Demirkan

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Meet the Faculty

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

Hale Ören, MD
Professor of Pediatrics,
Dokuz Eylul University

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

Josep-Maria Ribera, MD, PhD
Chair, Clinical Hematology Department, Catalan Institute of Oncology, University Hospital Germans Trias i Pujol

Andre Schuh, MD
Staff Physician,
Princess Margaret Cancer Centre

Objectives of the Program

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

Virtual Plenary Sessions (Day 1)

TIME UTC+3	TITLE	SPEAKER
15.00 – 15.10	Welcome and meeting overview; introduction to the voting system	Elias Jabbour, Fatih Demirkan
15.10 – 15.25	Review of prognostic value of MRD in ALL	Elias Jabbour
15.25 – 15.40	How and when to check for MRD in ALL	Josep-Maria Ribera
15.40 – 15.55	CR1 vs CR2 – where is MRD control more useful and how to achieve it?	Elias Jabbour
15.55 – 16.10	AYA ALL patients – what is the current treatment approach for this diverse patient population?	Rob Pieters
16.10 – 16.25	Bispecific T-cell engagers as post-reinduction therapy improves survival in pediatric and AYA B-ALL	Patrick Brown
16.25 – 16.45	Break	
16.45 – 17.00	Genetic variants in ALL – Ph+ and Ph-like	Andre Schuh
17.00 – 17.45	Panel discussion on the role of HSCT • Experience of HSCT in the region • Pros and cons of HSCT • How does COVID-19 influence your approach? • Discussion and voting	Moderator: Elias Jabbour Fatih Demirkan Fatih Demirkan, Andre Schuh All faculty All faculty
17.45 – 18.25	Debate on CD19-targeted approaches • CAR T • Monoclonal antibodies and bispecifics • Discussion and voting	Moderator: Elias Jabbour Josep-Maria Ribera Elias Jabbour All faculty
18.25 – 18.55	Emerging data and the management of ALL patients during COVID-19 • Presentation • Panel discussion	Moderator: Fatih Demirkan Elias Jabbour All faculty
18.55 – 19.00	Session close	Elias Jabbour, Fatih Demirkan

Virtual Breakout: Pediatric ALL Patients (Day 2)

Chair: Rob Pieters

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

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Virtual Breakout: Adult ALL Patients (Day 2)

Chair: Elias Jabbour

TIME UTC+3	TITLE	SPEAKER
15.00 – 15.15	Session opening • Educational ARS questions for the audience	Elias Jabbour
15.15 – 15.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation • Q&A	Elias Jabbour
15.35 – 15.55	Current treatment options for relapsed ALL in adult and elderly patients • Presentation • Q&A	Fatih Demirkan
15.55 – 16.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, Fatih Demirkan, Andre Schuh, Josep-Maria Ribera	Fatih Demirkan Andre Schuh Discussion
16.45 – 17.00	Session close • Educational ARS questions for the audience	Elias Jabbour

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Introduction to the Voting System

Elias Jabbour

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Question 1

Where are you from?

- Algeria
- Kuwait
- Morocco
- Oman
- Saudi Arabia
- South Africa
- Turkey
- United Arab Emirates
- Other

Question 2

How many patients with ALL are you currently following?

- 0
- 1–5
- 6–15
- 16–20
- ≥21

Question 3

How do you assess for minimal residual disease (MRD)?

- We do not check for MRD
- Multicolor flow
- Molecular PCR
- Next-generation sequencing platform

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Review of Prognostic Value of MRD in ALL

Elias Jabbour

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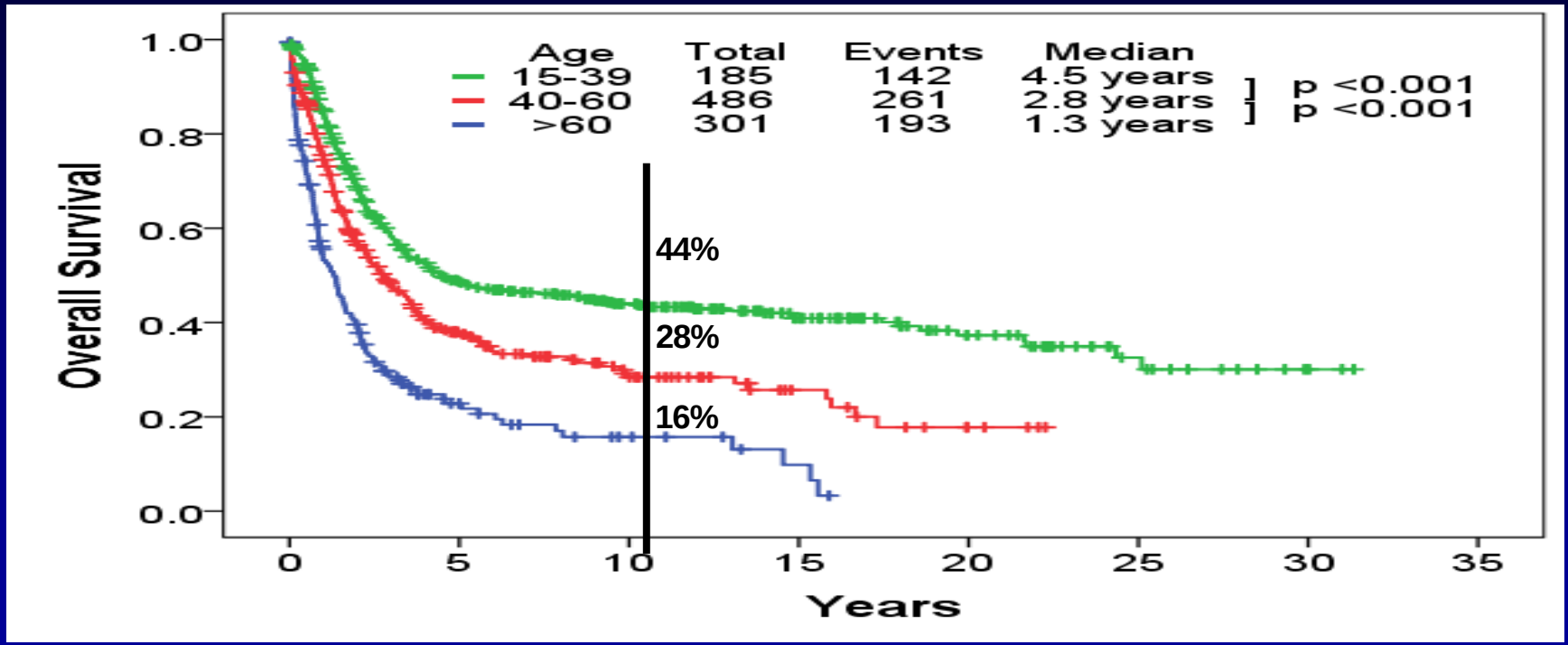
Review of Prognostic Value of MRD in ALL

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX

Summer 2020

Survival of 972 Adults With Ph– ALL

- 972 pts Rx 1980–2016; median F/U 10.4 years



Sasaki. *Blood*. 2016;128:3975.

Minimal (measurable) Residual Disease

- Concept first described 40 years ago
- Main methods are flow cytometric detection of leukemic immunophenotype (LIP), detection of ALL fusion transcripts, and detection of antigen receptor rearrangements commonly to 10^{-4} (1:10000 cells)
- Timing of testing varies widely
- Important interaction with leukemic subtype and genomic alterations
- Role of more-sensitive tests, and with newer treatment approaches less clear

Question 1

When do you assess for MRD?

- Monthly
- At CR
- At 3 months from induction
- At CR and 3 months from induction, and every 3 months thereafter
- I never check for MRD

How to Define the Risk?

➔ Can be defined **BEFORE** treatment

➔ And/or redefined **DURING** treatment

- MRD, which can possibly better define transplant candidates

- Steroid pretreatment

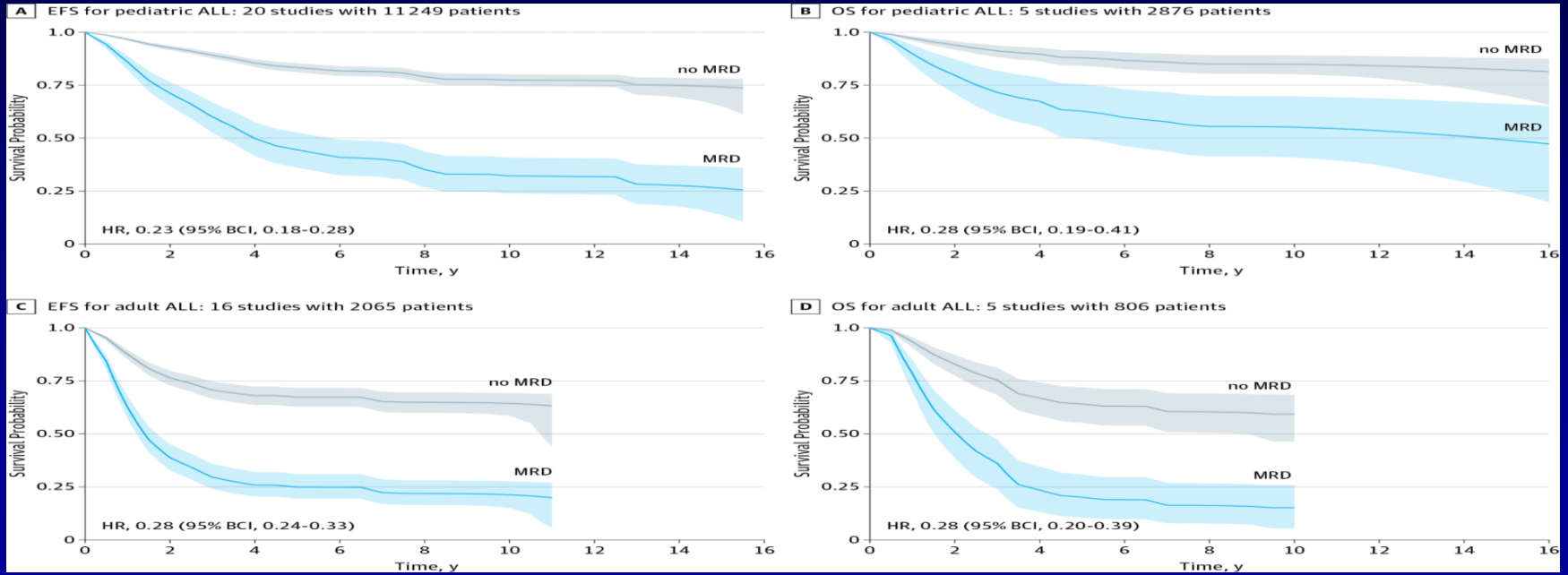
Treatment of ALL Before the MRD Era: High CR Rates but Relapse Is Common

Study	N	Median Age, Year (range)	Ph+, %	T Cell, %	CR, %	DFS, %
MRC/ECOG E2993	1826	31 (15-65)	19	20	91	38 at ≥3 yr
CALGB 19802	163	41 (16-82)	18	–	78	35 at 3 yr
GIMEMA ALL 0288	778	27.5 (12.0-60.0)	22	22	82	29 at 9 yr
GMALL 05/93	1163	35 (15-65)	24	24	83	35-40 at 5 yr
GOELAMS 02	198	33 (15-59)	22	21	86	41 at 6 yr
HyperCVAD	288	40 (15-92)	17	13	92	38 at 5 yr
JALSG-ALL93	263	31 (15-59)	22	21	78	30 at 6 yr
LALA-94	922	33 (15-55)	23	26	84	36 at 5 yr

Adapted from Pui CH, et al. *N Engl J Med.* 2006;354:166-178.

MRD in ALL

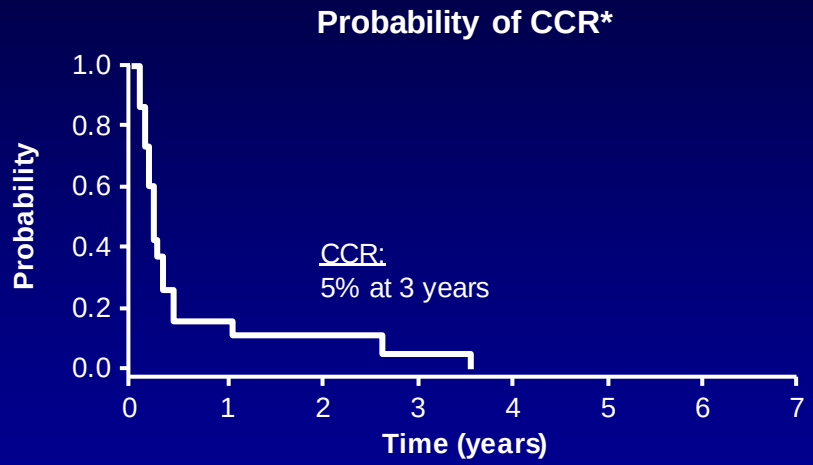
- Meta-analysis of 39 studies (pediatric and adult), including 13,637 patients with all subtypes
- Prognostic impact of MRD clearance consistent across therapies, MRD method, timing, level of cutoff, and subtypes

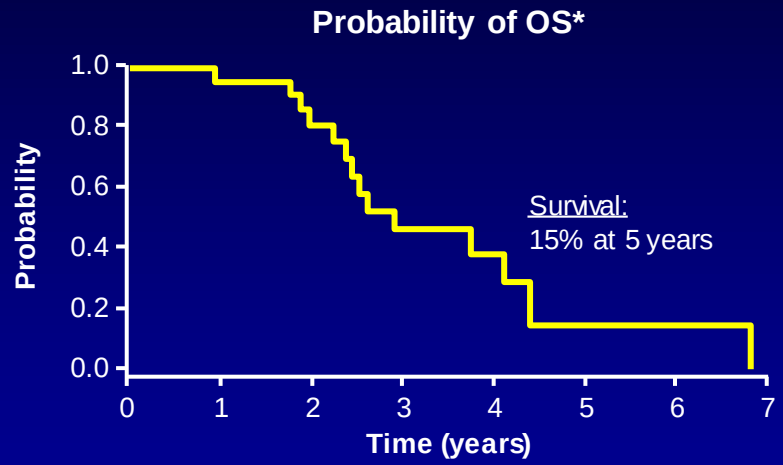


Berry DA. *JAMA Oncol*. 2017;3(7):e170580.

Molecular Relapse (MRD– → MRD+) Is Predictive of Cytologic Relapse in Patients in CR1

Probability of continuous CR and survival in n = 24 adult ALL patients in first CR but with molecular relapse





Conversion from MRD– to MRD+ preceded hematologic relapse by a median 2.6 months and predicted poor survival

*Patients with SCT in CR1 excluded.

Gökbuget N, et al. *Blood.* 2012;120:1868-1876.

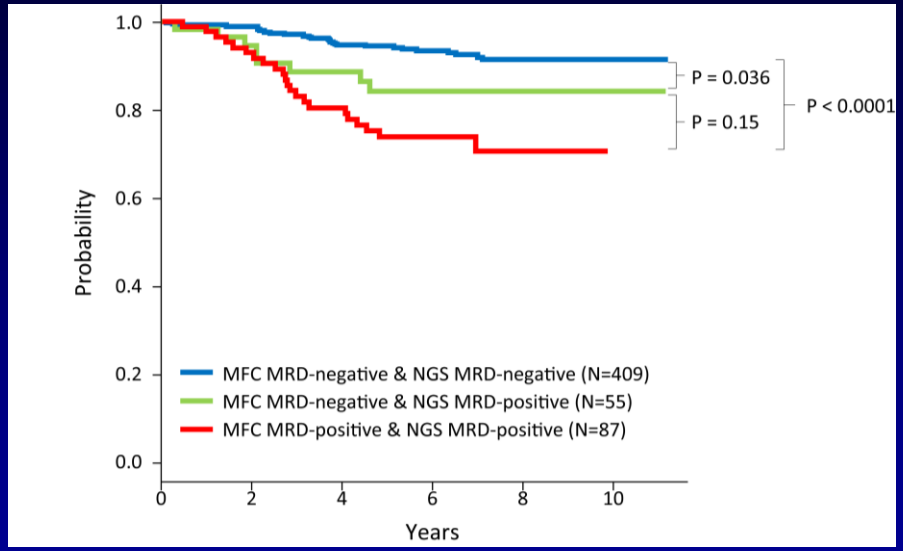
MRD Methods

Method	Sensitivity	Advantages	Disadvantages
Flow cytometry for "difference from normal"	~10^{-4}	• Fast • Relatively inexpensive • Potential to detect phenotypic shifts	• Confounders: increased benign B-cell precursors during marrow recovery; potential phenotypic shifts • Requires significant technical expertise • Limited standardization (though attempts in progress)
RQ-PCR for IGH/TCR gene rearrangements	~10^{-4} to 10^{-5}	• Sensitive • Well standardized with consensus guidelines	• Time consuming and labor intensive • Requires significant technical expertise • May not detect small subclones at diagnosis • Expensive
RQ-PCR for recurrent gene fusions	~10^{-4} to 10^{-5}	• Sensitive • Uses standard primers utilized for diagnostic purposes	• Applicable to <50% of ALL cases • Limited standardization
Next-generation sequencing	~10^{-6}	• Very sensitive • Fast (uses consensus primers) • Potential to track small subclones and clonal evolution	• Requires complex bioinformatics • Minimal clinical validation • Expensive

Short NJ, et al. *Am J Hematol.* 2019;94(2):257-265.

NGS Identified Patients With Improved EFS

Event-free survival
(Sensitivity 10^{-5})



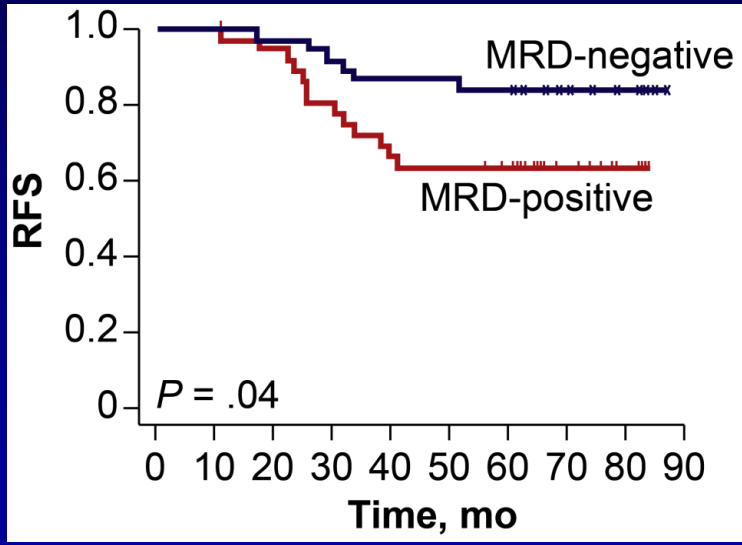
EFS was significantly worse in the NGS MRD+/flow cytometry MRD– group than patients who were MRD– by both methods (*P* = .036).
Six patients were identified as NGS MRD– and MFC MRD+.

NGS, next-generation sequencing; MFC, multiparameter flow cytometry.
Wood B, et al. *Blood.* 2018; 131(12):1350-1359.

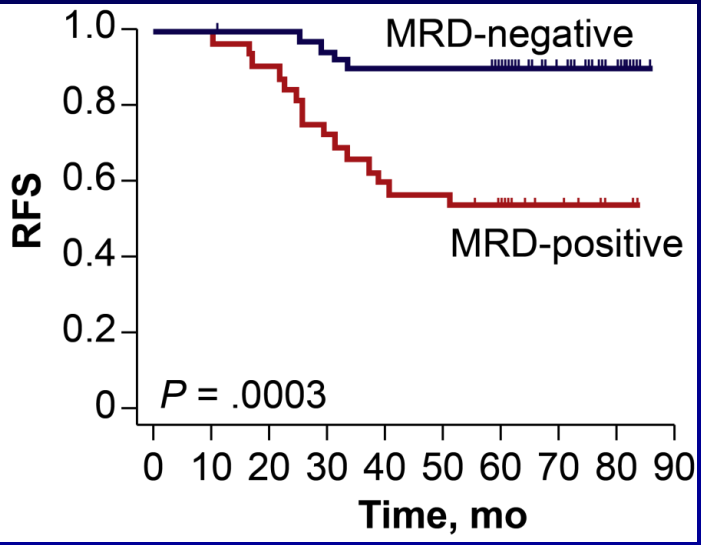
Comparison: NGS With RQ-PCR

- **Prognostic value of d+33 MRD (pediatric ALL, BFM-based treatment)**

Day 33 RQ-PCR
MRD–, n = 37, 5-yr RFS: 84% ± 6%
MRD+, n = 36, 5-yr RFS: 63% ± 8%



Day 33 NGS
MRD–, n = 41, 5-yr RFS: 90% ± 5%
MRD+, n = 32, 5-yr RFS: 53% ± 9%



Kotrova M, et al. *Blood*. 2015;126:1045-1047.

Next-Generation Sequencing vs FMC MRD in ALL

- FDA accepted MRD negativity as Rx endpoint in ALL, regardless of methodology
- Blinatumomab FDA approved (April 2018) for Rx of MRD-positive ALL in CR1-CR2 on the basis of *JAMA Oncology* meta-analysis (Don Berry) and German single-arm trial results
- NGS detects MRD at 10^{-6}; 4- to 8-color FCM detects MRD at 10^{-4}
- In adult ALL, MRD >0.1% at CR and >0.05%–0.01% 2–3 mo in CR predictive of worse survival on chemoRx
- NGS may predict better – ongoing studies at MDACC of outcome at MRD $<10^{-6}$ vs 10^{-6}–10^{-4} vs $>10^{-4}$

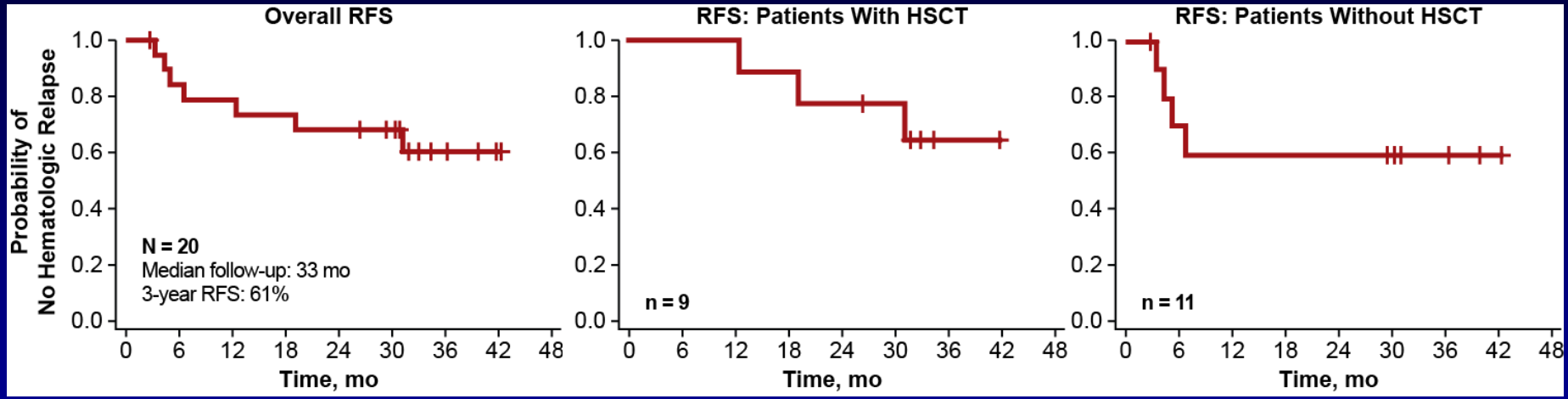
Post-remission Rx of ALL According to FCM-MRD

- 307 pts age 15–60 yr with pre-B ALL
- ORR 91%; 83% after induction 1
- If MRD >0.1% at end of induction (week 5), >0.01% at mid-consolidation (week 17): chemoRx then alloSCT, otherwise chemoRx alone
- ORR 277/307 = 81%; 94 (31%) assigned to alloSCT and 190 (62%) chemoRx

	5-yr CIR, %	5-yr OS, %
Overall	44	48
AlloSCT	37	38
ChemoRx	48	55
MRD <0.1 at CR and <0.01 at consolidation	42	66
MRD <0.01 at CR	17	90

Ribera. *Blood.* 2019;134:abstract 826.

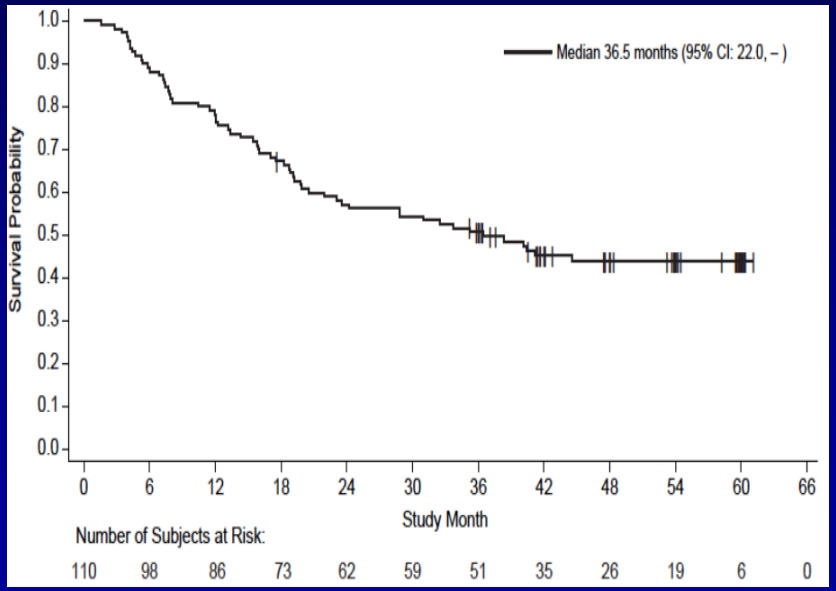
Blinatumomab in MRD+ BCP-ALL: MT103-202 Trial (2/2)

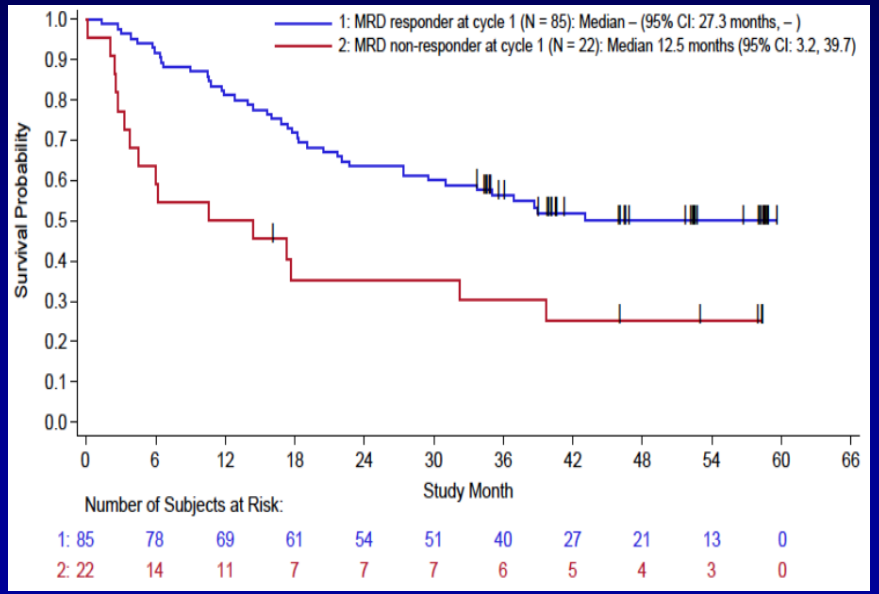


Topp MS, et al. *Blood*. 2012;120:5185-5187.

Blinatumomab for MRD+ ALL in CR1/CR2

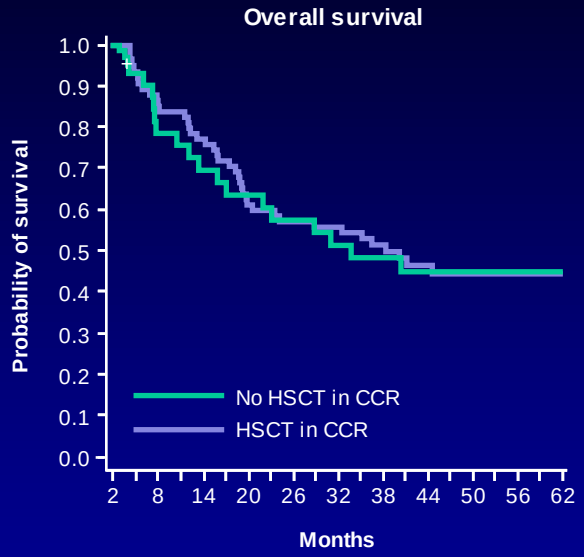
- 113 pts Rx. Post-blina MRD– 88/113 = 78%
- 110 evaluated (blasts <5%, MRD+); 74 received allo-SCT. Median FU 53 mo
- Median OS 36.5 mo; 4-yr OS 45%; 4-yr OS if MRD– 52%
- Continuous CR 30/74 post–allo-SCT (40%); 12/36 without SCT (33%)

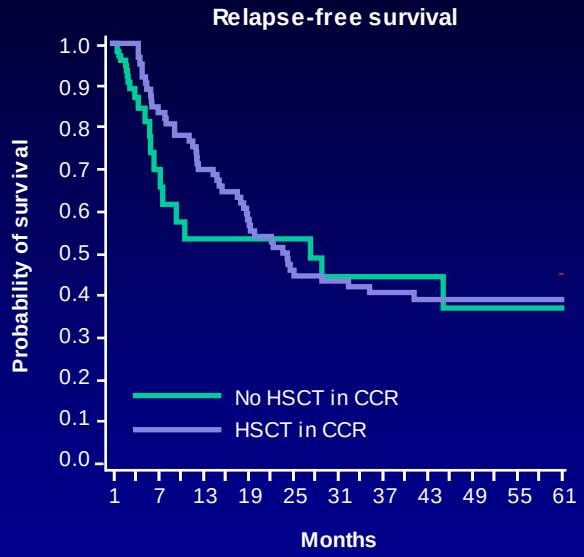


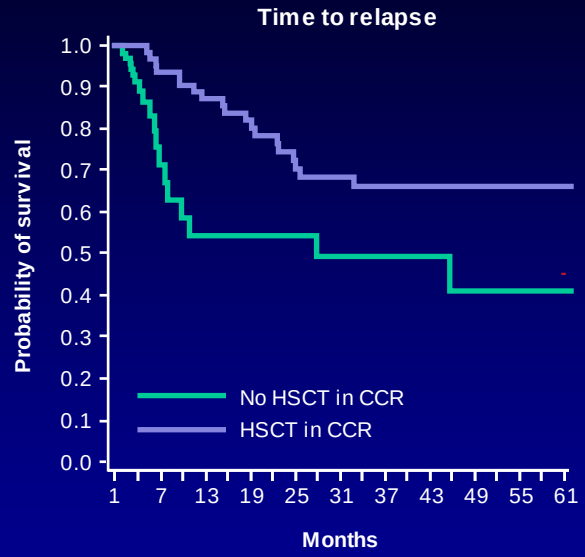


Goekbuget N, et al. *Blood.* 2018;132:abstract 554.

Outcomes by HSCT Use in CCR: Simon-Makuch Analyses – Landmark of 2 Months







Number of patients at risk:

Non-HSCT	94	27	23	21	19	17	14	10	10	9	0
HSCT	15	63	58	45	42	41	31	22	15	7	0

Non-HSCT	103	16	12	12	12	10	8	6	5	5	0
HSCT	2	62	53	42	34	33	25	19	14	7	0

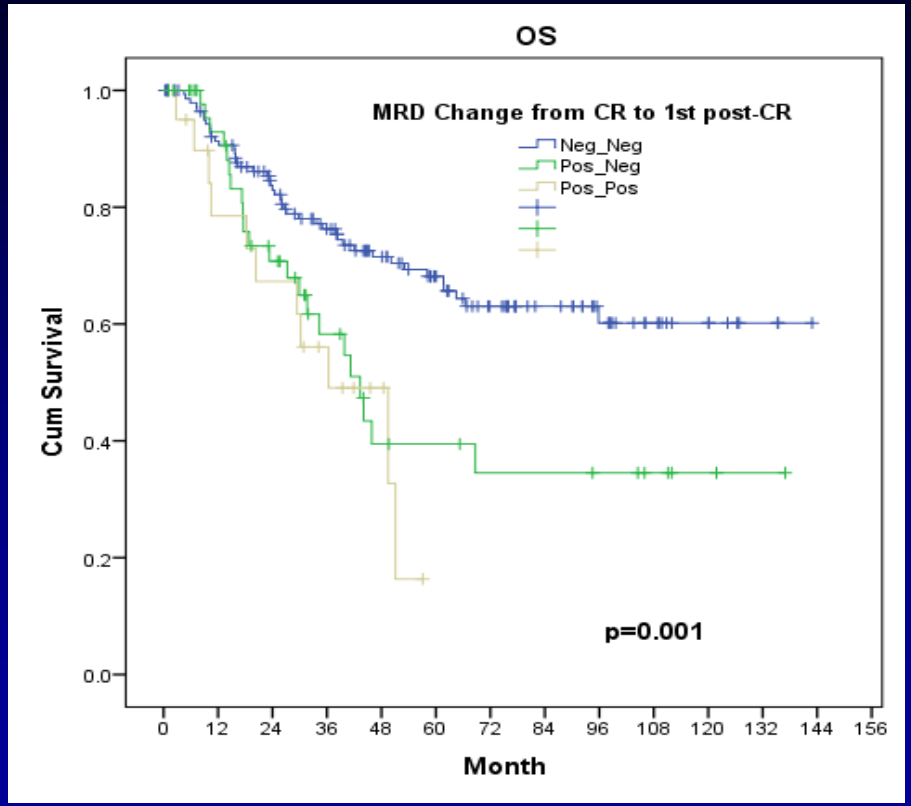
Non-HSCT	101	16	12	12	11	10	8	6	5	5	0
HSCT	2	61	53	42	34	33	25	19	14	7	0

Landmark of 2 months for overall survival and 40 days for other analyses was used to ensure non-zero number of patients in the HSCT group.
CCR, continuous complete remission; HSCT, hematopoietic stem cell transplantation.

Goekbuget N, et al. Slides presented at: 60th ASH Annual Meeting & Exposition of the American Society of Hematology; December 1-4, 2018; San Diego, CA.

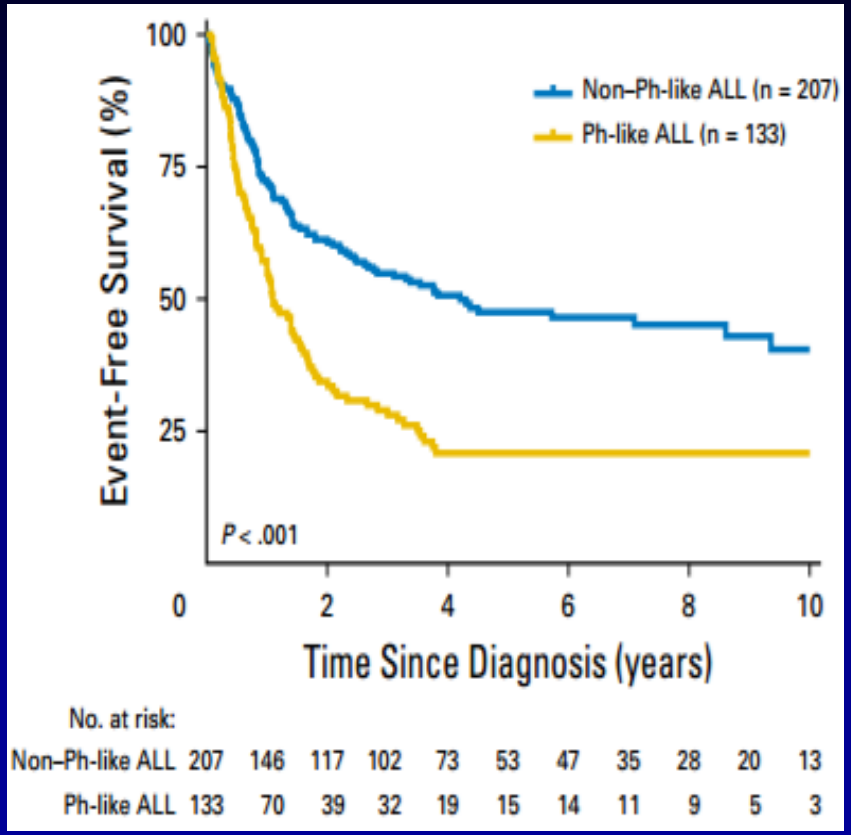
Dynamics of MRD: Outcome

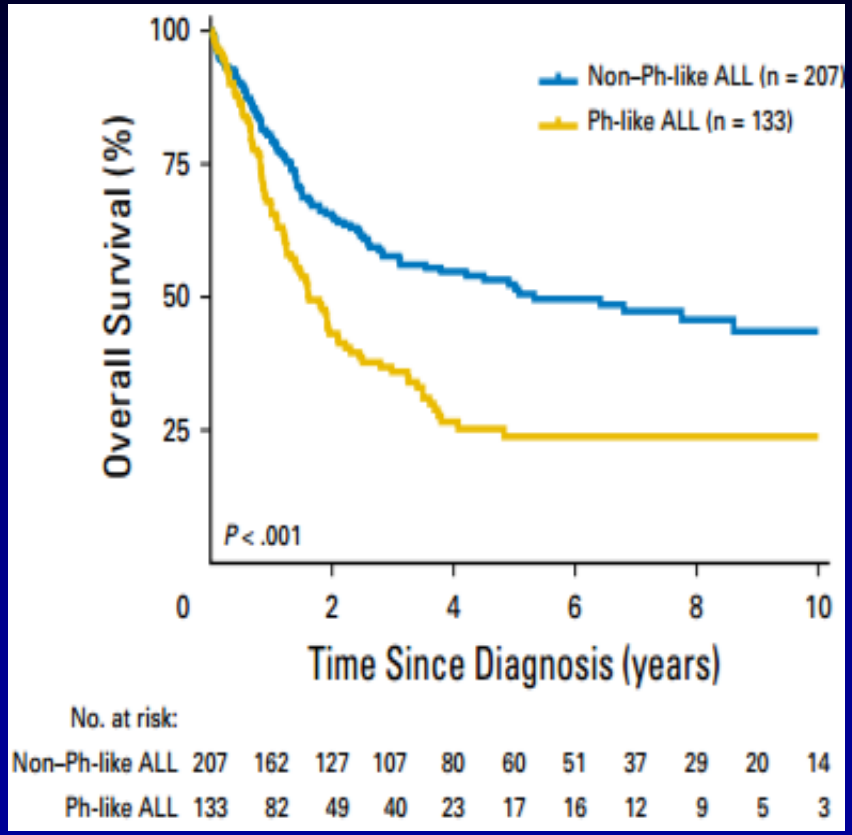
MRD Status		Patients (%) (n = 214)	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA



Yilmaz. *Blood.* 2019;134:abstract 1297.

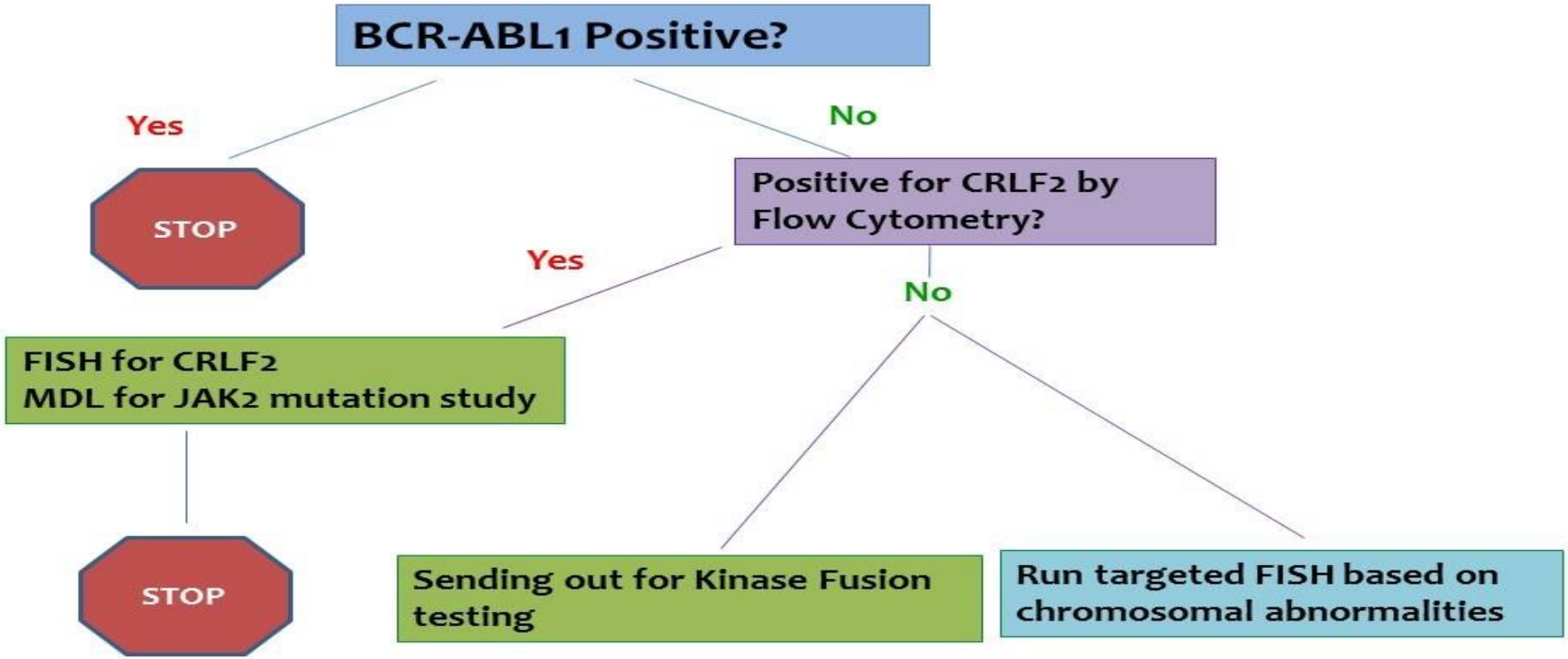
Ph-Like ALL: Survival and EFS





Roberts, et al. *J Clin Oncol.* 2017;35:394.

Ph-Like FISH Testing Algorithm



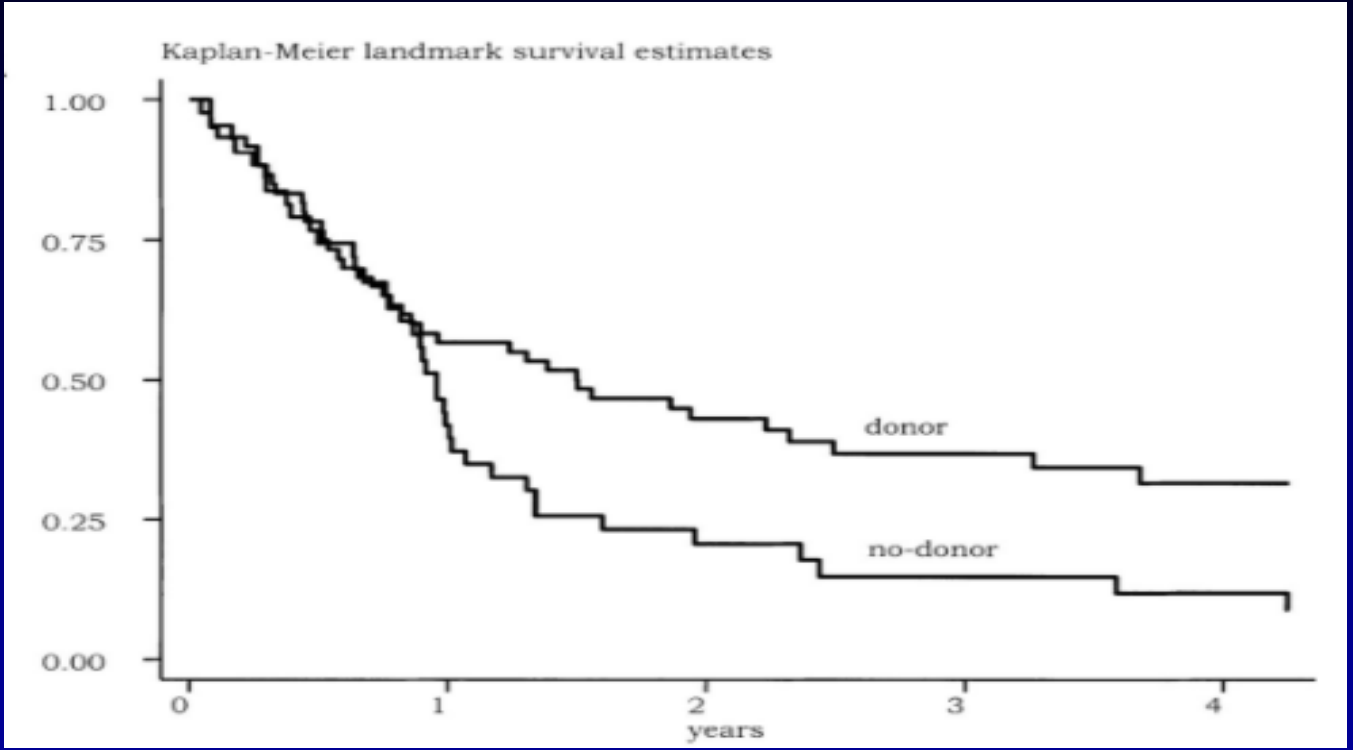
Personal communication from Dr Jabbour.

Ph-Like ALL: Higher MRD+ Rate

	B-ALL Categories (N = 155)			
	Ph-like	Ph+	B – other	*P* value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	.57
MRD at CR				
Positive	23 (70)	15 (44)	4 (13)	<.001
Negative	10 (30)	19 (56)	27(87)	

Jain. *Blood.* 2017;129:572-581.

SCT for Ph+ ALL: Pre-TKI

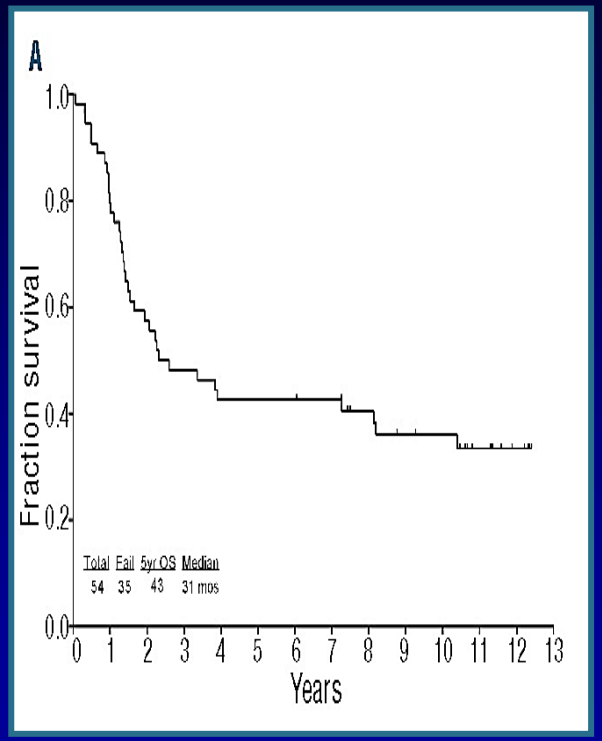


- Donor (n = 60): 3-year OS 37%
- No donor (n = 43): 3-year OS 12%

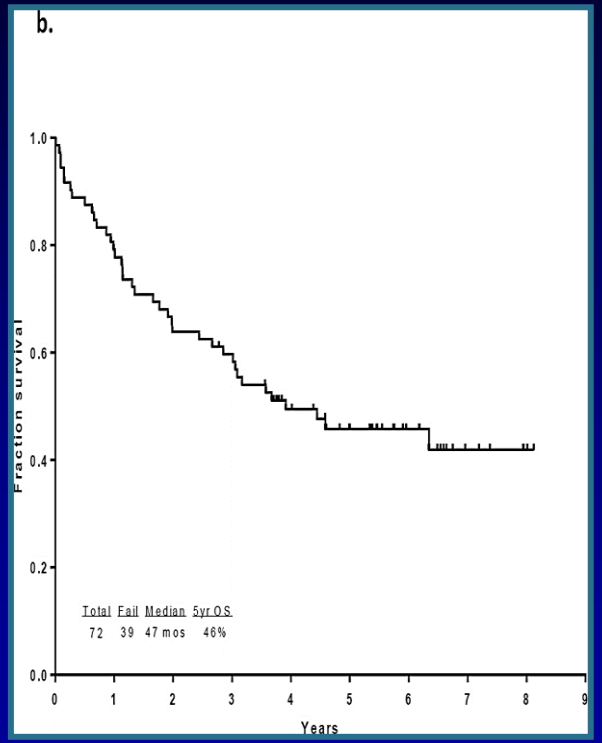
Dombret H, et al. *Blood.* 2002.

TKI for Ph+ ALL

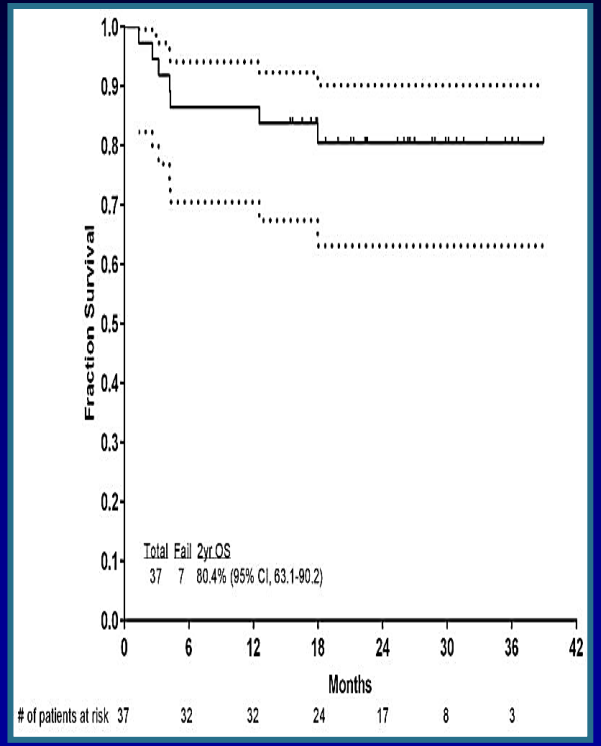
Imatinib: 5-yr OS = 43%



Dasatinib: 5-yr OS = 46%



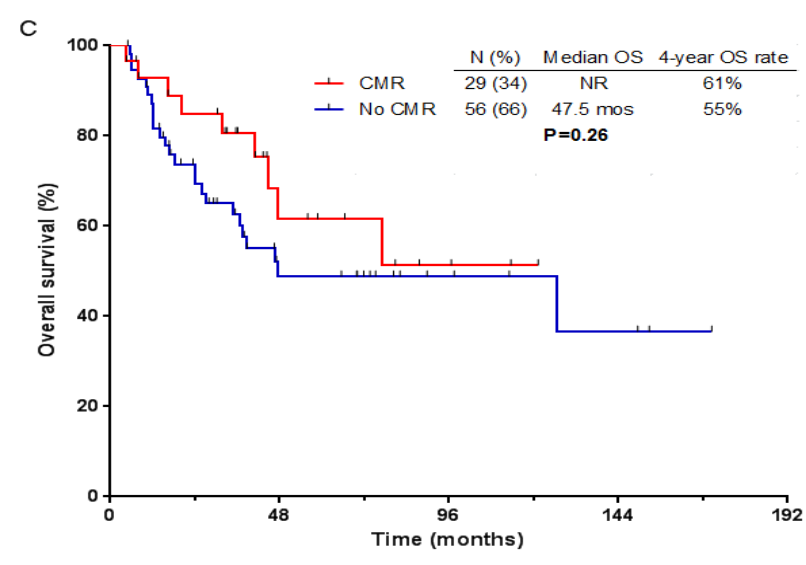
Ponatinib: 5-yr OS = 71%



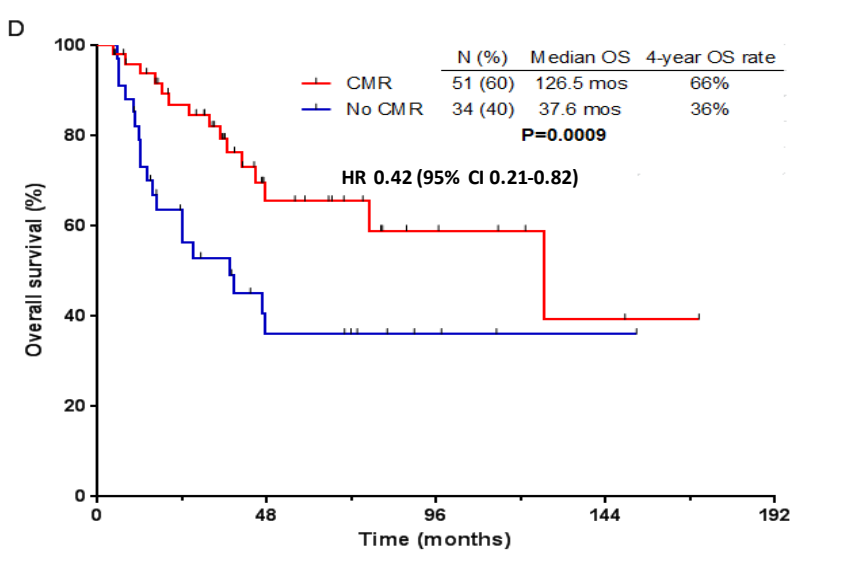
Daver. *Haematologica*. 2015; Ravandi. *Cancer*. 2015; Jabbour. *Lancet Oncol*. 2015; Jabbour. *Lancet Hematol*. 2018.

CMR in Ph+ ALL: OS for CMR vs Others

At CR



At 3 months

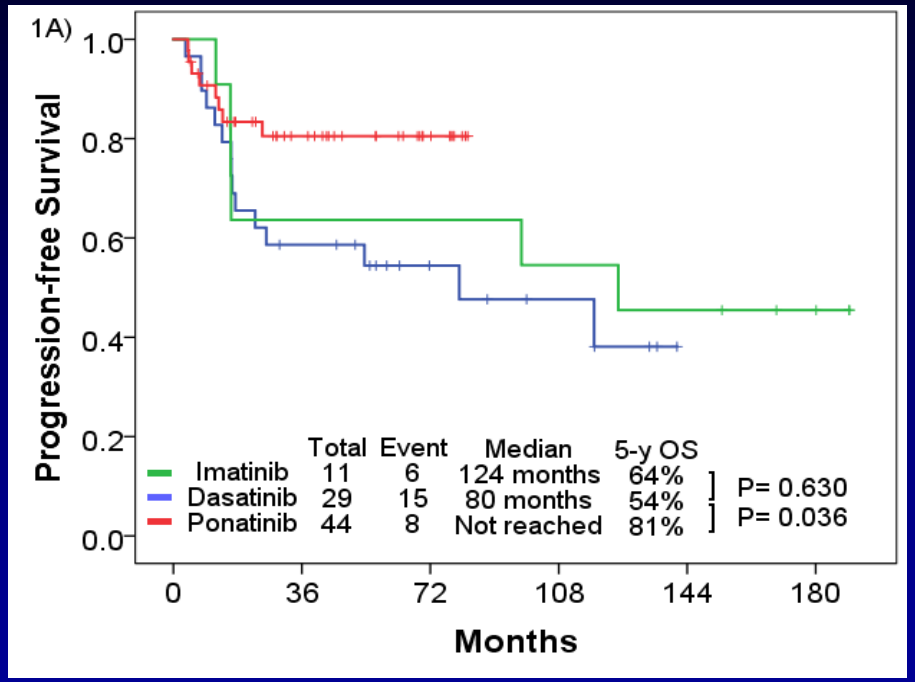


- **MVA for OS**
  CMR at 3 months (HR 0.42 [95% CI: 0.21-0.82]; *P* = .01)

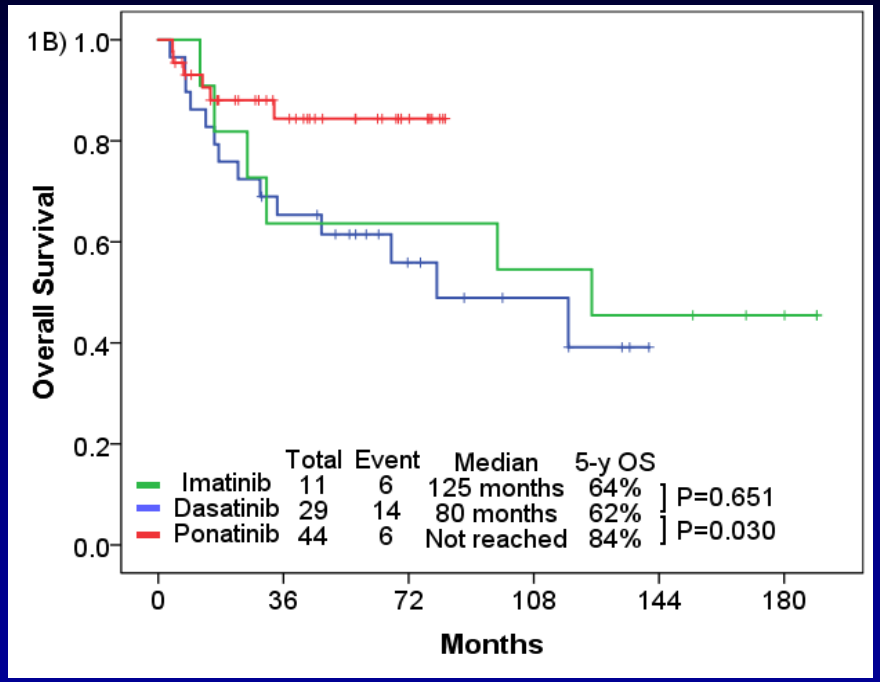
Short. *Blood.* 2016;128(4):504-507.

Outcome of 3-Month CMR by TKI

PFS



OS

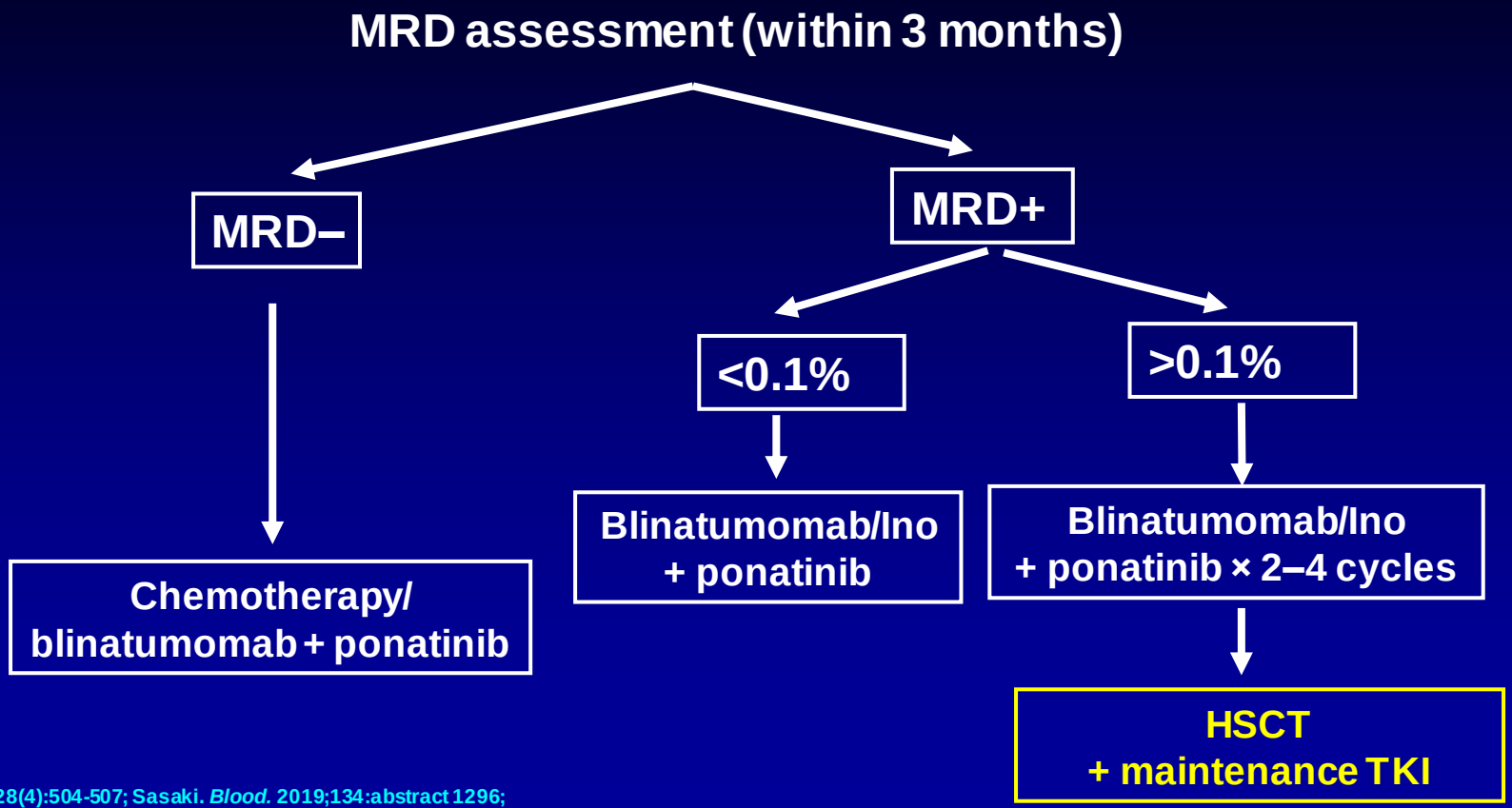


- **MVA for outcome**

Ponatinib only predictive factor for PFS (HR 0.39; *P* =.03) and OS (HR 0.38; *P* = .04)

Sasaki. *Blood.* 2019;134:abstract 1296.

Indications for HSCT: Ph+ ALL



Short. *Blood*. 2016;128(4):504-507; Sasaki. *Blood.* 2019;134:abstract 1296; Samra. *Blood.* 2019;134:abstract 1296.

MRD+ Identifies Candidates for Allogeneic SCT

Effect of allogeneic SCT on 5-year outcome of adult Ph– ALL patients with molecular failure after consolidation (week 16)

Parameter		No Allogeneic SCT		Allogeneic SCT	
	N	n	%	n	%
CCR	120	63	12	57	66 P <.0001
CCR (landmark analysis)*	60	35	17	25	73 P =.0001
DFS	120	63	11	57	44 P <.0001
DFS (landmark analysis)*	60	35	16	25	50 P =.004
OS	120	63	33	57	54 P = .06

Patients with molecular failure who underwent allogeneic SCT had significantly better CCR and DFS than those who did not

*All patients undergoing chemotherapy with CRD < median time to SCT + 1 month were excluded.
DFS, disease-free survival.
Gökbuget N, et al. *Blood.* 2012;120:1868-1876.

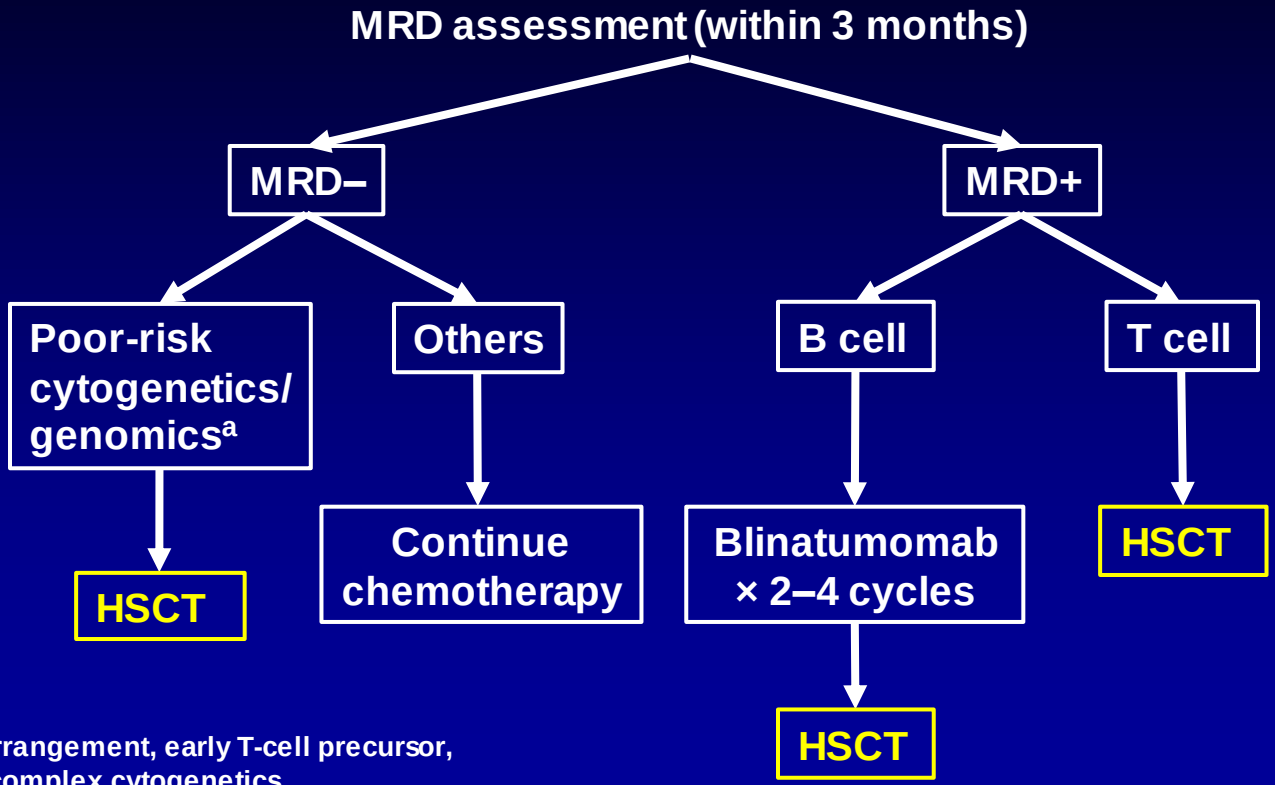
Impact of MRD on Outcome After Allo-SCT: Selected Major Published Trials

Study	Type of SCT	N	Method	Estimate	MRD–	MRD+ (low/high)	P
Knechtli (1998)	Allo	64 (P)	PCR	2-y EFS	73%	36%	<.001
Dombret (2002)	Allo	63 (A)	PCR (BCR-ABL)	3-y IOR	41%	75%	.01
Krejci (2003)	Allo	140 (P)	PCR	5-y EFS	75%	41%/21%	<.001
Spinelli (2007)	Allo	37 (A)	PCR	3-y IOR 3-y OS	0% 80%	46% 49%	.027 NS
Bader (2009)	Allo	91 (				20%/57% 48%/31%	<.001
Patel (2010)	Allo Auto	36 (A) 25 (A)	PCR	5-y EFS	50% 77%	52% 25%	NS .01
Leung (2011)	Allo	64 (P)	Flow	5-y IOR	6%	28%	.03
Sanchez-Garcia (2012)	Allo	102 (P+A)	Flow	5-y LFS 5-y OS	66% 52%	43%/0% 29%/0%	<.001 <.001
Bachanova (2012)	UCB	86 (P+A)	Flow	2-y IOR 3-y LFS	16% 55%	30% 30%	.05 .02
Zhou (2014)	Allo	149	Flow	2-y PFS 2-y OS	47% 55%	28% 40%	.08 .22

Treat MRD Prior to Allo-SCT?

Campana D, Leung W. *Br J Haematol.* 2013;162:147-161.

Indications for HSCT: Ph– B-ALL and T-ALL



[a]Ph-like, 11q23 rearrangement, early T-cell precursor, low hypodiploidy, complex cytogenetics.

Short NJ, et al. *Am J Hematol.* 2019;94(2):257-265.

SO . . . MRD in ALL

- Despite achievement of CR with induction and consolidation, up to 60% of patients with ALL may still be MRD+
- In adult ALL, MRD+ in CR is predictive of worse survival on chemoRx
- FDA accepted MRD negativity as Rx endpoint in ALL, regardless of methodology
- Blinatumomab FDA approved (April 2018) for Rx of MRD+ ALL in CR1–CR2
- No clear benefit for alloSCT after conversion to MRD– with blina, particularly in CR1
- Maintenance blina post-alloSCT?
- Role of Ino? CAR T cells in MRD+ ALL?

Global Leukemia Academy

How and When to Check for MRD in ALL

Josep-Maria Ribera

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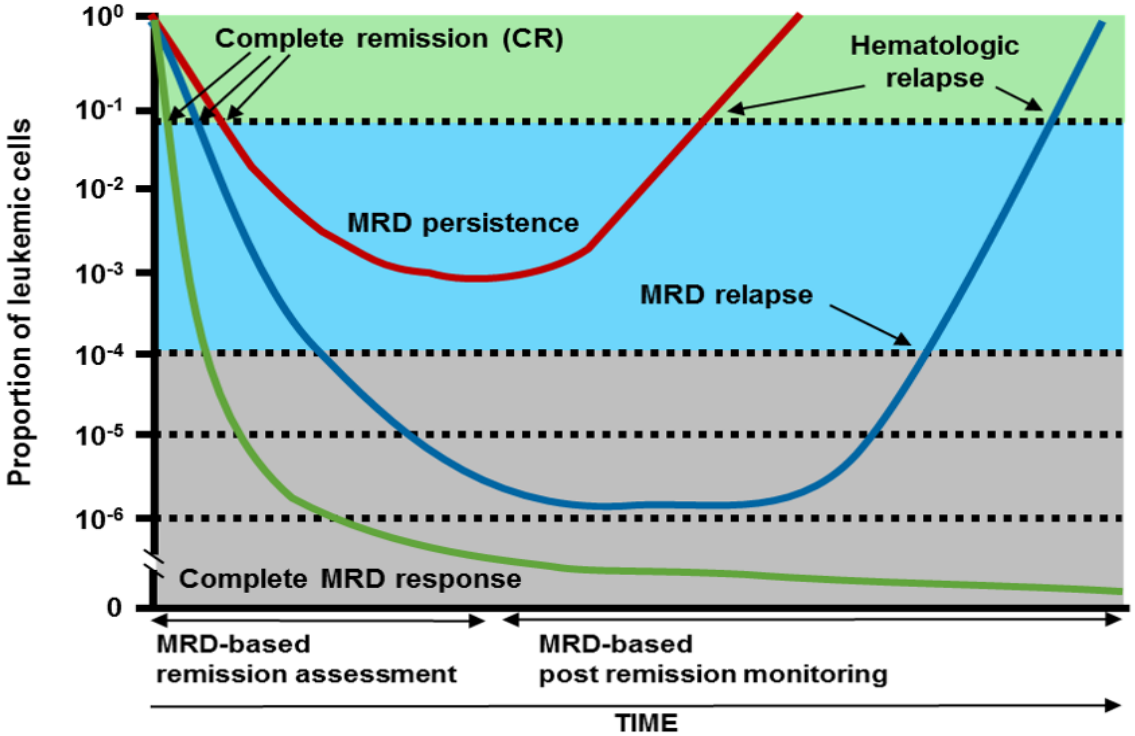
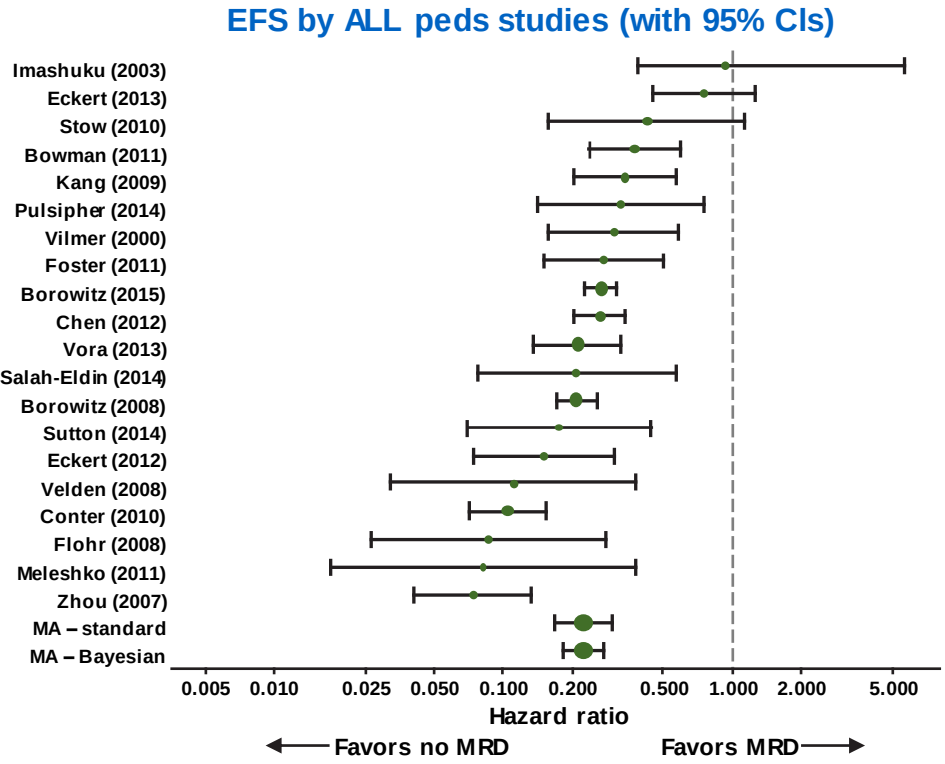
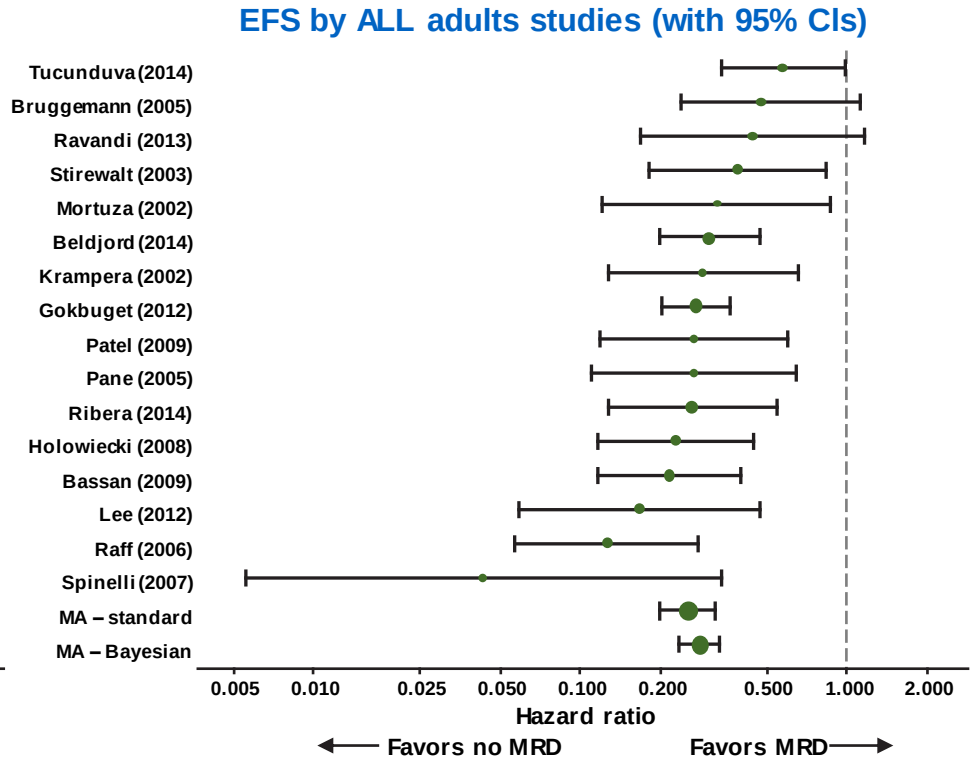
Hypothetical correlation of MRD and risk of relapse*



*Defined as the reappearance of MRD after prior achievement of molecular complete response.
CR, complete remission; MRD, minimal residual disease.
Adapted from Brüggemann M, et al. *Blood.* 2012;120:4470-4481.

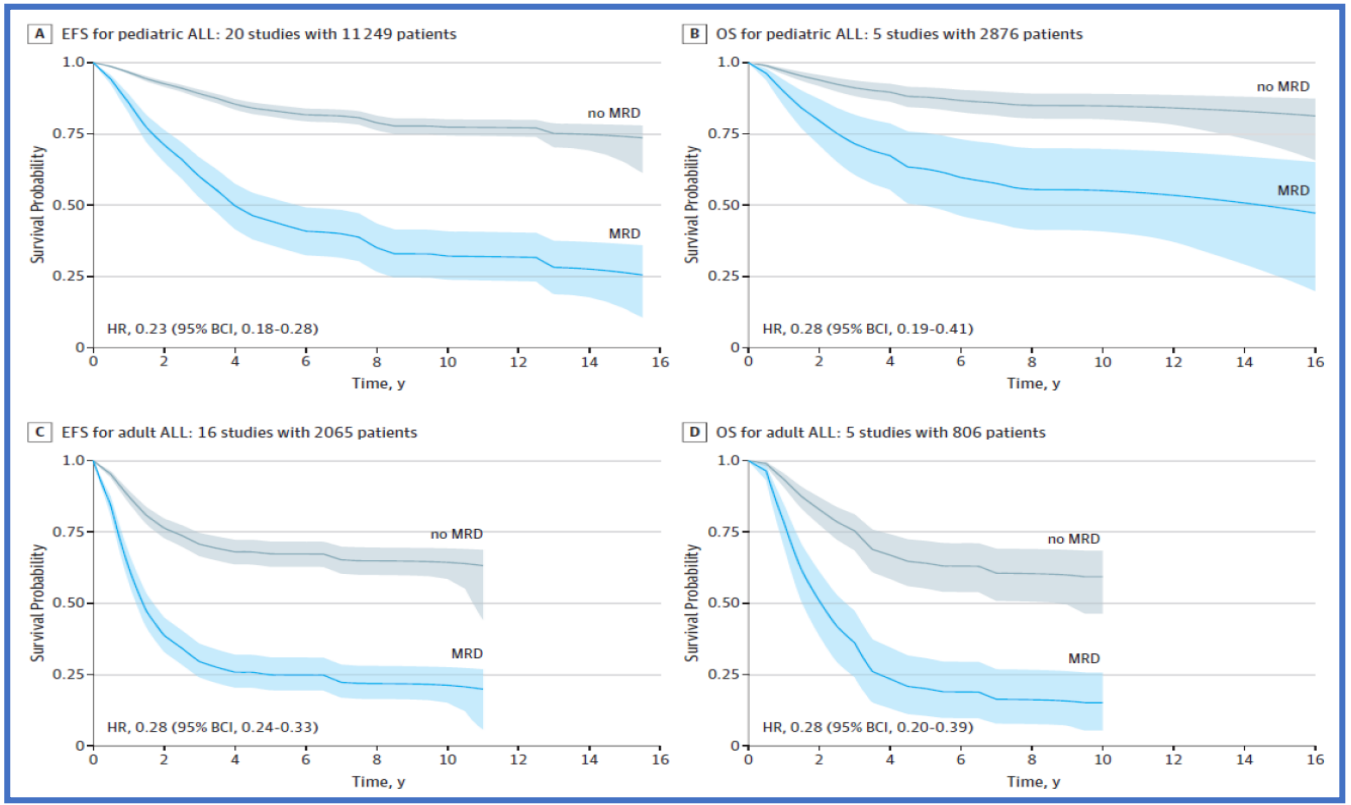
MRD and EFS in pediatric and adult ALL





Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

Negative MRD is associated with longer EFS and OS in childhood and adult ALL

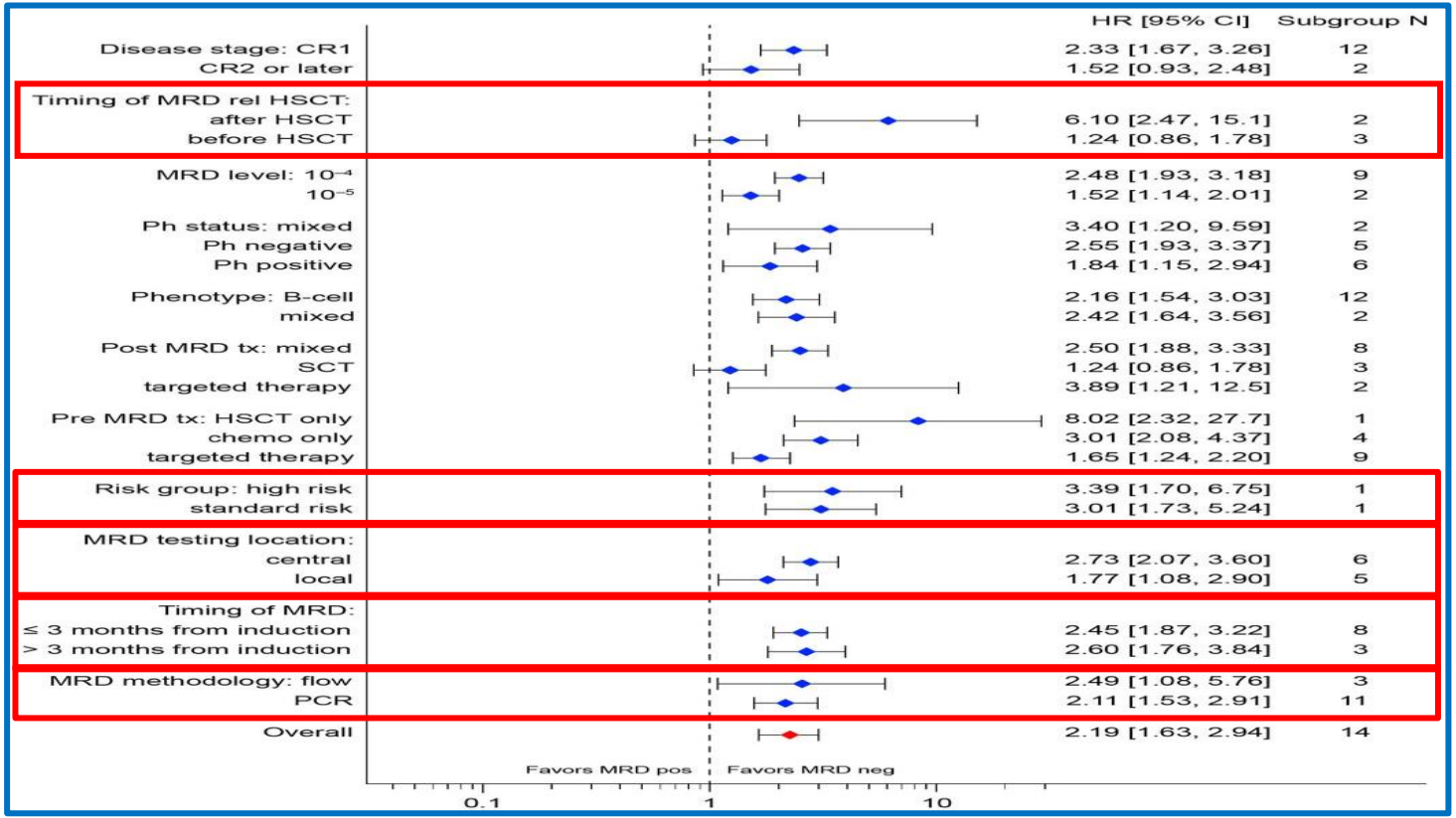


Meta-analysis of 20 pediatric ALL trials >11,000 patients

Meta-analysis of 16 adult ALL trials >2,000 patients

Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

Forest plot of OS hazard ratios by subgroup (random effects model)



Bassan R, et al. *Haematologica*. 2019;104:2028-2039.

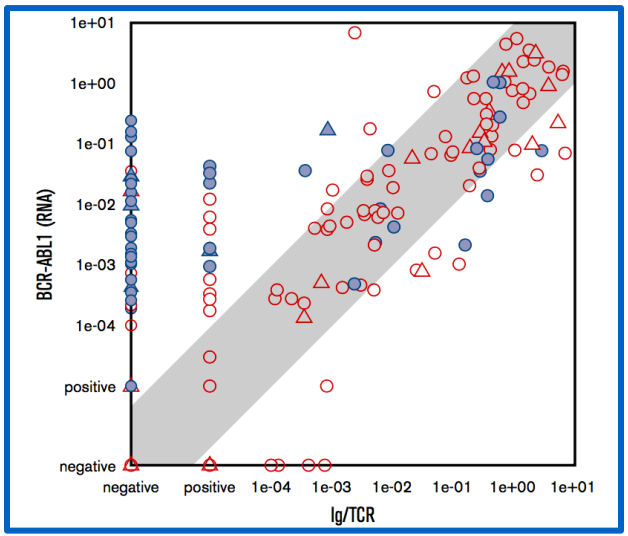
Comparison of MRD detection methods

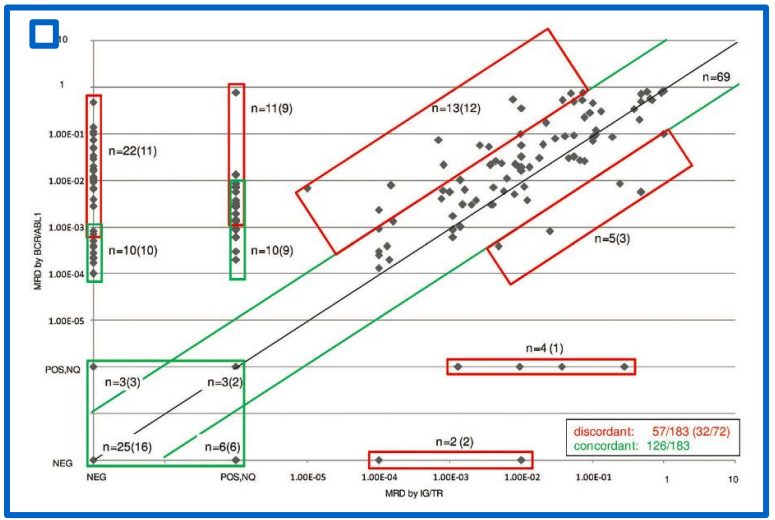
Method	Target	Sensitivity	Considerations	~Percentage of patients evaluated
Flow cytometry[1-4]	Leukemic immunophenotypes	3- to 4-color: 10^{-3} to 10^{-4} 6- to 9-color: 10^{-4}	Rapid Limited sensitivity, but improved Limited standardization	~95% of all patients with ALL[1]
PCR[1-4]	Ig and TCR gene rearrangements	10^{-4} to 10^{-5}	Sensitive Time consuming High degree of standardization Potential instability of targets	~90% of all patients with ALL[1]
PCR[1-4]	Fusion transcripts	10^{-4} to 10^{-6}	Sensitive Stability of target during course of treatment Limited standardization Risk of cross-contamination	~40% of all patients with ALL[1]
NGS[5]	DNA sequence; mutations	10^{-6}	Accurate Not yet widely available Less feasible for common gene mutations due to high costs[5]	~90% of all patients with ALL

ALL, acute lymphoblastic leukemia; Ig, immunoglobulin; MRD, minimal residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; TCR, T-cell receptor.

1. Campana D. *Hematology Am Soc Hematol Educ Program*. 2010;2010:7-12; 2. Brüggemann M, et al. *Blood*. 2012;120:4470-4481; 3. Schrappe M. *Hematology Am Soc Hematol Educ Program*. 2012;2012:137-142; 4. van Dongen JJ, et al. *Blood*. 2015;125:3996-4009; 5. Thol F, et al. *Genes Chromosomes Cancer*. 2012;51:689-695.

Discordance between MRD methods: The case of Ph+ ALL





In patients with discordant MRD results, *BCR*-ABL1 fusion was detected in

- Non-ALL B cells (15% to 83%)
- T cells (12% to 21%)
- Myeloid cells (15% to 80%)

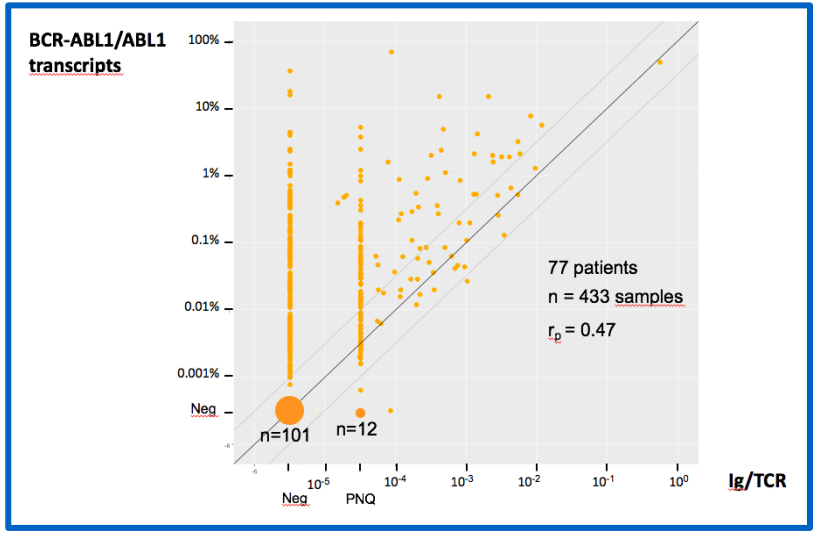
Hovorkova L, et al. *Blood*. 2017;129(20):2771-2781.

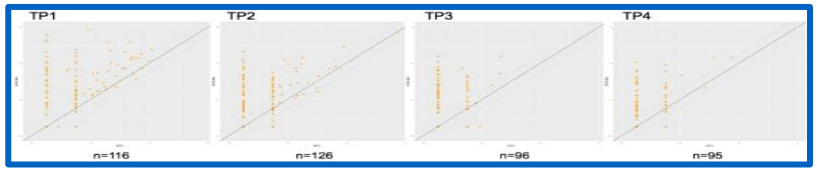
Nagel I, et al. *Blood*. 2017;130(18):2027-2031.

Cazzaniga G, et al. *Haematologica*. 2018;103(1):107-115.

Ig-TCR vs *BCR*-ABL1 MRD in Ph+ ALL

Persistent *BCR*-ABL1 clonal hematopoiesis after blast clearance identifies a CML-like subgroup of Ph+ ALL



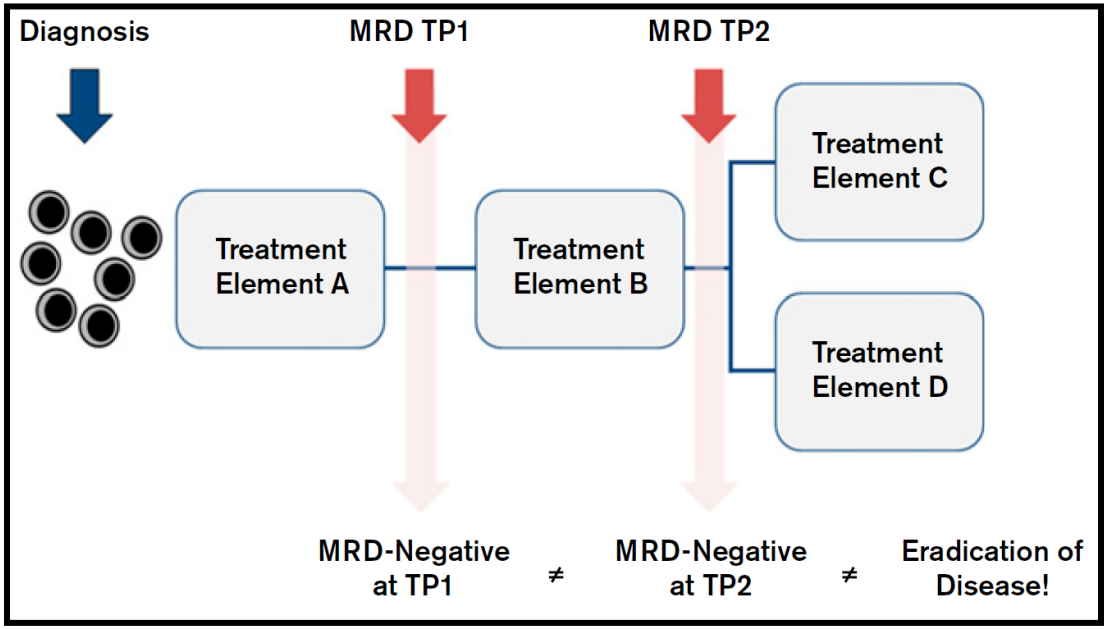


	Dissociated N = 36	Parallel N = 41	*P* value
Median age, years	45	48	.66
Male:female ratio	2.6	1.05	.067
Organ infiltration, %	32	29	.80
Median WBC, G/L	27.1	12.3	.056
Median PMN count, G/L	**4.5**	**1.8**	**.0009**
Median lymphocyte count, G/L	3.1	2.8	.20
Median monocyte count, G/L	**0.4**	**0.1**	**.019**
Median blast count, G/L	8.4	6.9	.5
BM blast, %	**84**	**92**	**.028**
Major BCR, %	**47**	**12**	**.0009**
IKZF1 intragenic deletion, %	**44**	**76**	**.0094**

Clappier E, et al. EHA 2018. S1568.

Courtesy of H Dombret

Importance of time points in MRD assessment



- **Negative** MRD at **TP1:** useful for recognizing patients with **low risk** of relapse
- **Positive** MRD at **TP2:** useful for recognizing patients with **high risk** of relapse

Brüggemann M, Kotrova M. *Blood Adv.* 2017;1:2456-2466.

What is known

✓Adolescents and adults (15–60 yr) with **SR, Ph– ALL**

- **Good MRD response** after induction/consolidation: **no alloHSCT**
- **Poor MRD response**: **alloHSCT better**

✓Adolescents and adults (15–60 yr) with **HR, Ph– ALL**

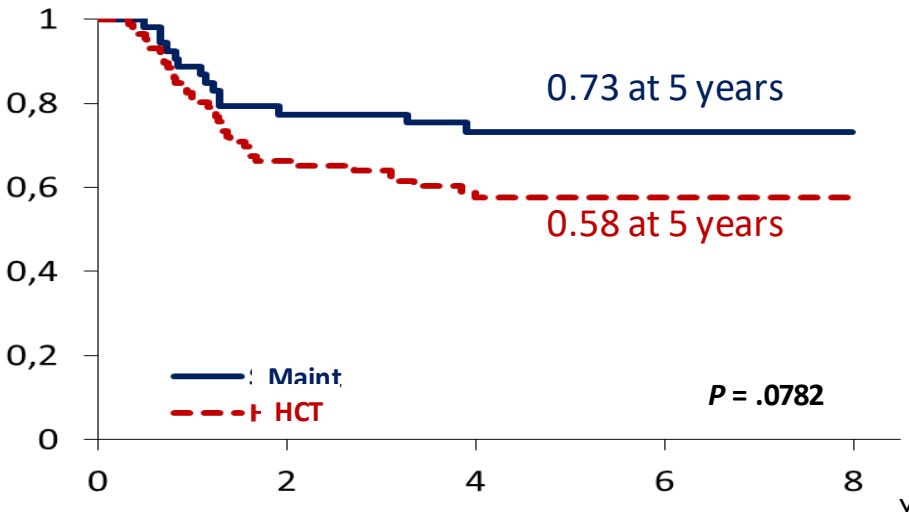
- **Poor MRD response** after induction/consolidation: **alloHSCT better**
- **Good MRD response**: **can we spare alloHSCT?**

Prospective studies with indication for HSCT on the basis of MRD data (adult Ph– ALL)

Trial	Risk groups	MRD assessment	Randomization assignment	References
NILG	SR and HR	PCR	No Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood.* 2009;113:4153-4162
PETHEMA HR03	HR	4-color flow	No AlloHSCT in poor early cytologic responders or MRD+ pts	Ribera JM. *J Clin Oncol.* 2014;32:1595-1604
NILG 10/07	SR and HR	PCR	No Allo(auto)HSCT in MRD+ pts	Bassan R. ASH 2016. #176
PETHEMA HR11	HR	8-color flow	No AlloHSCT in MRD+ pts	Ribera. ASH 2019. #826
GMALL 08/2013	SR and HR	PCR	Yes AlloHSCT vs chemo in MRD– HR pts AlloHSCT in MRD+ pts	Ongoing NCT02881086

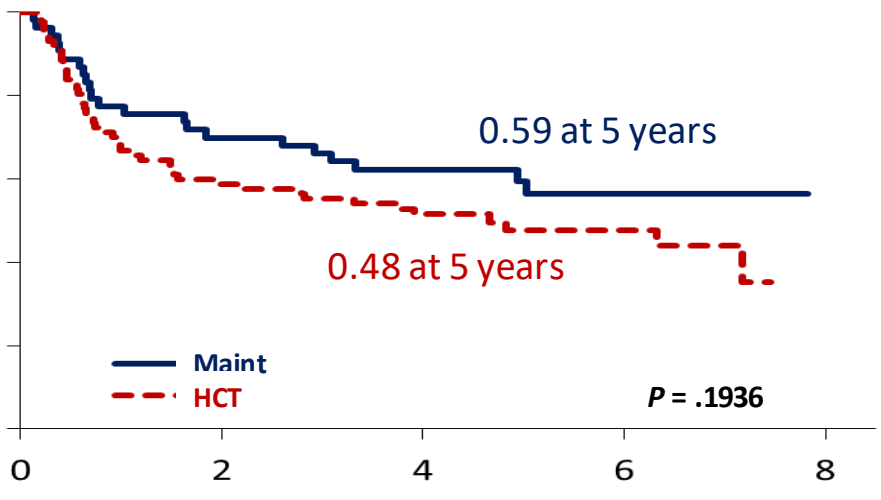
NILG 10/07: SR and HR ALL – Main outcomes by treatment allocation (ITT analysis)

Overall survival



Pts at risk (events)									
Maint	55	(12)	41	(2)	29	(0)	16	(0)	0
HCT	87	(29)	56	(6)	41	(1)	16	(0)	1

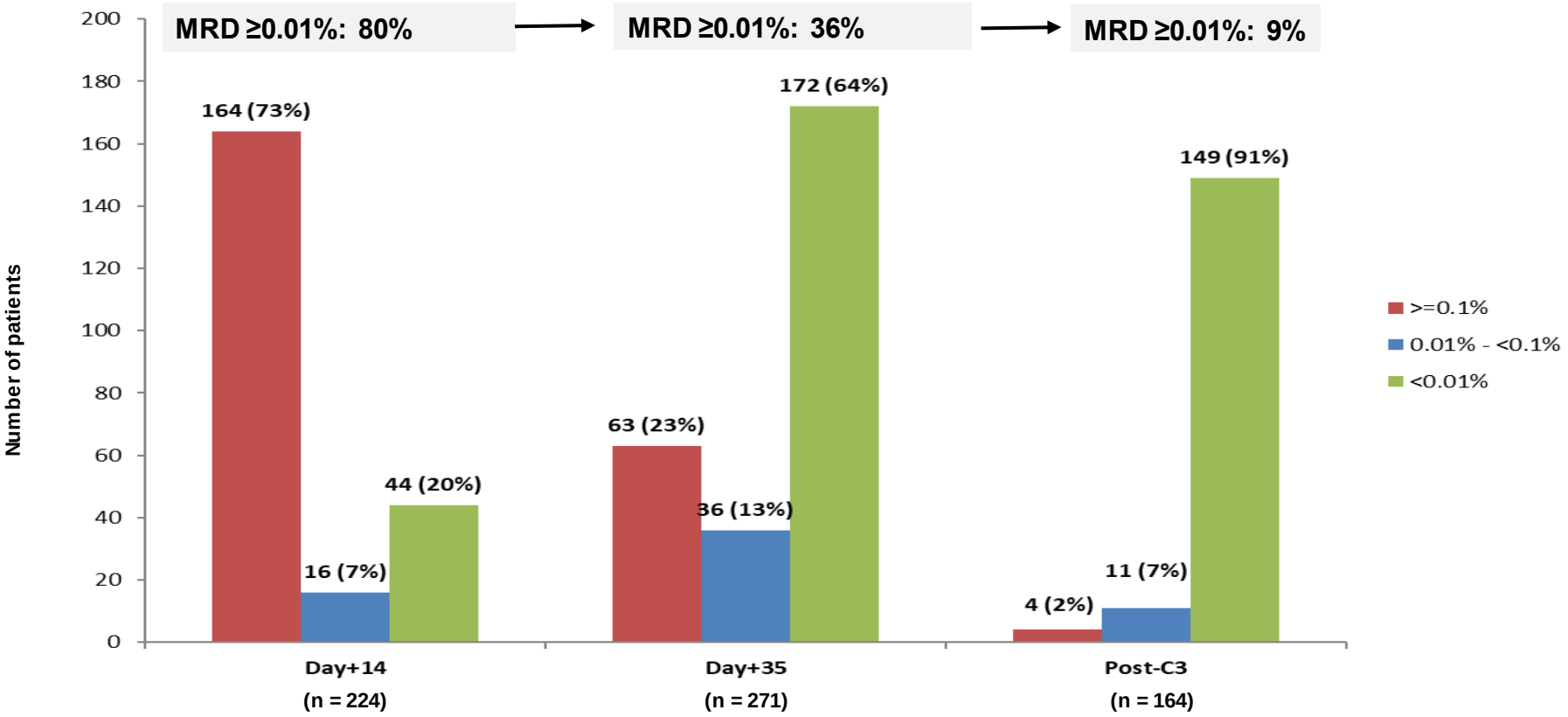
Disease-free survival



	55	(16)	37	(4)	24	(2)	13	(0)	0
	87	(36)	51	(6)	38	(2)	16	(2)	0

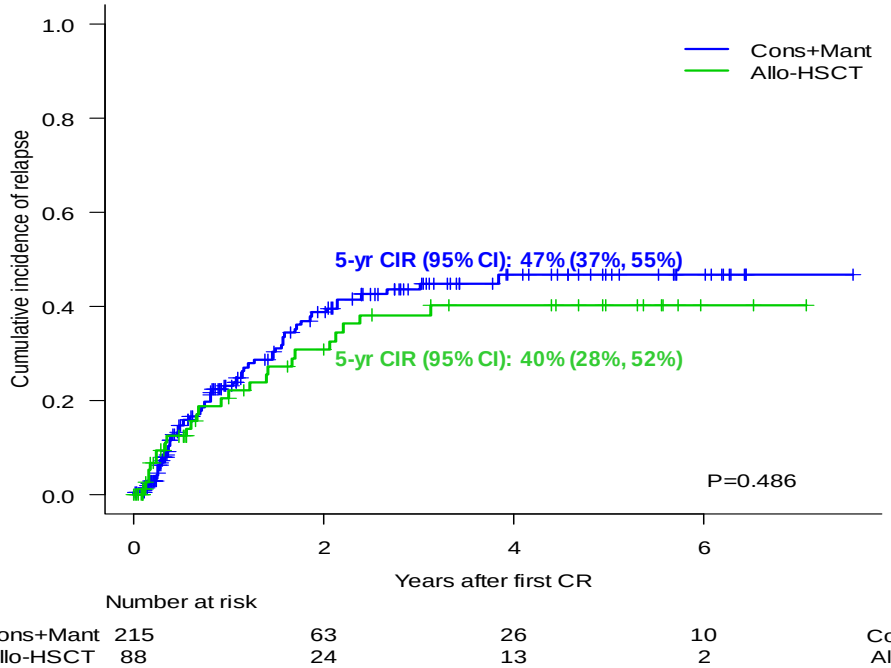
Courtesy of Bassan R. ASH 2016, #176.

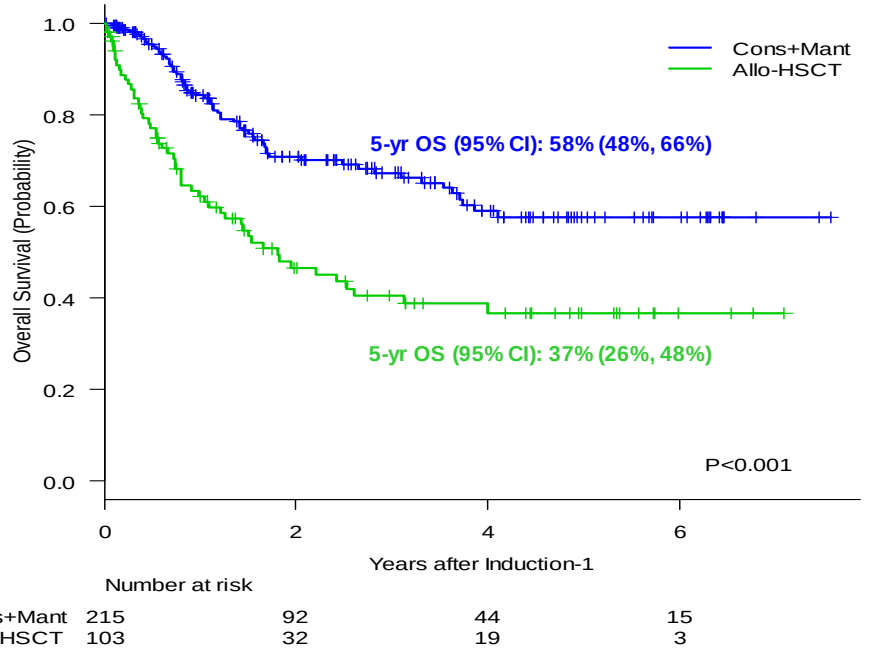
MRD level according to time points: ALL HR11 trial (high-risk patients only)



Ribera JM, et al. ASH 2019. #826 and manuscript submitted.

CIR and OS for HR-ALL patients assigned to chemotherapy vs alloHSCT according to MRD level (analysis by intention to treat)





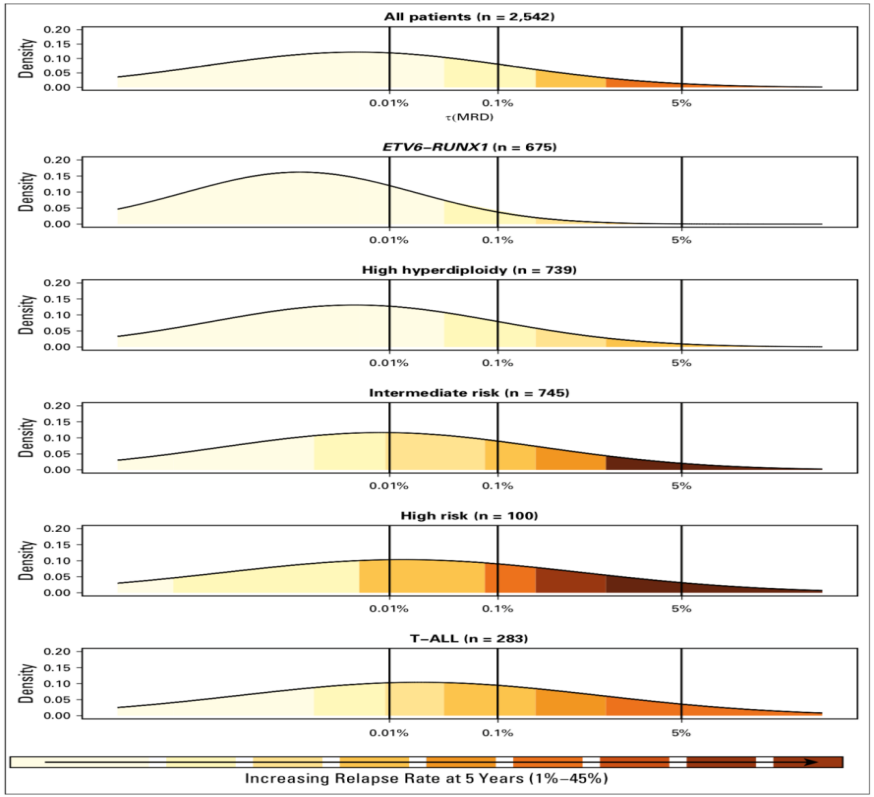
Ribera JM, et al. ASH 2019. #826 and manuscript submitted.

Value of MRD according to genetic subgroups

- **The value of MRD may depend on**
  - Response kinetics
  - Existence of resistant subclones

- Pediatric UKALL2003 study
  - The risk of relapse was proportional to the MRD level within each genetic risk group
  - However, absolute relapse rate that was associa with a specific MRD value varied significantly by genetic subtype

Integration of genetic subtype/subclone-specific MRD could allow a more refined risk-stratification



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

Conclusions: MRD how and when

How

- Each methodology has pros and cons
- Select the methodology with more experience
- Use MRD within specific trials
- Do not exchange the method of MRD assessment within a trial

When

- After induction **and** after consolidation (or before HSCT) are the critical time points

And . . .

- Do not forget the genetic background of ALL in addition to MRD

Question #1

- MRD assessment by fusion transcripts is especially useful in ALL with . . .

a. *IKZF1* mutation
b. *MYC* rearrangements
c. *BCR-ABL1* rearrangement
d. *TEL-AML1* rearrangement
e. None of the above

Question #2

- The MRD level considered for MRD response by consensus is . . .

a. 0.1%
b. 0.01%
c. 0.001%
d. 0.0001%
e. 0.00001%

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PETHEMA Data Management: M. Morgades, O. Garcia

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J. Ribera, E. Genescà

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A. Orfao, J. Ciudad, S. Barrena

Catalan Institute of Oncology, Hematology Department

Global Leukemia Academy

CR1 vs CR2 – Where Is MRD Control More Useful and How to Achieve It?

Elias Jabbour

APTITUDE HEALTH®

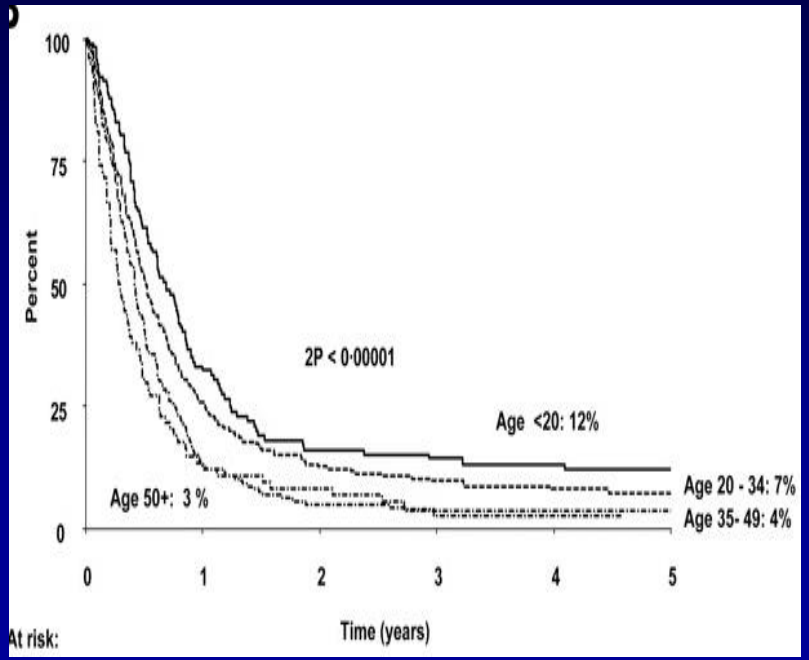
ALL Salvage Standards of Care in 2020

- Refer for investigational therapies: MoAb + chemo Rx; CAR T
- Ph+ ALL: TKIs + chemo Rx; blinatumomab
- Pre-B ALL
  - Blinatumomab (FDA approval 12.2014)
  - Inotuzumab (FDA approval 8.2017)
  - 2 CAR Ts (FDA approvals 8.2017 and 10.2017)
- T-ALL: nelarabine
- Chemo Rx: FLAG-IDA, hyper-CVAD, augmented HCVAD, MOAD

ALL: Historical Survival Rates After First Relapse

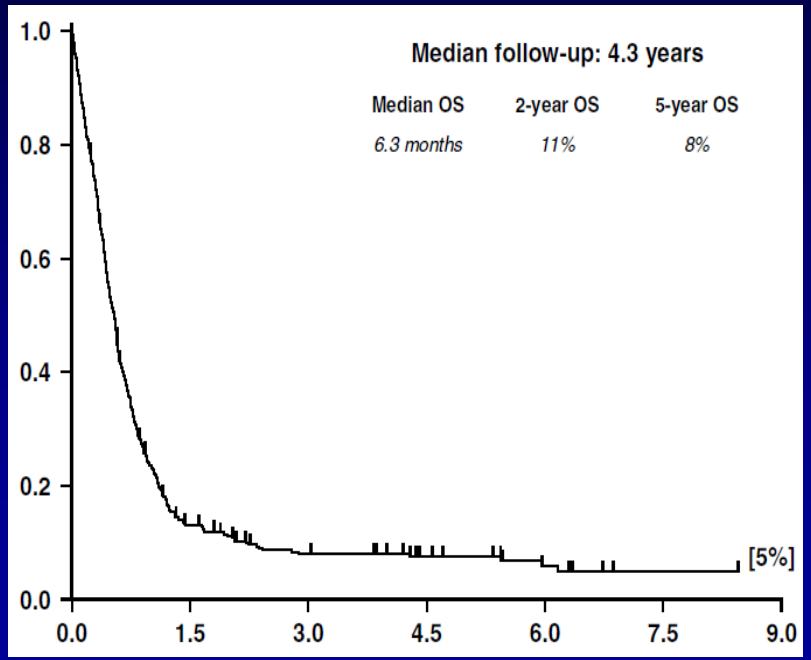
MRC UKALL2/ECOG2993 study (n = 609)

Outcome of patients after <u>first relapse</u>
5-yr OS: 7%



LALA-94 study (n = 421)

Outcome of patients after <u>first relapse</u>
2-yr OS: 11%; 5-yr OS: 8%



Fielding, et al. *Blood.* 2007;109:944-950; Tavernier E, et al. *Leukemia.* 2007;21:1907-1914.

Question 1

When compared with SOC in patients with relapsed/refractory ALL, inotuzumab ozogamicin (select all that apply):

- **Improves response rate**
- **Improves duration of response**
- **Improves MRD-negativity rate**
- **Improves overall survival**
- **I am not aware of the data**

Question 2

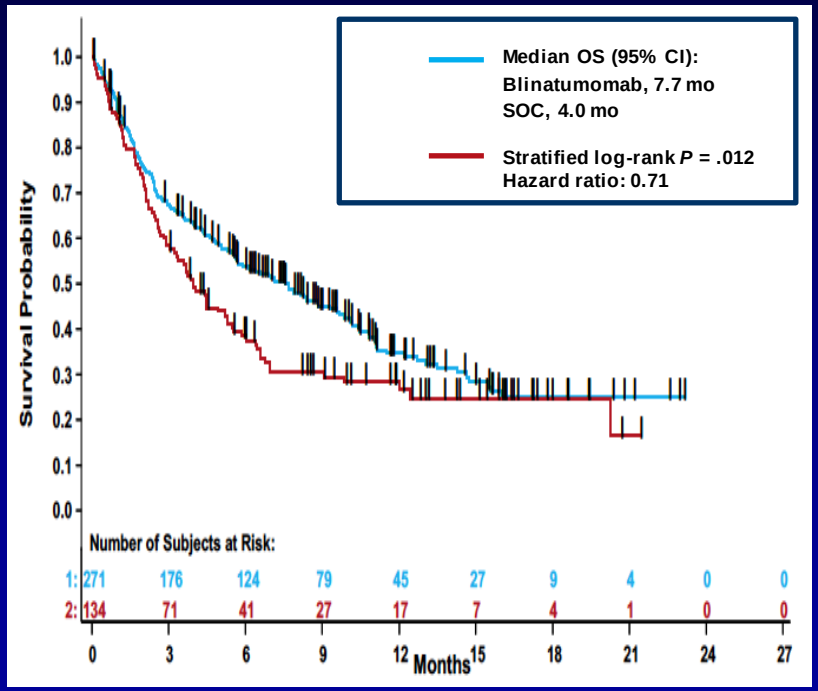
When compared with SOC in patients with relapsed/refractory ALL, blinatumomab improves OS.

- **True**
- **False**
- **I’m not sure**

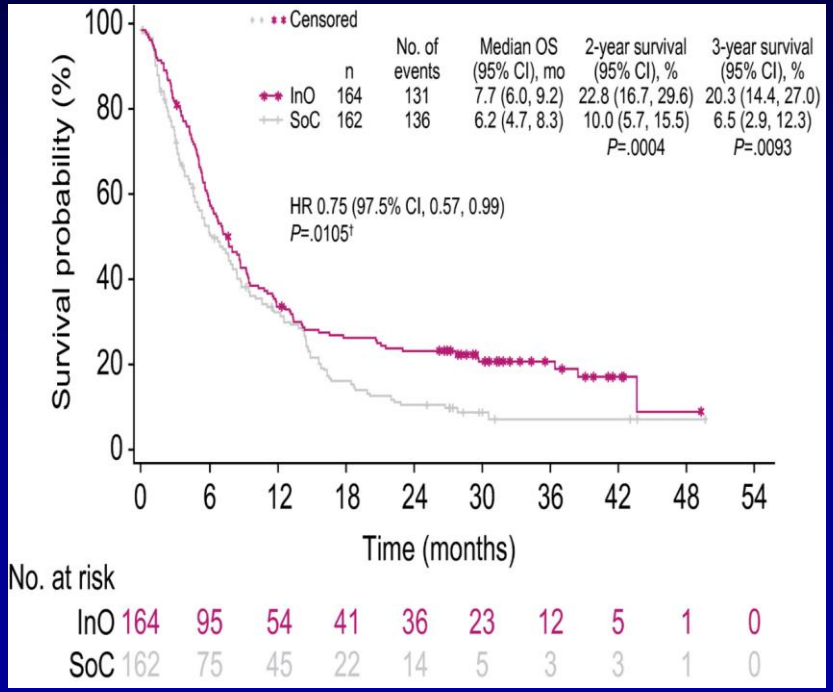
Blinatumomab-Inotuzumab vs Chemo Rx in R-R ALL

- **Marrow CR**

Blina vs SOC: 44% vs 25%



Ino vs SOC: 74% vs 31%



Kantarjian. *N Engl J Med.* 2017;376:836-847.

Kantarjian. *N Engl J Med.* 2016;375:740; *Cancer.* May 2019

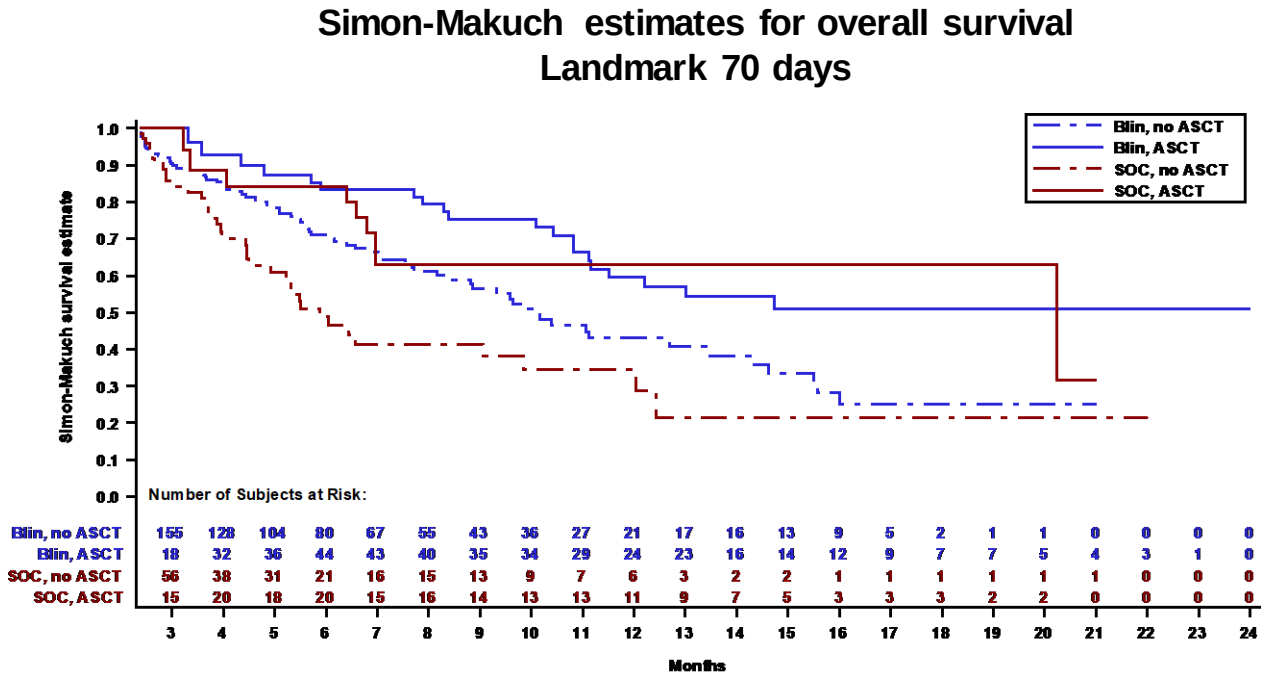
Blinatumomab vs Chemo Rx in R-R ALL (phase III TOWER)

Parameter	Blinatumomab	Chemo Rx	*P* Value
CR, %	34	16	<.001
Marrow CR, %	44	25	<.001
MRD– in CR, %	76	48	--
Median OS, mo	7.7	4.0	.01
Safety profile	CRS/NE+++		

Kantarjian. *N Engl J Med.* 2017;376:836-847.

Overall Survival in Patients Receiving On-Study HSCT: Blinatumomab and SOC

	Blin n = 195	SOC n = 81
n_{HSCT}, $n_{no\ HSCT}$	65, 130	31, 50
HSCT vs No HSCT		
Odds ratio (95% CI)	0.55 (0.33, 0.94)	0.41 (0.19, 0.89)
P value	.026	.020
Median OS (95%CI), Months		
No HSCT	10.1 (8.5, 11.8)	5.9 (4.8, 7.0)
HSCT	NE	20.2 (9.1, 31.3)



- Data suggest outcomes may be better with transplant in both groups

Landmark at day 70 was used to ensure adequate number of HSCT patients at the earlier time points; MRD status is also at day 70.

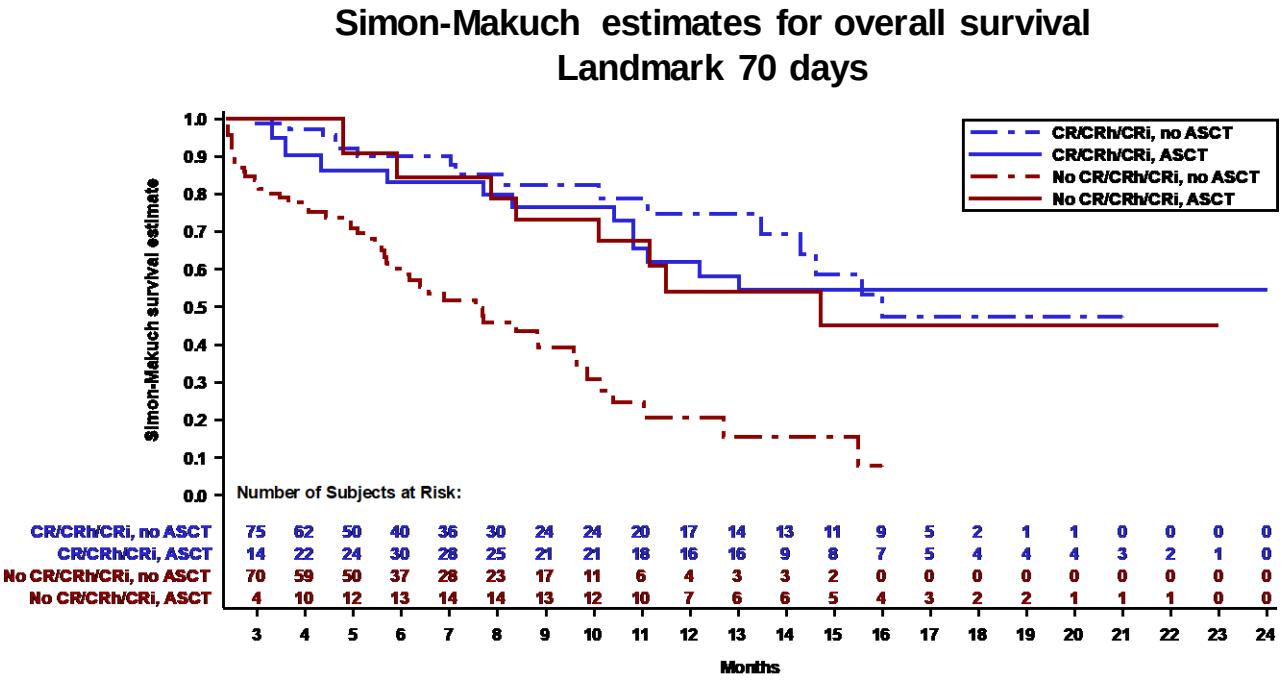
Jabbour E, et al. *Biol Blood Marrow Transplant*. 2018;24:S25-S118.

Overall Survival by CR/CRh/CRi ± HSCT

Blinatumomab arm only

	CR/CRh/Cri[a] n = 91	No CR/CRh/CRi n = 93
n_{HSCT}, $n_{no\ HSCT}$	44, 47	20, 73
HSCT vs No HSCT		
Odds ratio (95% CI)	1.17 (0.54, 2.53)	0.36 (0.16, 0.84)
P value	.69	.014
Median OS (95%CI), Months		
No HSCT	16 (NE, NE)	7.54 (5.5, 9.58)
HSCT	NE (NE, NE)	14.72 (NE, NE)

[a]Last response before landmark day 70.



Landmark at day 70 was used to ensure adequate number of HSCT patients at the earlier time points.

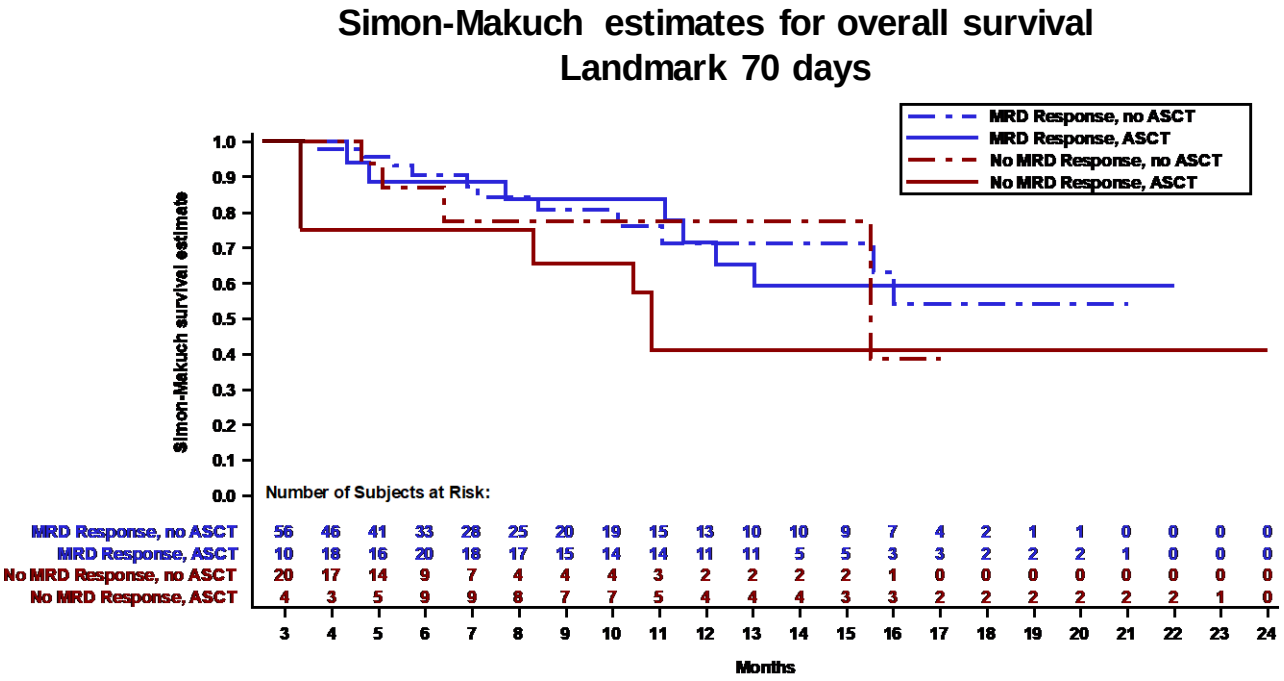
Jabbour E, et al. *Biol Blood Marrow Transplant*. 2018;24:S25-S118.

Overall Survival by MRD Response ± HSCT

Blinatumomab
CR/CRh/CRi only

	MRD Response[a] n = 67	No MRD Response n = 24
n_{HSCT}, $n_{no\ HSCT}$	31, 36	12, 12
HSCT vs No HSCT		
Odds ratio (95% CI)	1.01 (0.38, 2.69)	1.30 (0.30, 5.66)
P value	.99	.72
Median OS (95%CI), Months		
No HSCT	NE	15.51 (8.86, 22.16)
HSCT	NE	10.82 (10.01, 11.63)

[a]Last response before landmark day 70.



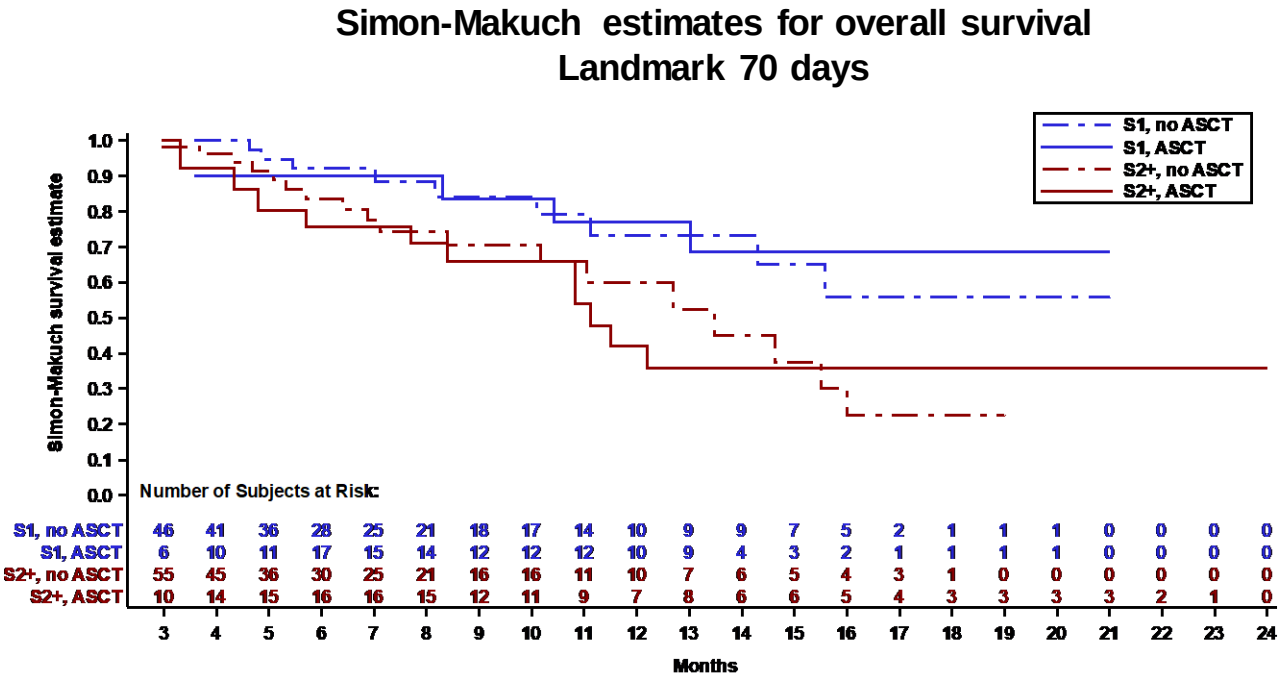
Landmark at day 70 was used to ensure adequate number of HSCT patients at the earlier timepoints. MRD status is also at day 70.

Jabbour E, et al. *Biol Blood Marrow Transplant*. 2018;24:S25-S118.

Overall Survival by Salvage Line ± HSCT

Blinatumomab
CR/CRh/CRi only

	S1 n = 53	S2+ n = 66
n_{HSCT}, $n_{no\ HSCT}$	21, 32	29, 37
HSCT vs No HSCT		
Odds ratio (95% CI)	0.82 (0.24, 2.75)	1.00 (0.47, 2.12)
P value	.74	.99
Median OS (95%CI), Months		
No HSCT	NE	13.48 (11.52, 15.43)
HSCT	NE	11.11 (9.79, 12.44)



Jabbour E, et al. *Biol Blood Marrow Transplant*. 2018;24:S25-S118.

Overall Survival in Blinatumomab Patients by Last Response Prior to HSCT and Salvage Line

Overall Survival Among HSCT Patients	HSCT (n = 65)	HSCT + CR/CRh/CRi[a] (n = 44)	HSCT + MRD Response[a] (n = 28)	HSCT + S1 (n = 30)	HSCT + S1 + MRD Response[a] (n = 12)
Death, n (%)	**20 (31)**	**14 (32)**	**4 (14)**	**6 (20)**	**1 (8)**
Due to disease progression	**11**	**5**	**1**	**3**	**0**
Alive at last follow-up, n (%)	44 (68)	30 (68)	23 (82)	23 (77)	10 (83)
KM survival rates, %					
At 12 months	66	64	85	84	**100**
At 18 months	57	55	77	68	**80**

S1 + MRD Response

- Too few deaths for a meaningful analysis
- Patients treated with blinatumomab following S1 who attain MRD response and receive HSCT are surviving beyond study follow-up

[a]Last response before on-study HSCT; MRD response defined as MRD level below 10^{-4} by PCR or flow cytometry.

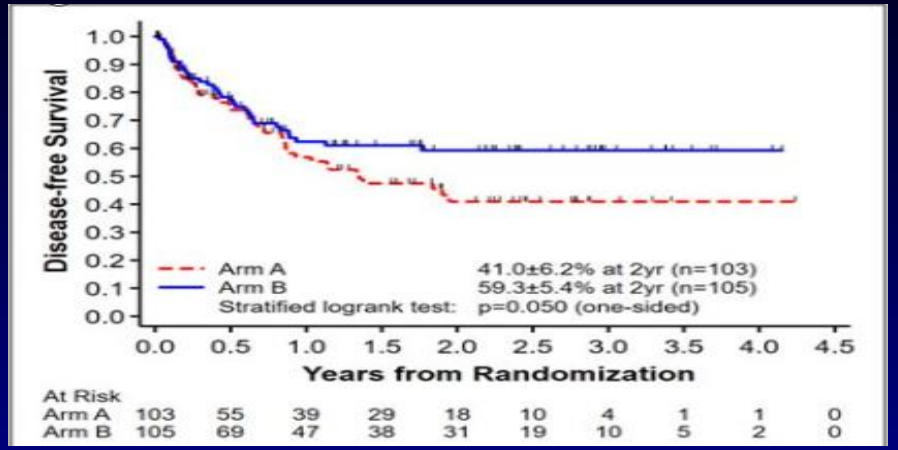
Jabbour E, et al. *Biol Blood Marrow Transplant*. 2018;24:S25-S118.

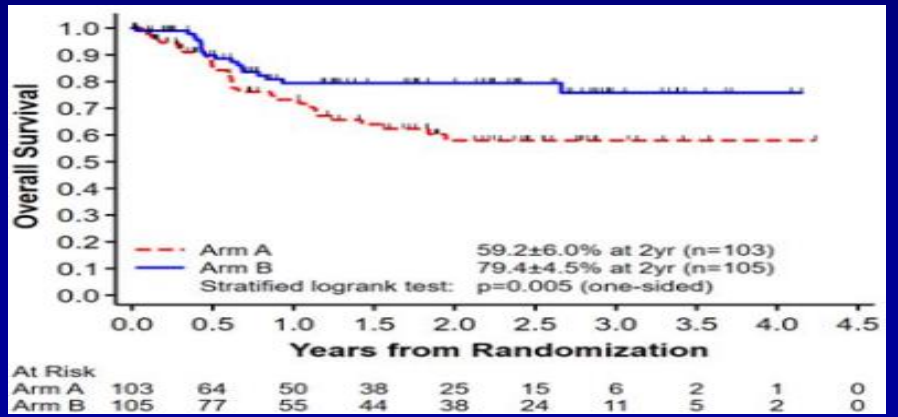
Phase III Study of Blinatumomab vs Chemo Rx in Children – AYA in Salvage 1

- 208 pts randomized 1:1 to blina (n = 105) vs chemo Rx (n = 103)

Parameter	Blina	Chemo	*P*
2-yr DFS, %	59	41	.05
2-yr OS, %	79	59	.005
SCT, %	73	49	<.001
MRD clearance, %	79	21	<.001

- Rates of FUO, infections, sepsis, all significantly lower with blina





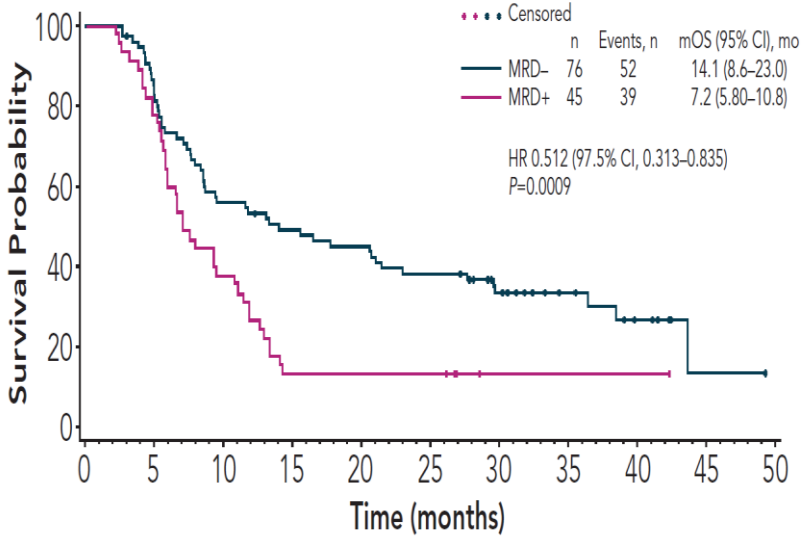
Brown. *Blood.* 2019;134:LBA1.

Inotuzumab vs Chemo Rx in R-R ALL (phase III INOVATE trial)

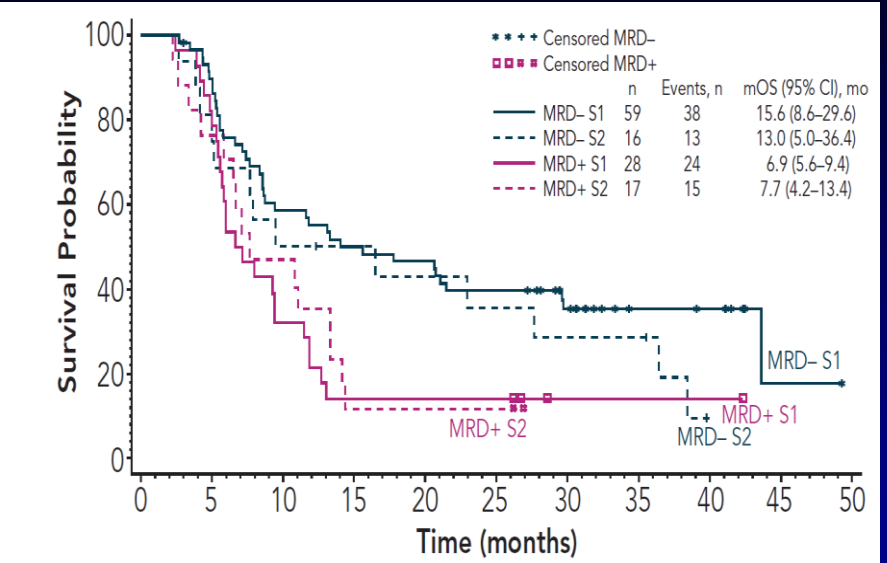
Parameter	Inotuzumab	Chemo Rx	*P* Value
CR/CRi, %	81	29	<.0001
MRD– in CR, %	78	28	<.0001
Median OS, mo	7.7	6.2	.01
Safety profile	VOD +++		

Kantarjian. *N Engl J Med.* 2016;375:740.

Impact of MRD in R-R ALL Rx With Ino



CI=confidence interval; HR=hazard ratio; InO=inotuzumab ozogamicin; mOS=median overall survival; MRD=minimal residual disease



CI=confidence interval; Ino=inotuzumab ozogamicin; MRD=minimal residual disease; S1=first salvage status; S2=second salvage status

Jabbour E. *Leukemia Res.* 2019.

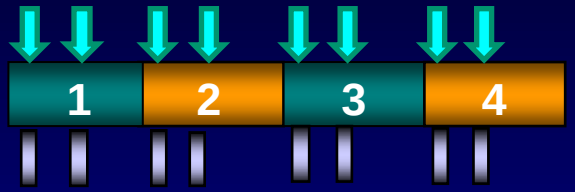
Mini-HCVD–Ino–Blina in ALL: Design

- Dose-reduced hyper-CVD for 4–8 courses
  - Cyclophosphamide (150 mg/m^2 × 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 × 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1 and 8) and 0.6 mg/m^2 C2–4 (0.3 and 0.3 on D1 and 8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Jabbour. *Cancer.* 2018 Oct 11.

Mini-HCVD + Ino ± Blinatumomab in R-R ALL: Modified Design

Intensive phase



Mini-HCVD

Mini-MTX–cytarabine

IT MTX, ara-C

Blinatumomab

POMP

Consolidation phase

Ino	Total Dose (mg/m²)	Dose per Day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2–4	0.6	0.3 D1 and D8

Total ino dose = 2.7 mg/m²

Maintenance phase

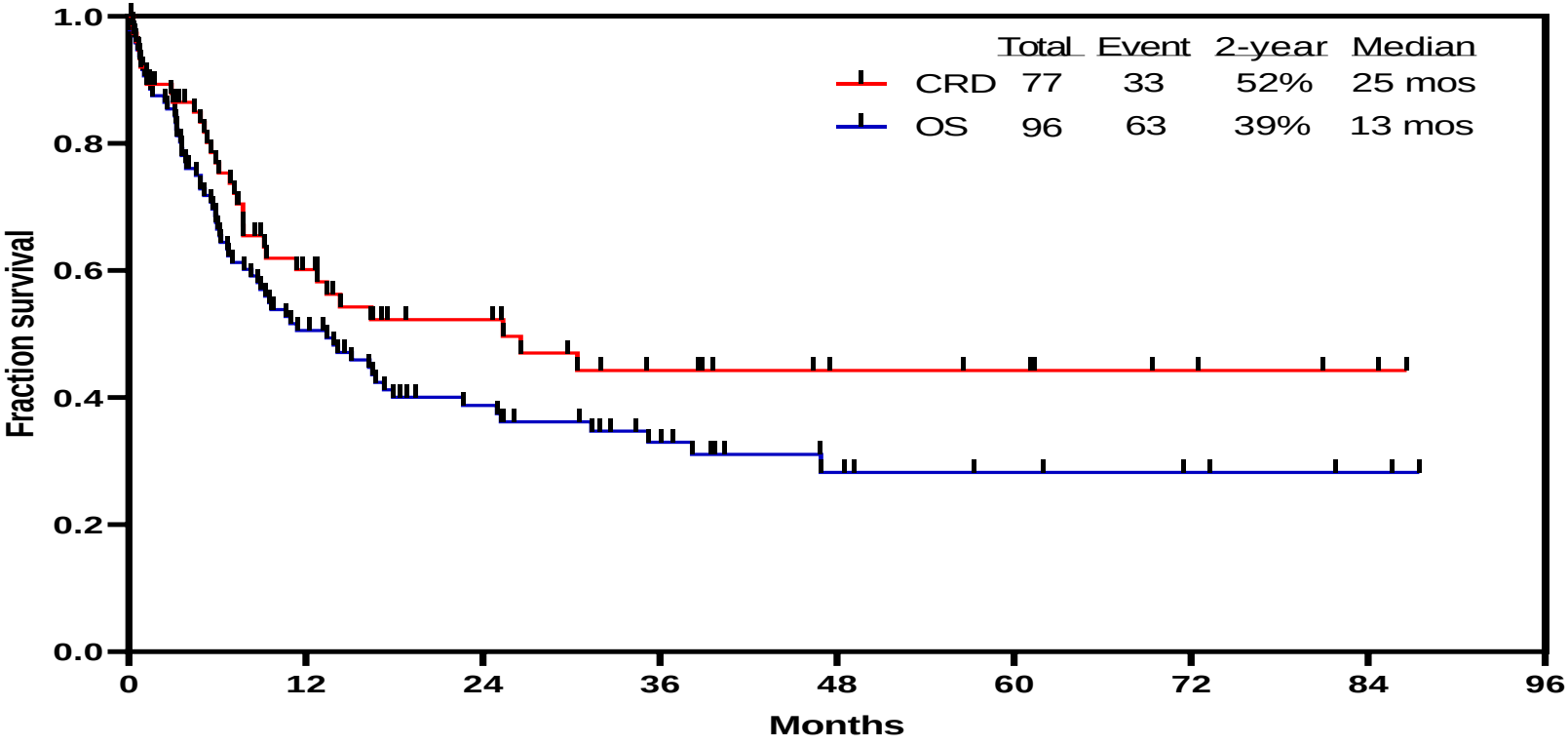
Jabbour. *Cancer.* 2018 Oct 11; Sasaki. *Blood.* 2018;132:abstract 553.

Mini-HCVD + Ino ± Blinatumomab in R-R ALL: Response by Salvage (N = 96)

Response	N	Percentage
Salvage 1	58/64	**91**
S1, primary refractory	8	100
S1, CRD1 <12 mo	21	84
S1, CRD1 ≥12 mo	29	94
Salvage 2	11	61
Salvage ≥3	8	57
Overall	**77**	**80**
MRD–	62/75	83
Salvage 1	**50/56**	**89**
Salvage ≥2	12/19	63
Early death	7	7

Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Sasaki K, et al. *Blood*. 2018;132(suppl):553.

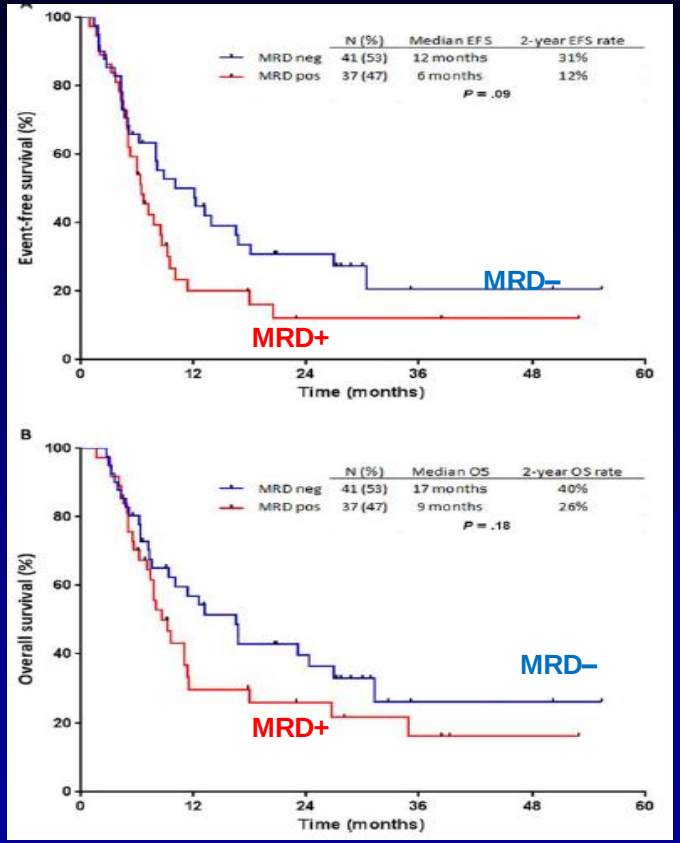
Mini-HCVD + Ino ± Blinatumomab in R/R ALL: CR Duration and OS (median F/U 48 months)



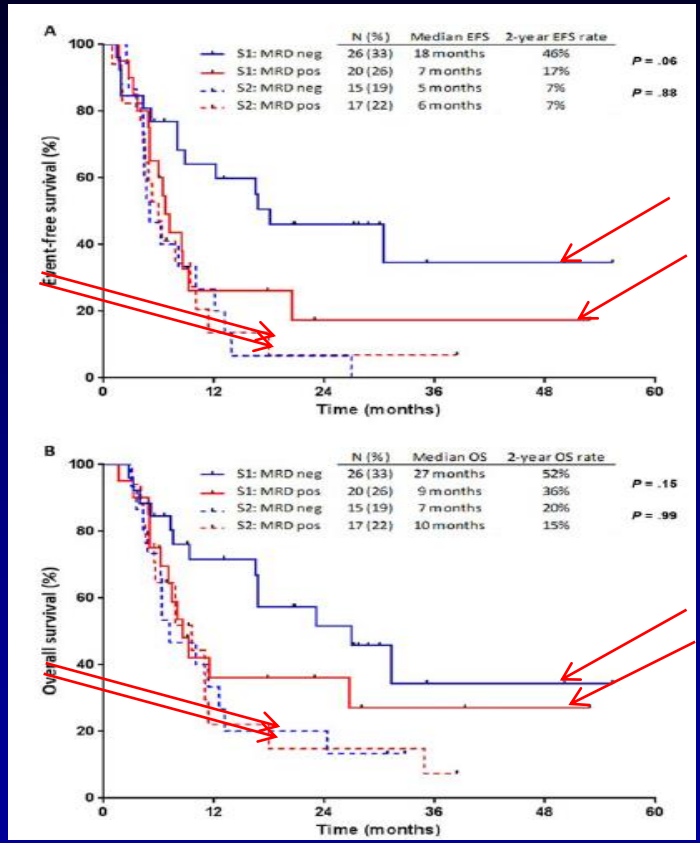
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Sasaki K, et al. *Blood*. 2018;132(suppl):553.

MRD in R/R ALL: Impact of Salvage Status

EFS



S2



S1

OS

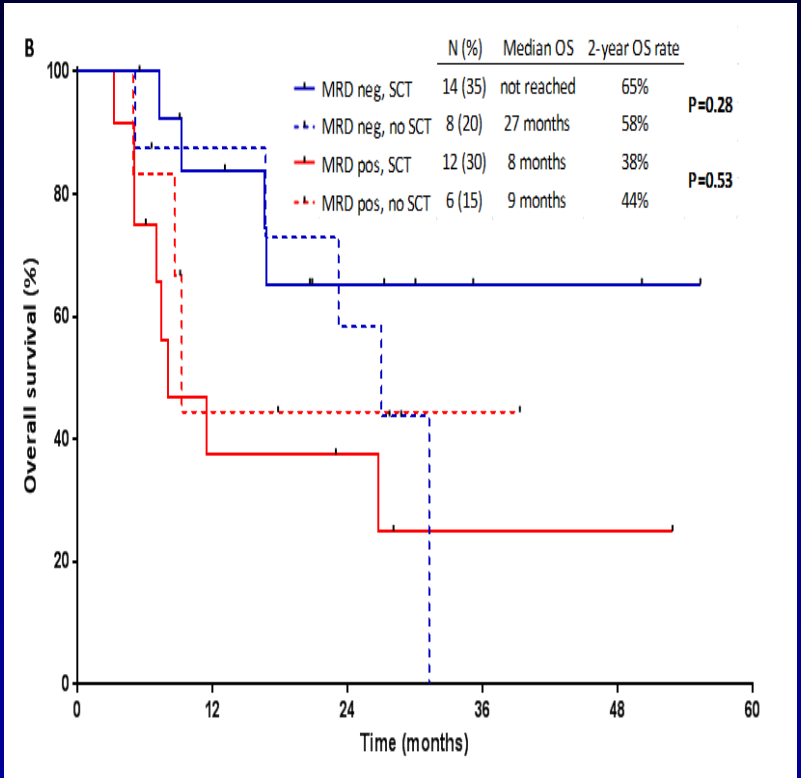
S2

S1

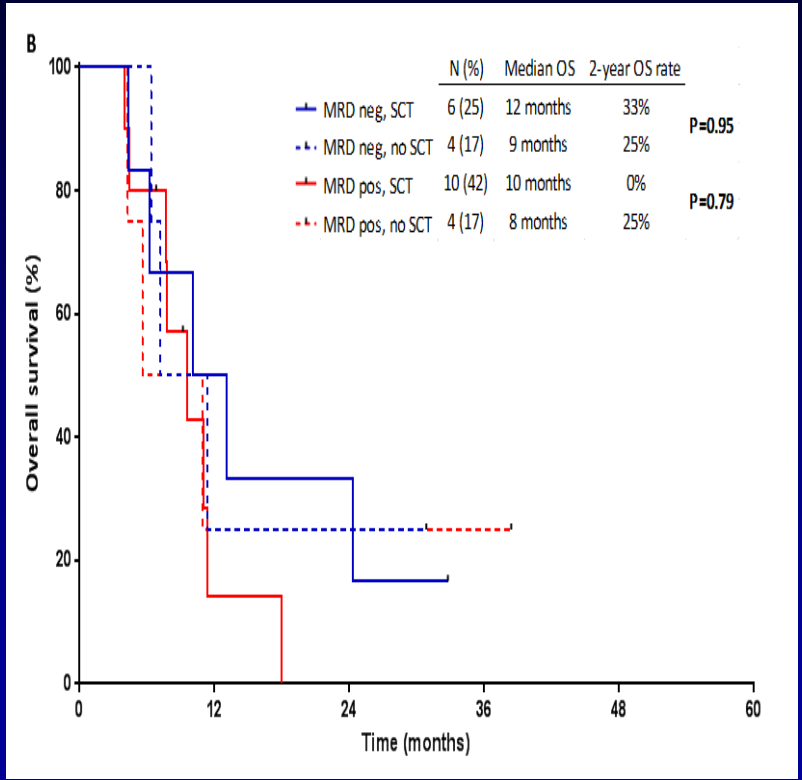
Jabbour. *Cancer*. 2017;123(2):294-302.

MRD in R/R ALL: Impact of ASCT and Salvage Status

Salvage 1



Salvage 2



Jabbour. *Cancer*. 2017;123(2):294-302.

Impact of MRD Status in R-R ALL: Conclusions

- Very effective salvage therapy in R/R ALL
  - High MRD negativity rate
  - Best outcome in salvage 1
- Combination with low-dose chemotherapy
  - Safe and effective
  - Median survival 14 months
  - Salvage 1 24 months (2-year OS rate >50%)
- Eradication of MRD in the relapsed setting
  - Impact on long-term outcome
  - Higher impact in salvage 1
  - Best outcome in CR2– MRD post-alloSCT

Global Leukemia Academy

AYA ALL Patients – What Is the Current Treatment Approach for This Diverse Patient Population?

Rob Pieters

APTITUDE HEALTH®

Treatment of AYA ALL patients

Rob Pieters
Chief Medical Officer

Question:

Which assertion is NOT correct for adolescent and young adult ALL patients?

1. Pediatric-inspired protocols lead to a better outcome than adult-inspired protocols
2. Treatment within a clinical trial leads to a worse outcome
3. AYA patients experience more toxicity than young children
4. BCR-ABL–like ALL is more frequent in AYA ALL than in children <10 years old with ALL

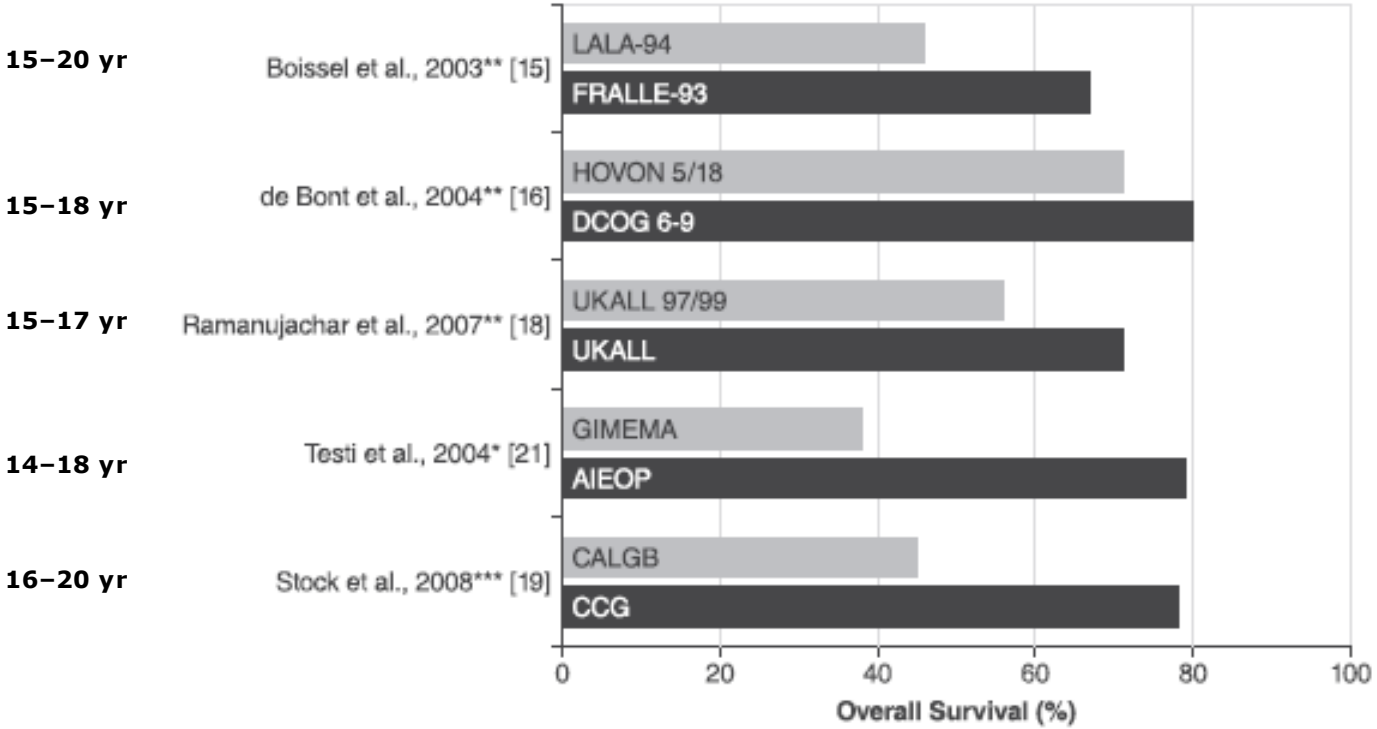
Inferior outcome for AYA patients; why?

- Role of “pediatric-” vs “adult”-inspired treatment protocols
- Site of treatment
- Trial enrollment
- Toxicity profile
- Biology/genetics of the leukemia
- Adherence

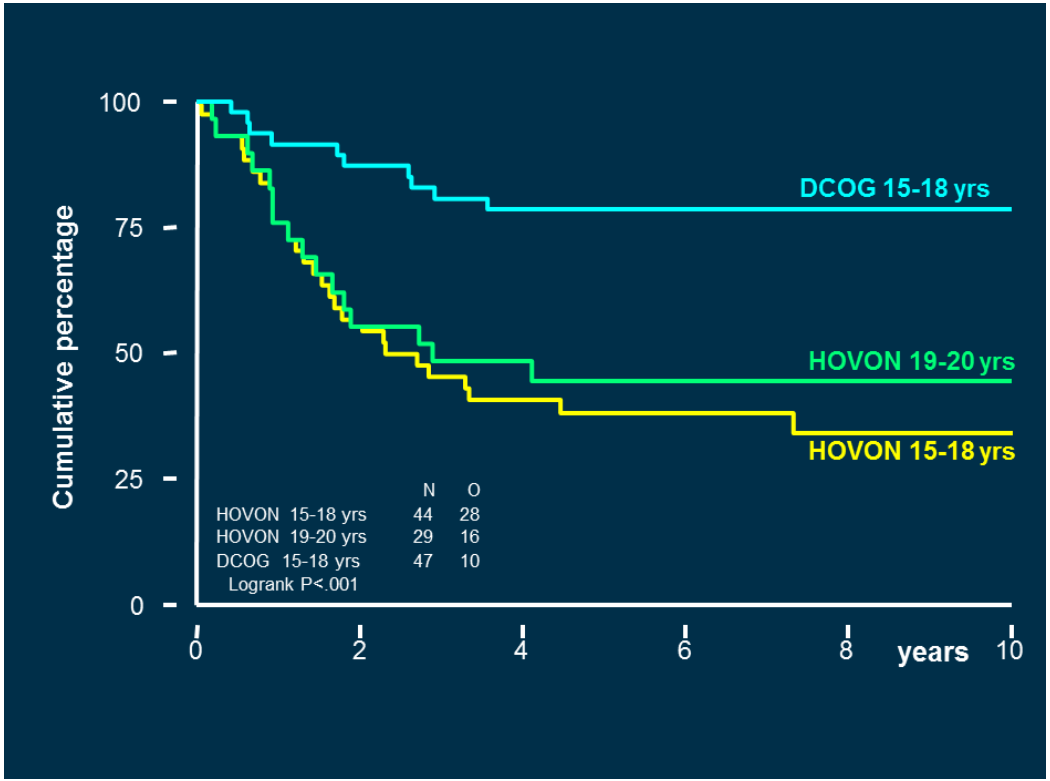
Pediatric vs adult treatment protocols

- More intensive use of
  - Glucocorticoids
  - Vincristine
  - Asparaginase
  - Methotrexate
  - 6-mercaptopurine
- Less intensive use of
  - Anthracyclines
  - Cyclophosphamide
- Less frequent use of alloSCT
- Prolonged maintenance, delayed intensification, CNS-directed therapy

Retrospective comparison of outcomes in AYA patients treated on pediatric and adult protocols



Outcome of adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands



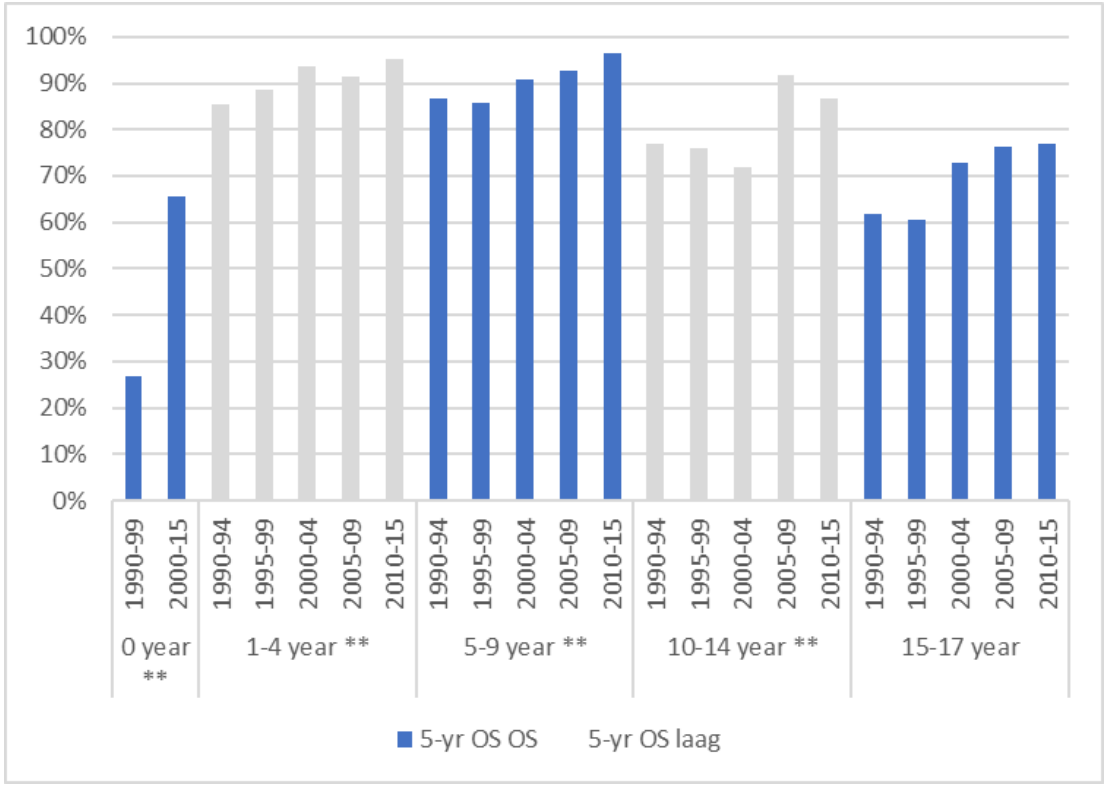
Outcome of adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands

5 yrs actuarial probabilities

	CR	OS (sd)	EFS (sd)	DFS (sd)	pREL (sd)	TRM (sd)
DCOG 15-18 yrs (n=47)	**98%**	**79%** (±6)	**69%** (±7)	**71%** (±7)	**27%** (±7)	**4%** (±3)
HOVON 15-18 yrs (n=44)	**91%**	**38%** (±7)	**34%** (±7)	**37%** (±8)	**55%** (±8)	**25%** (±7)
HOVON 19-20 yrs (n=29)	**90%**	**44%** (±9)	**34%** (±9)	**38%** (±10)	**50%** (±10)	**21%** (±8)
p-value	***0.24***	***0.0001***	***<0.0001***	***0.0002***		

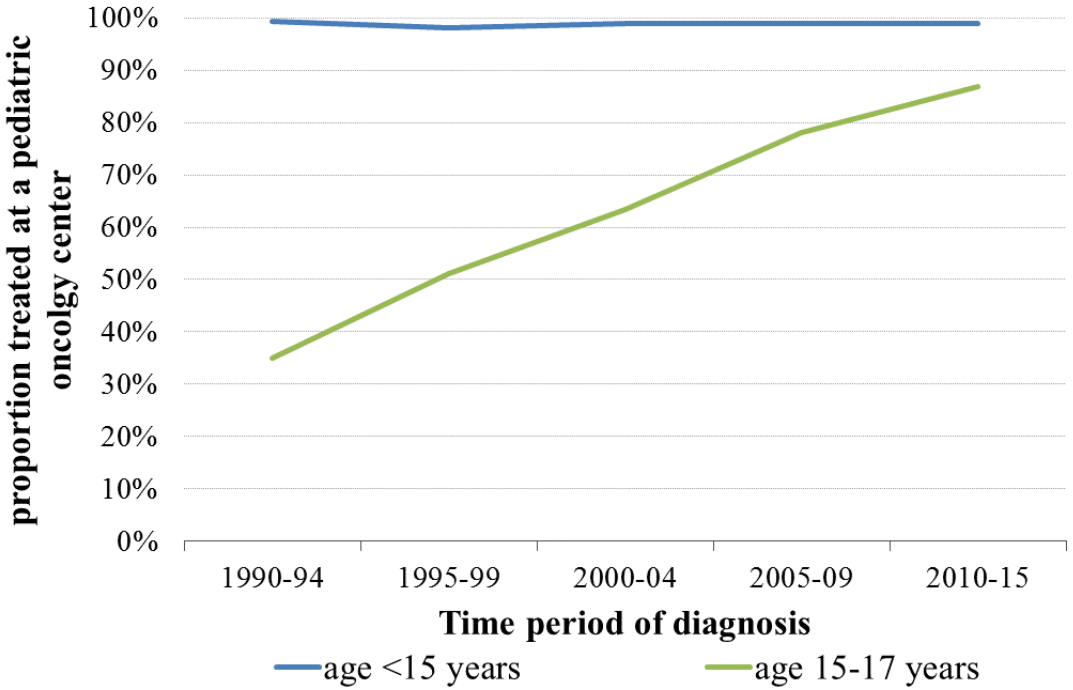
De Bont JM, et al. *Leukemia.* 2004;18(12):2032-2035.

5-year overall survival by age group over time in the Netherlands



Reedijk M, et al. 2020. (submitted manuscript)

Proportion of patients with ALL treated at a pediatric oncology center in the Netherlands



Reedijk M, et al. 2020. (submitted manuscript)

Multivariate analysis of risk of death: Patients aged 15–17 years with ALL in the Netherlands between 1990 and 2015

		Hazard Risk	95% CI	95% CI	*P* Value
Period	1990–1994	Reference			
	1995–1999	0.97	0.50	1.91	.94
	2000–2004	0.67	0.32	1.42	.30
	2005–2009	0.64	0.30	1.37	.25
	2010–2015	0.80	0.38	1.68	.56
Sex	Male	Reference			
	Female	1.45	0.89	2.37	.14
Immunophenotype	Precursor B-cell	Reference			
	Precursor T-cell	1.59	0.97	2.62	.07
Site of treatment	Outside pediatric oncology center	Reference			
	Pediatric oncology center	0.32	0.20	0.53	<.01

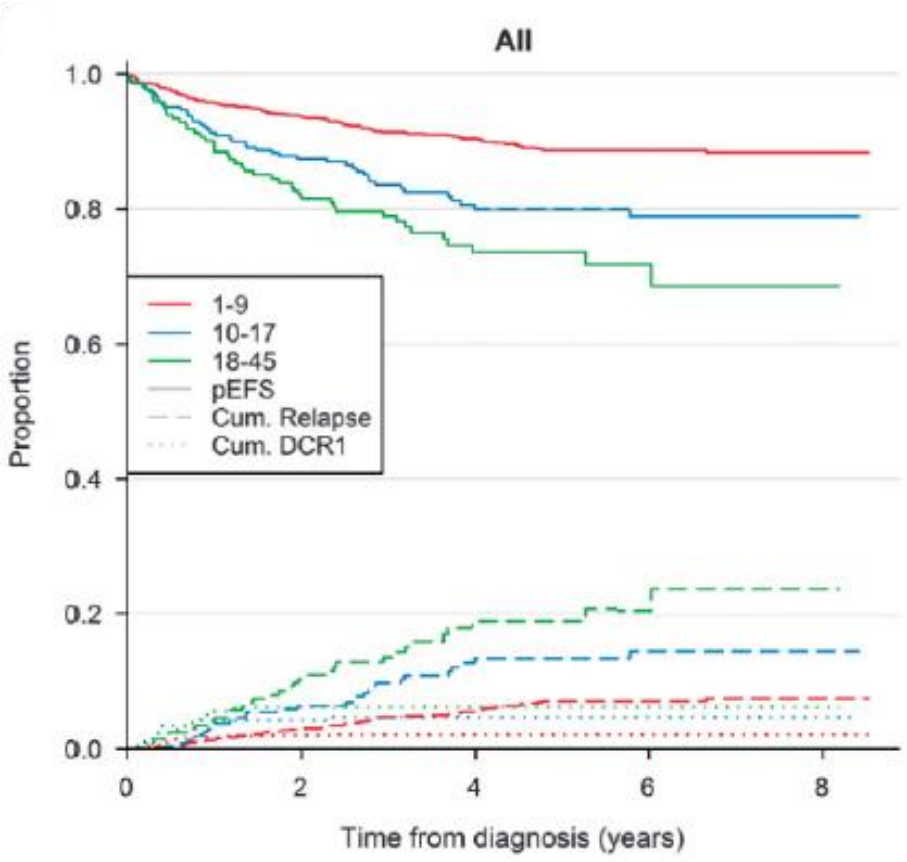
Reedijk M, et al. 2020. (submitted manuscript)

Outcomes in older adolescents treated in recent pediatric trials

Trial	No. of Patients	Age Range, y	Early Death, %	Death in CR, %	HSCT, %	EFS		OS	
						Y	%	Y	%
CCG 1961	262	16–21	2	3	4	5	72	5	78
DFCI 9101/9501	51	15–18	4	2	NR	5	78	5	81
Total therapy XV	45	15–18	0	7	11	5	86	5	88
UKALL 2003	229	16–24	NR	6	6.1	5	72	5	76
FRALLE 2000	186	15–19	2	2	12	5	74	5	80
DCOG ALL-10	57	15–18	NR	NR	NR	5	79	5	82

Adapted from Boissel N, Baruchel A. *Blood.* 2018;132(4):351-361. and Pieters R, et al. *J Clin Oncol.* 2016;34(22):2591-2601.

EFS, relapse, and death in first remission by age

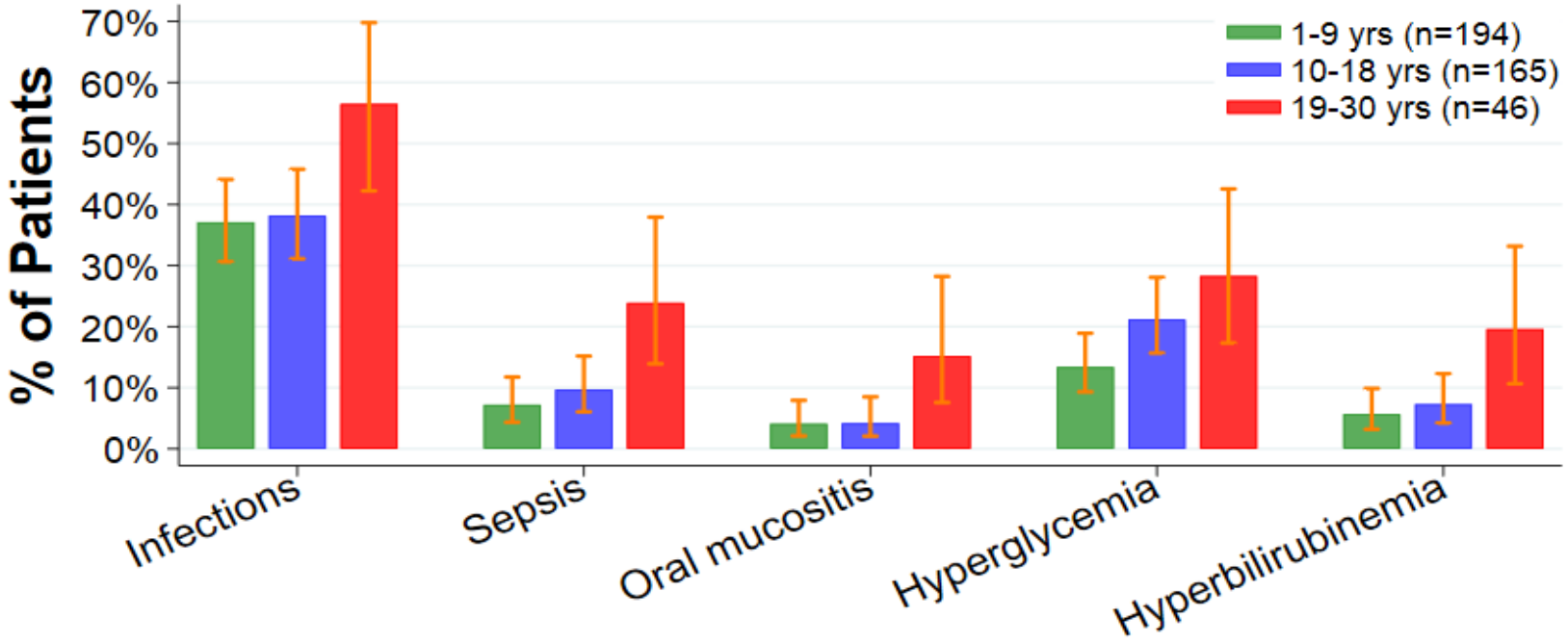


Toxicity by age

	Y/N (%)	OR (95% CI)	P
Intensive care w/wo assisted ventilation			
1-9	145 / 864 (14.4%)	1.0 (1.0- 1.0)	
10-17	54 / 208 (20.6%)	1.3 (0.9- 1.9)	0.14
18-45	40 / 172 (18.9%)	1.1 (0.7- 1.6)	0.68
Anaphylatic reaction to asparaginase			
1-9	146 / 863 (14.5%)	1.0 (1.0- 1.0)	
10-17	25 / 237 (9.5%)	0.6 (0.4- 0.9)	0.016
18-45	11 / 201 (5.2%)	0.3 (0.1- 0.5)	<0.001
Invasive Fungal infection			
1-9	98 / 911 (9.7%)	1.0 (1.0- 1.0)	
10-17	32 / 230 (12.2%)	0.9 (0.6- 1.4)	0.68
18-45	28 / 184 (13.2%)	0.9 (0.5- 1.4)	0.54
Peripheral paralysis			
1-9	100 / 909 (9.9%)	1.0 (1.0- 1.0)	
10-17	30 / 232 (11.5%)	1.3 (0.8- 2.1)	0.21
18-45	20 / 192 (9.4%)	1.1 (0.7- 1.9)	0.61
Pancreatitis			
1-9	60 / 949 (5.9%)	1.0 (1.0- 1.0)	
10-17	29 / 233 (11.1%)	2.2 (1.3- 3.5)	0.001
18-45	24 / 188 (11.3%)	2.4 (1.4- 4.0)	0.001
Hyperlipidemia			
1-9	72 / 937 (7.1%)	1.0 (1.0- 1.0)	
10-17	26 / 236 (9.9%)	1.7 (1.0- 2.8)	0.027
18-45	15 / 197 (7.1%)	1.3 (0.7- 2.3)	0.37
Thrombosis			
1-9	36 / 973 (3.6%)	1.0 (1.0- 1.0)	
10-17	40 / 222 (15.3%)	5.0 (3.1- 8.2)	<0.001
18-45	37 / 175 (17.5%)	6.0 (3.6-10.1)	<0.001
Osteonecrosis			
1-9	23 / 986 (2.3%)	1.0 (1.0- 1.0)	
10-17	35 / 227 (13.4%)	8.0 (4.6-14.1)	<0.001
18-45	18 / 194 (8.5%)	5.3 (2.7-10.3)	<0.001
Seizures			
1-9	38 / 971 (3.8%)	1.0 (1.0- 1.0)	
10-17	16 / 246 (6.1%)	1.7 (0.9- 3.1)	0.086
18-45	5 / 207 (2.4%)	0.7 (0.2- 1.6)	0.39
PCP			
1-9	29 / 980 (2.9%)	1.0 (1.0- 1.0)	
10-17	11 / 251 (4.2%)	1.3 (0.6- 2.6)	0.48
18-45	13 / 199 (6.1%)	1.8 (0.9- 3.7)	0.089
PRES			
1-9	37 / 972 (3.7%)	1.0 (1.0- 1.0)	
10-17	9 / 253 (3.4%)	0.8 (0.4- 1.7)	0.60
18-45	5 / 207 (2.4%)	0.5 (0.2- 1.3)	0.18

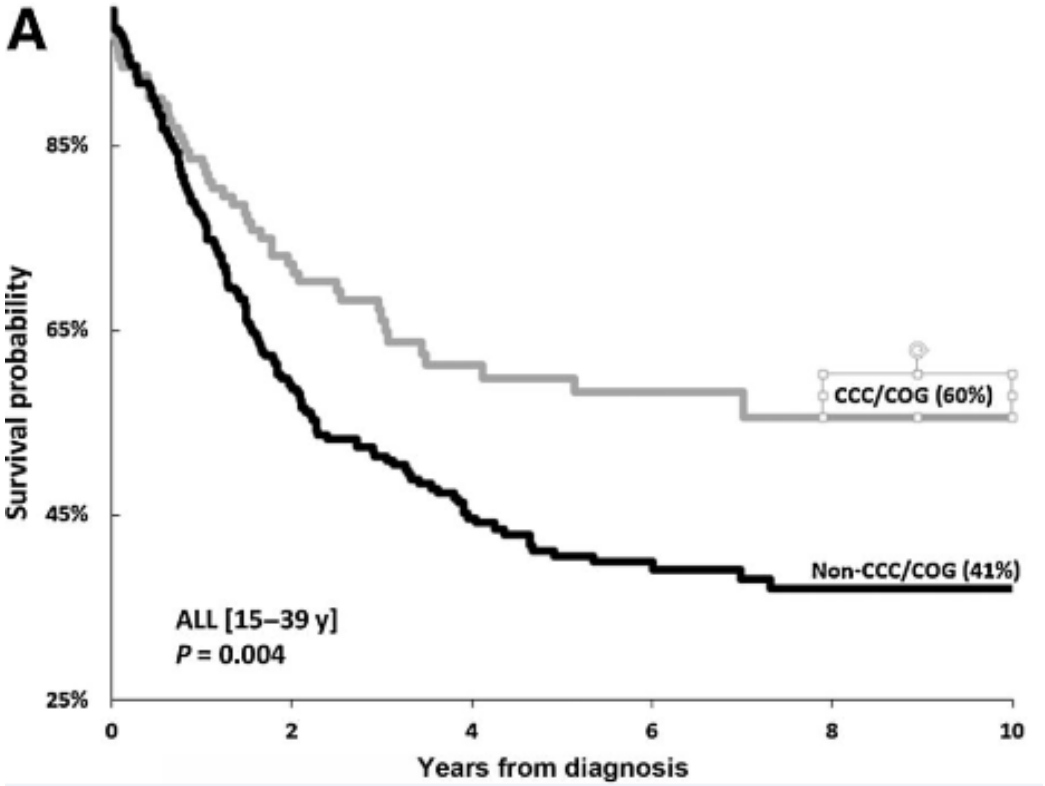
Toft N, et al. *Leukemia.* 2018;32(3):606-615.

Induction toxicities by age (COG first relapse B-ALL Clinical trial AALL1331)



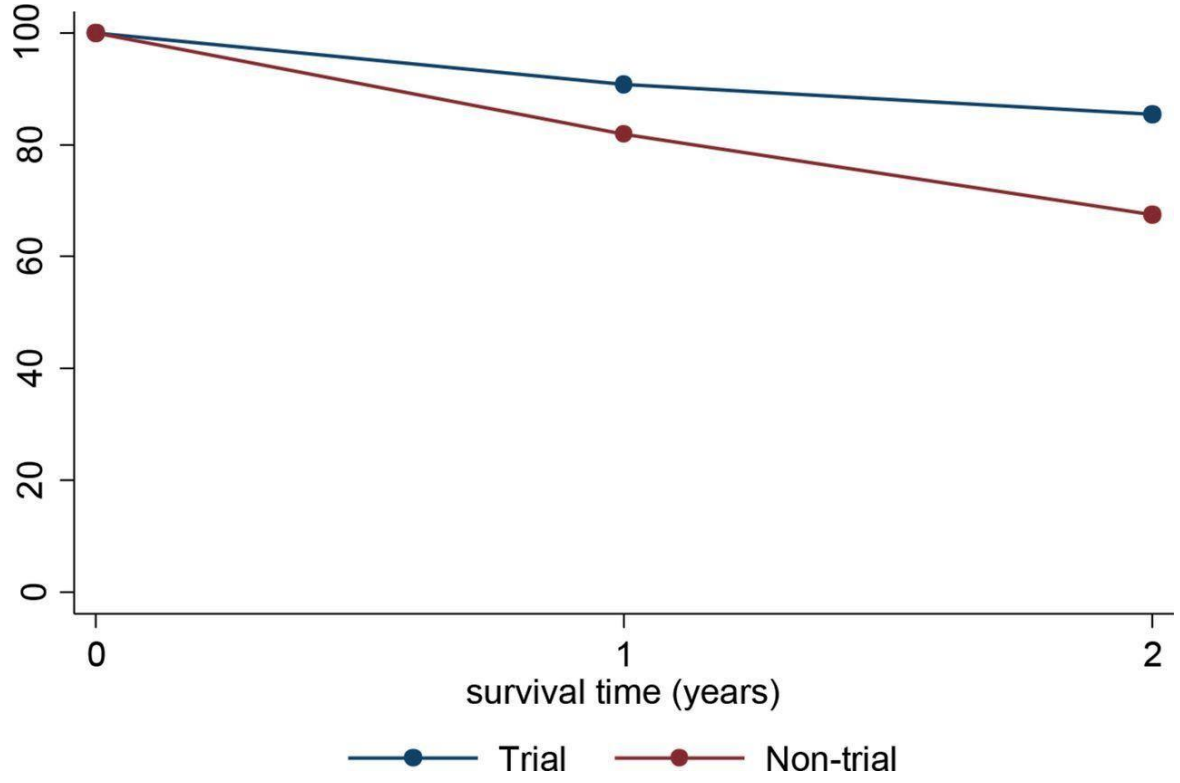
Hogan L, et al. *Blood.* 2018;132:1382 (courtesy of Mignon Loh).

Survival in AYA with ALL by treatment site (CCC/COG vs other)

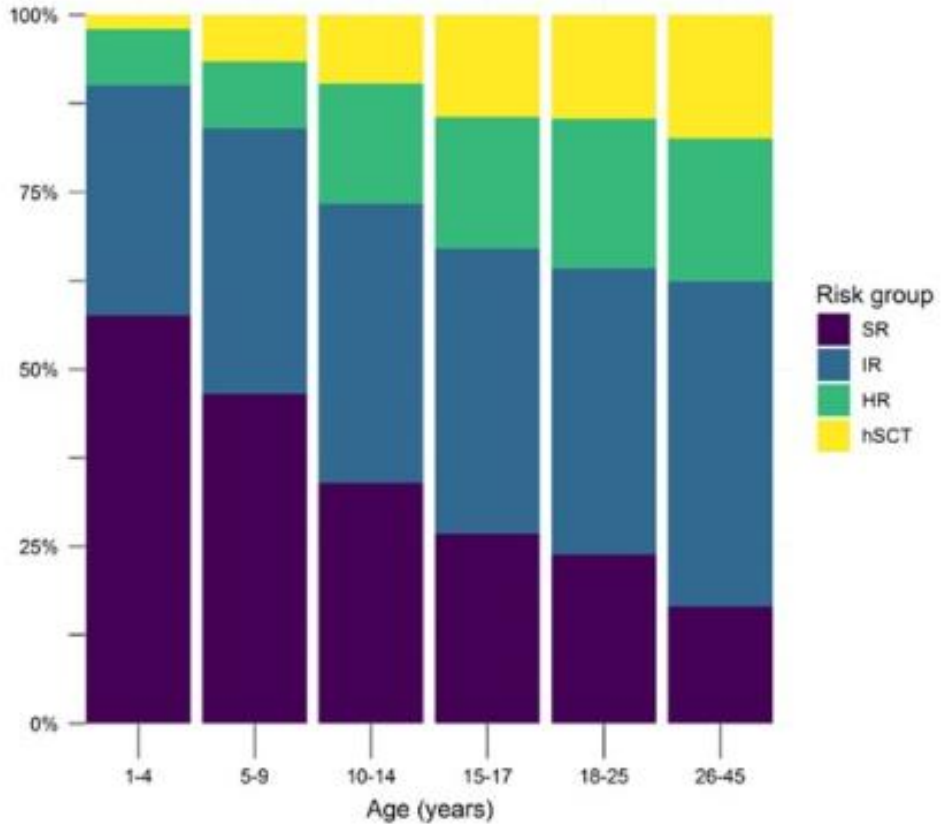


Wolfson J, et al. *Cancer Epidemiol Biomarkers Prev.* 2017;26(3):312-320.

Two-year relative survival in 15–24-year-old ALL patients (n = 503) by trial status

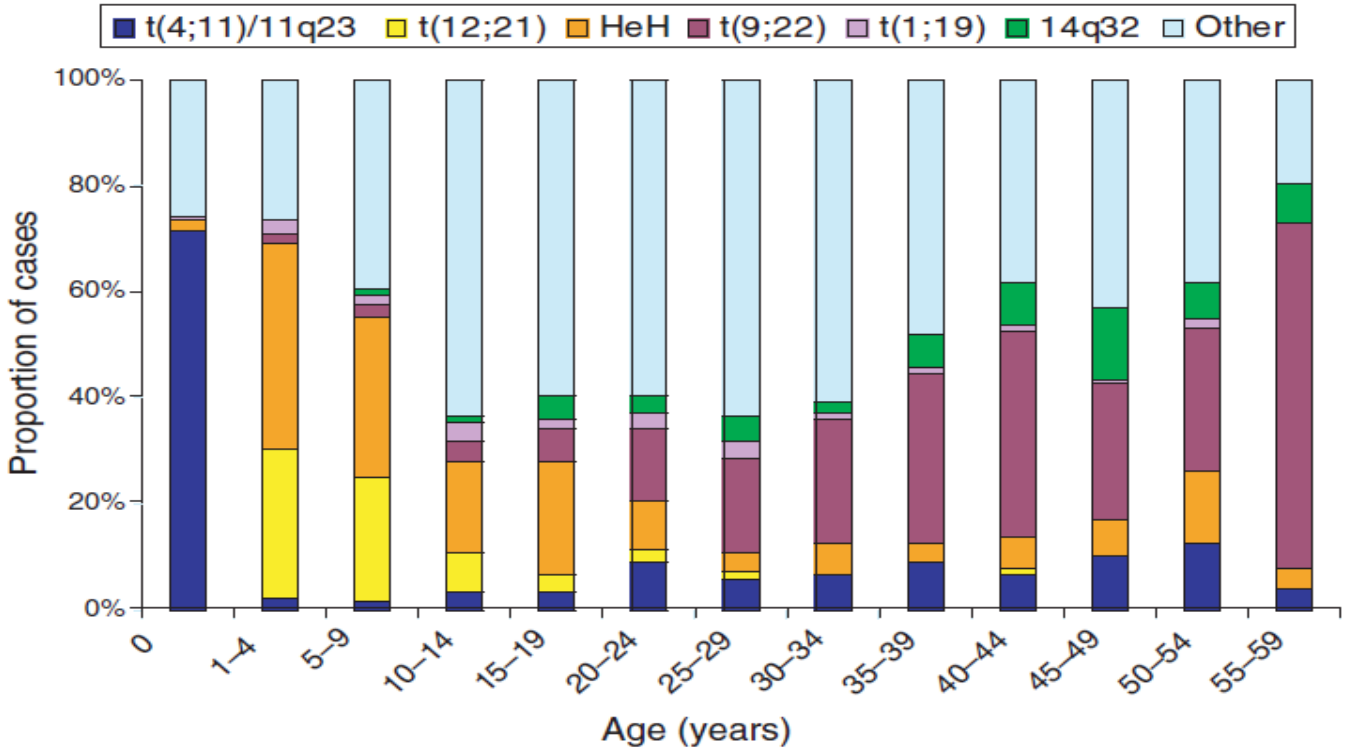


Risk group distribution by age

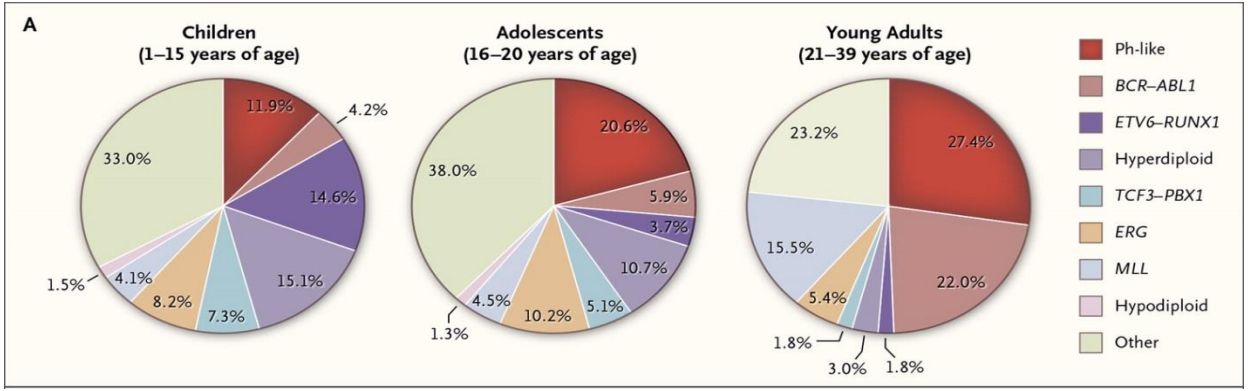


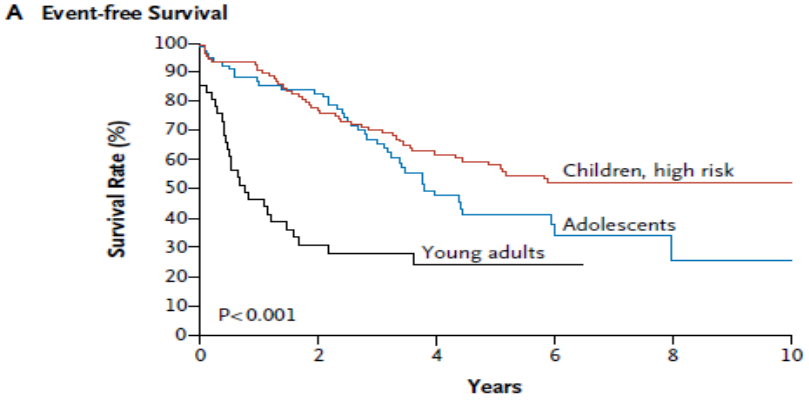
Toft N, et al. *Leukemia.* 2018;32(3):606-615.

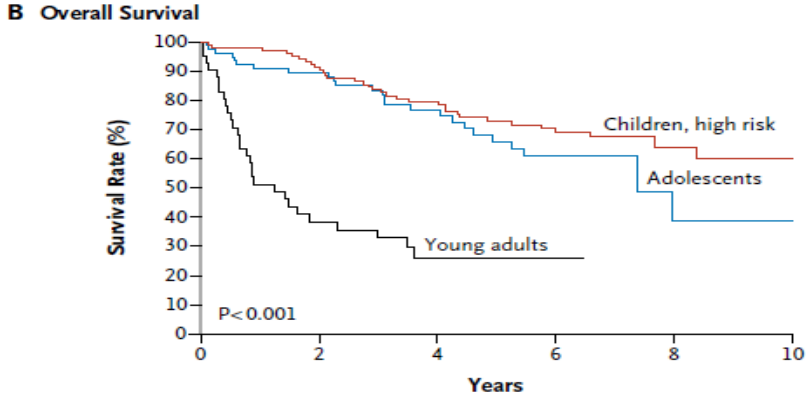
Distribution of cytogenetic subtypes of ALL by age



Ph-like ALL: Prevalence and outcomes

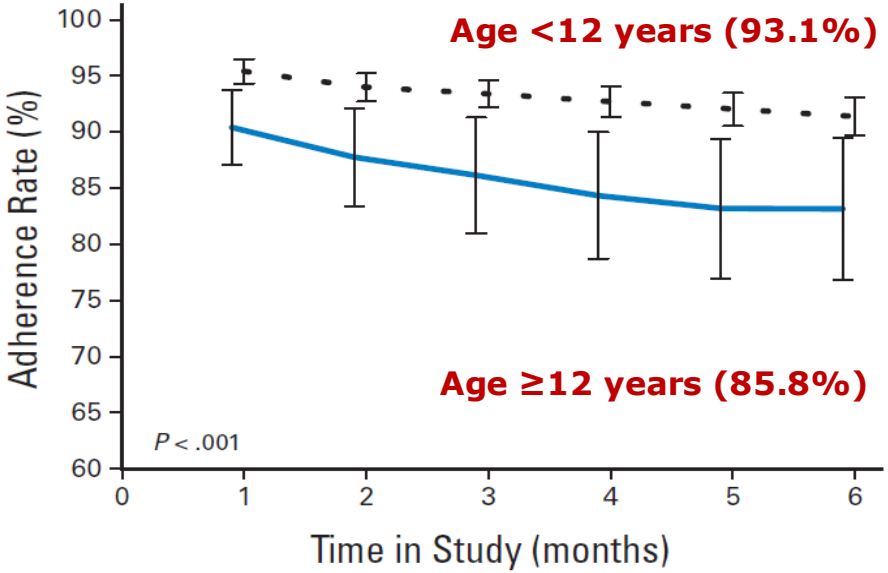


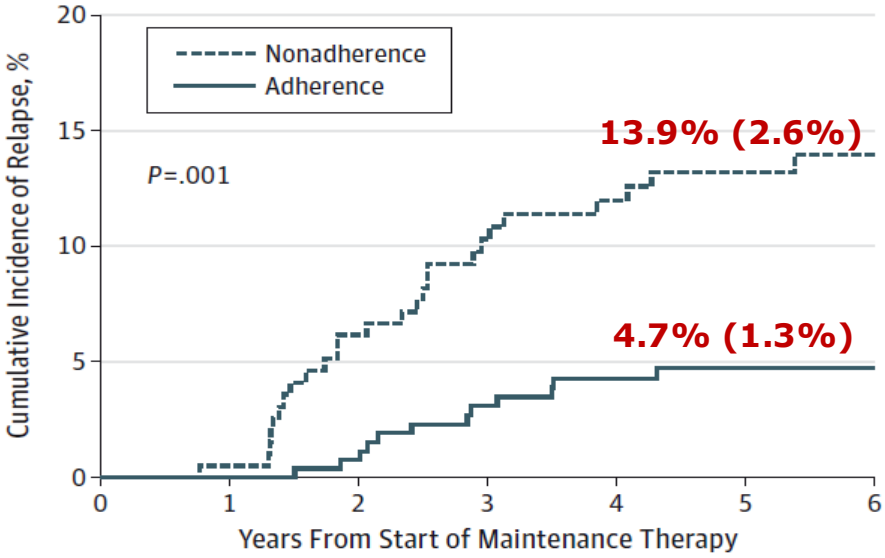




Roberts KG, et al. *N Engl J Med.* 2014;371:1005-1015; Graubert TA. *N Engl J Med.* 2014;371:1064-1066 (courtesy of Mignon

Low adherence to oral 6MP significantly increases relapse risk





Bhatia S, et al. *J Clin Oncol.* 2012;30:2094-2101 and *JAMA Oncol.* 2015;3:287-295 (courtesy of Mignon Loh).

AYA conclusions

- Outcome improved but still inferior to those in younger children
- Pediatric-inspired protocols better than adult-inspired protocols
- Treatment within trials better outcome
- Higher toxicity in AYA than in younger children, but manageable
- Higher incidence of unfavorable biology/genetics

Answer to the Question:

Which assertion is NOT correct for adolescent and young adult ALL patients?

1. Pediatric-inspired protocols lead to a better outcome than adult-inspired protocols
2. **Treatment within a clinical trial leads to a worse outcome**
3. AYA patients experience more toxicity than young children
4. BCR-ABL–like ALL is more frequent in AYA ALL than in children <10 years old with ALL

Thank you!

Global Leukemia Academy

Bispecific T-Cell Engagers as Post-reinduction Therapy Improves Survival in Pediatric and AYA B-ALL

Patrick Brown

APTITUDE HEALTH®

A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-ALL in Children and AYAs Demonstrates Superior Efficacy and Tolerability of Blinatumomab

A Report from Children's Oncology Group Study AALL1331

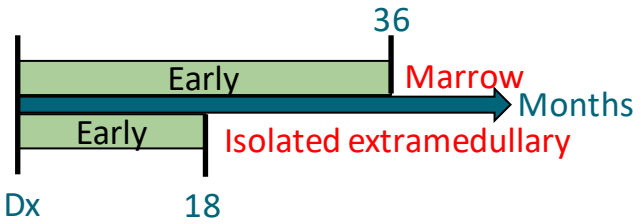
Patrick A. Brown, Lingyun Ji, Xinxin Xu, Meenakshi Devidas, Laura Hogan, Michael J. Borowitz, Elizabeth A. Raetz, Gerhard Zugmaier, Elad Sharon, Lia Gore, James A. Whitlock, Michael A. Pulsipher, Stephen P. Hunger, Mignon L. Loh

CHILDREN'S ONCOLOGY GROUP

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

Background

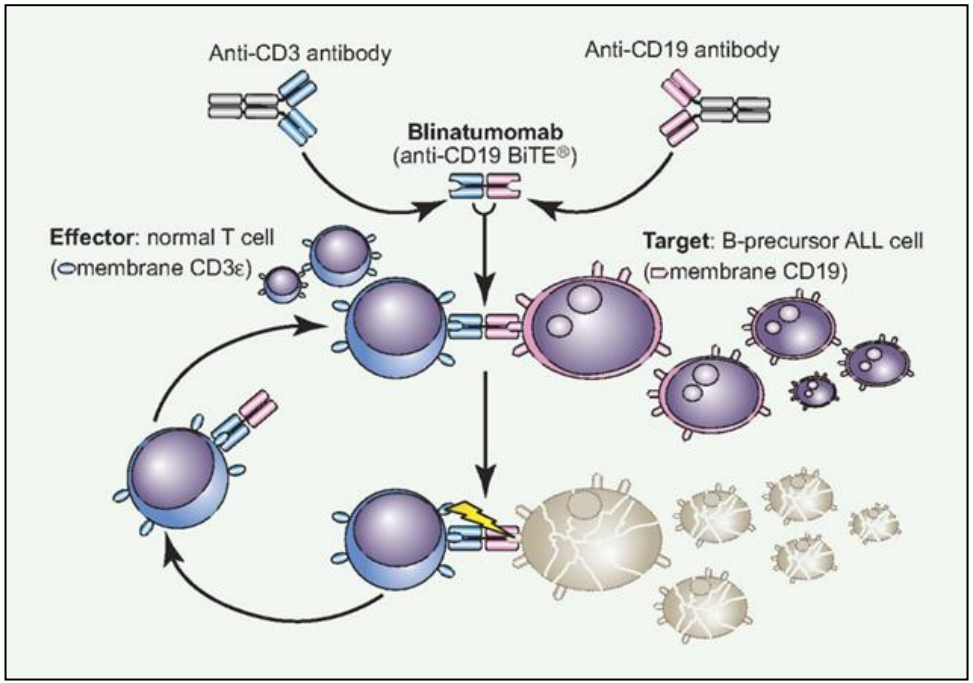
- Poor survival for first-relapse B-ALL in children, adolescents, and young adults (AYA), especially early relapses
- Standard treatment approach
  - Reinduction chemotherapy -> second remission
  - Consolidation
    - Early relapse: Intensive chemo -> HSCT
      - Goal: MRD negativity prior to HSCT
    - Late relapse
      - "MRD high": same as early
      - "MRD low": intensive chemo -> maintenance therapy



CHILDREN'S ONCOLOGY GROUP

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

Blinatumomab (CD19 BiTE)



Adapted from *Brown P. Blood. 2018; 131: 1497–1498*

- In multiply relapsed/refractory setting (pediatrics)
  - CR 35-40%
  - MRD-negative CR 20-25%

von Stackelberg et al. JCO. 2016; 34:4381-4389

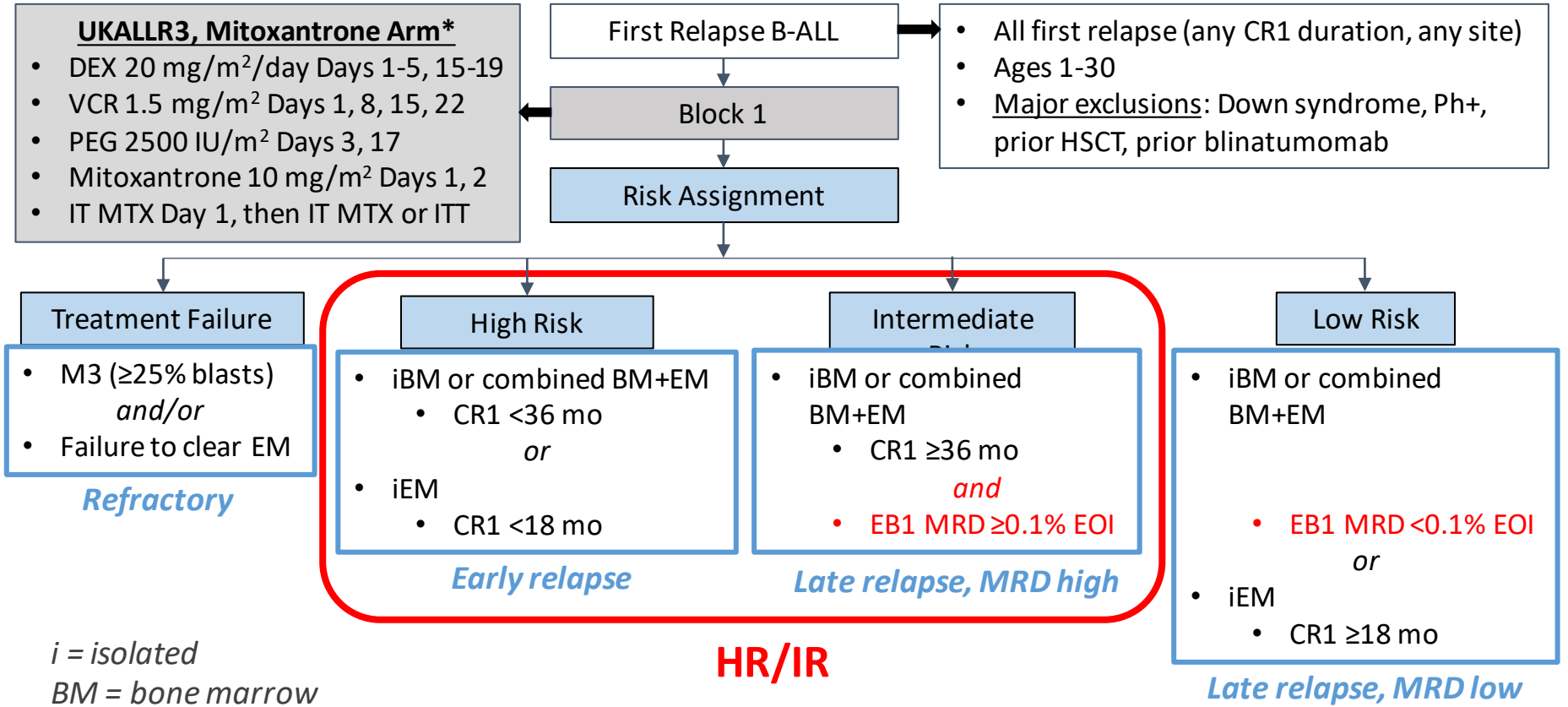
- In MRD+ setting (adults)
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

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

Objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in first relapse of childhood/AYA B-ALL

CHILDREN'S ONCOLOGY GROUP

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



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

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

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

Stratifications

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

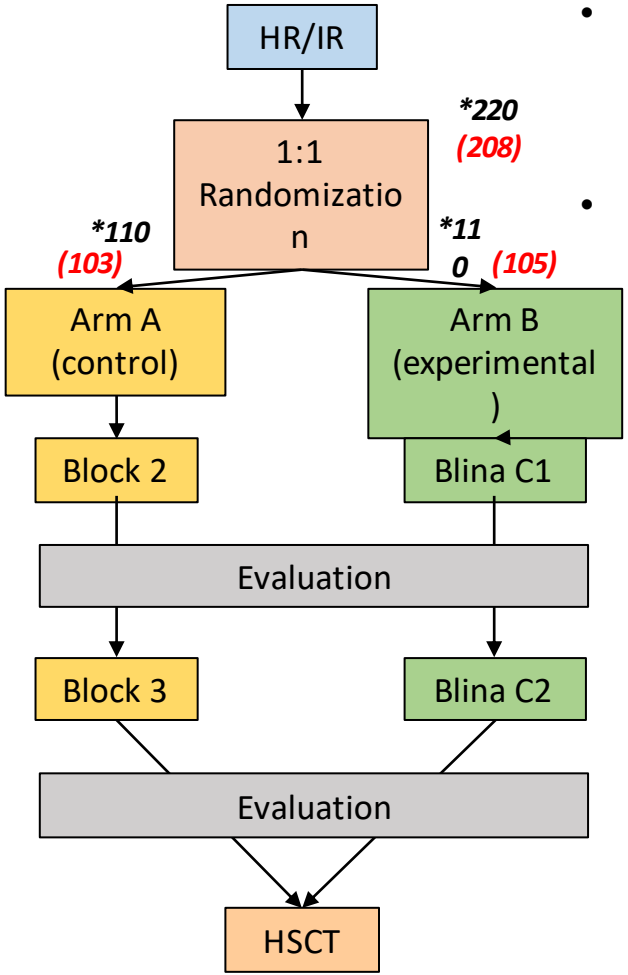
UKALLR3, Block 2*

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

UKALLR3, Block 3*

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

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



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

Blina C1 and Blina C2

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

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

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

Early Closure Recommended by DSMC

- Scheduled review by DSMC Sep 2019 using data cutoff 6/30/2019 (~60% of projected events)
- Despite the monitoring threshold for DFS not being crossed, the DSMC recommended
  - Permanent closure of accrual to HR/IR randomization
  - Immediate crossover to experimental Arm B for patients still receiving therapy
- DSMC recommendation based on
  - The difference in **DFS and OS** between arms
  - The profound difference in **toxicity** between arms
  - The highly significant difference in **MRD** clearance rates between arms

CHILDREN'S ONCOLOGY GROUP

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

Baseline Characteristics

16% AYA

	Arm A (n=103)	Arm B (n=105)
Age at enrollment, years		
Median (range)	*9 (1-27)*	*9 (1-25)*
1-9	55 (53%)	55 (52%)
10-17	30 (29%)	35 (33%)
18-30	18 (18%)	15 (14%)
Sex		
Female	49 (48%)	48 (46%)
Male	54 (52%)	57 (54%)
NCI risk group at diagnosis		
High risk	60 (58%)	59 (56%)
Standard risk	43 (42%)	46 (44%)
Cytogenetic groups at diagnosis		
Favorable (Tri 4/10, *ETV6-RUNX1*)	16 (18%)	21 (23%)
KMT2A rearranged	9 (10%)	7 (8%)
Hypodiploidy	1 (1%)	0
Other	65 (71%)	63 (69%)
None	12	14

CHILDREN'S ONCOLOGY GROUP

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

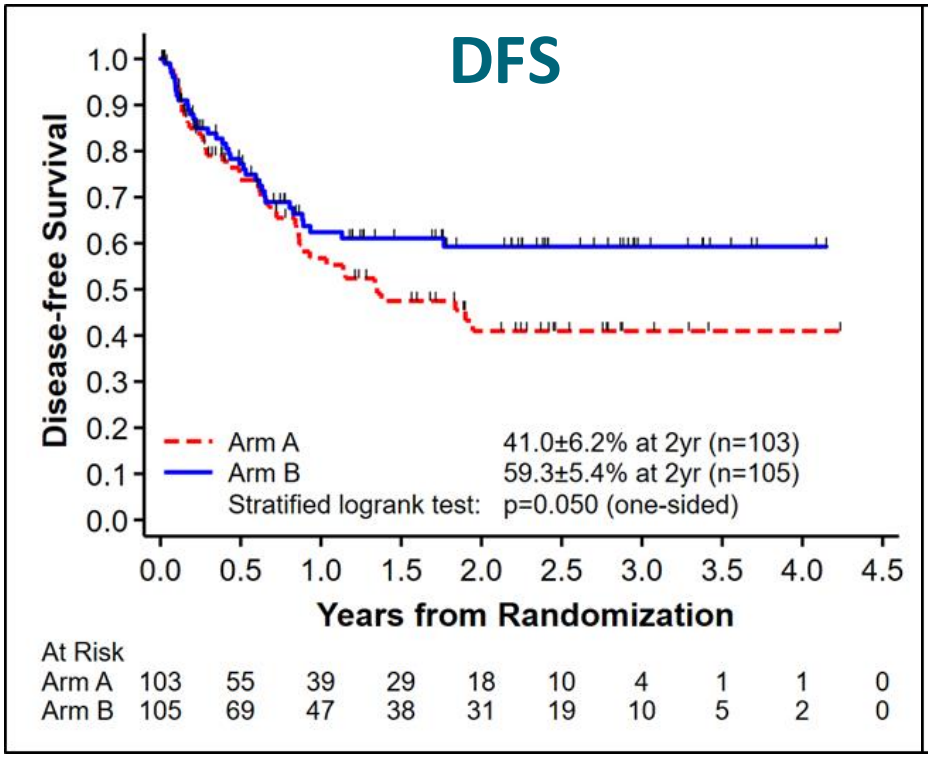
Randomization Stratification Factors

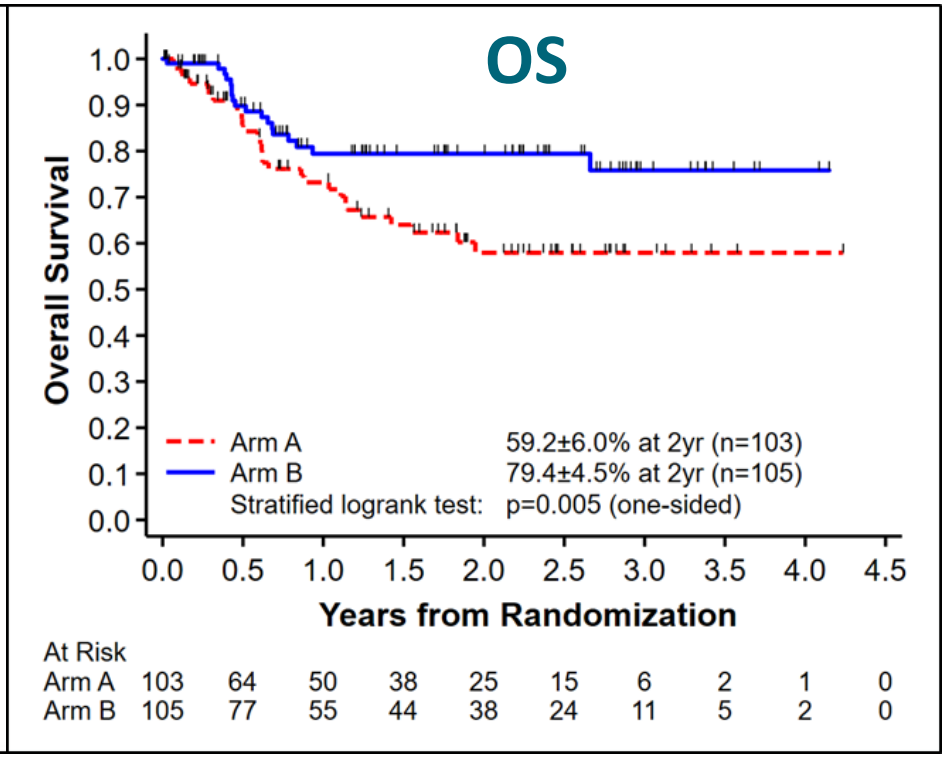
Stratification Factors	Arm A (n=103)	Arm B (n=105)
Risk Group Assignment After Block 1		
Intermediate risk (late relapse, MRD high)	34 (33%)	36 (34%)
High risk (early relapse)	69 (67%)	69 (66%)
High-Risk Subsets		
• Marrow, CR1 <18 months (very early)	18 (26%)	18 (26%)
• Marrow, CR1 18-36 months (early)	41 (59%)	41 (59%)
• IEM, CR1 <18 months	10 (14%)	10 (14%)

CHILDREN'S ONCOLOGY GROUP

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

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



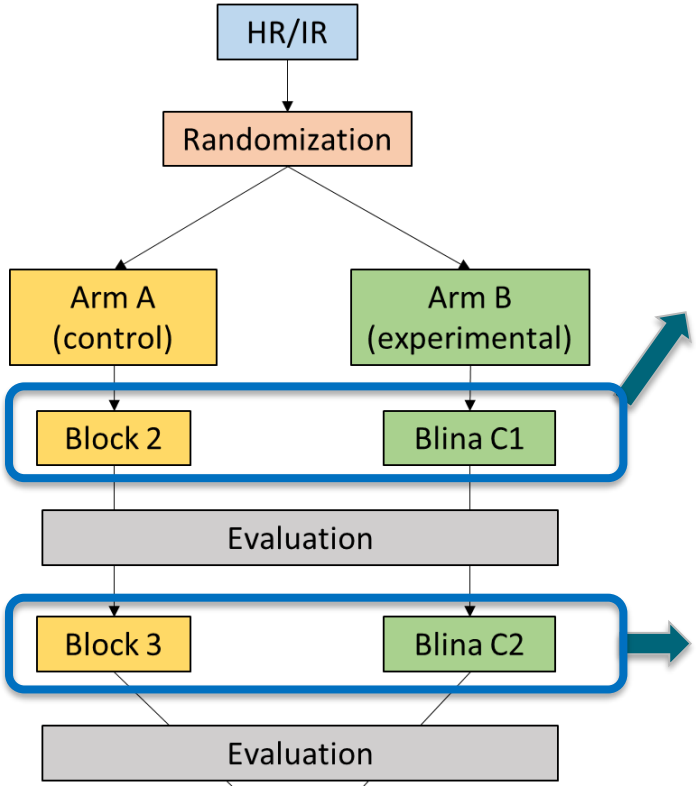


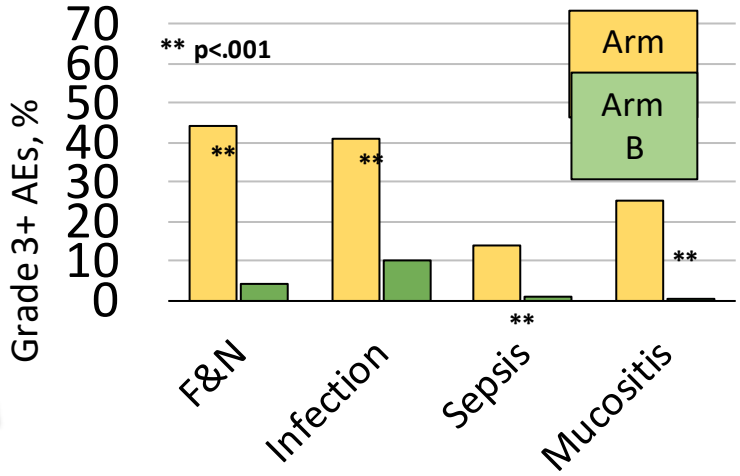
CHILDREN'S ONCOLOGY GROUP

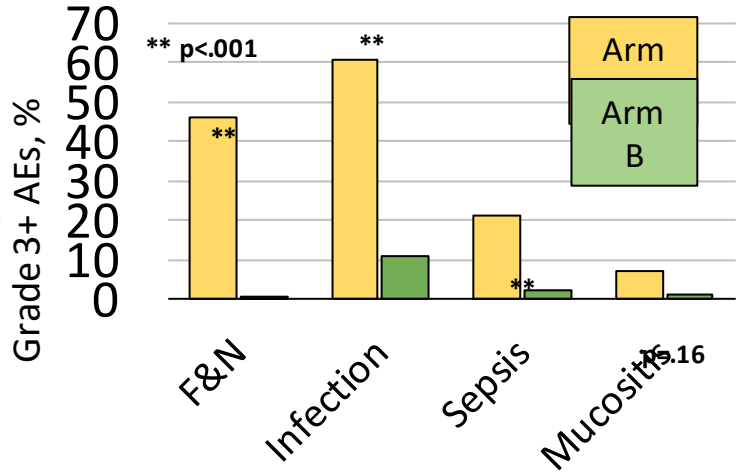
Median follow-up 1.4 years

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

Adverse Events







- *N=4 post-induction Grade 5 AEs on Arm A (all infections)*
- *N=0 on Arm B*
- *Ages of Arm A deaths: 2, 17, 23, and 26 years old (AYA-skewed)*
- *NOTE: AE rates significantly higher in AYA (Hogan, et al. ASH Abstract 2018)*

CHILDREN'S ONCOLOGY GROUP

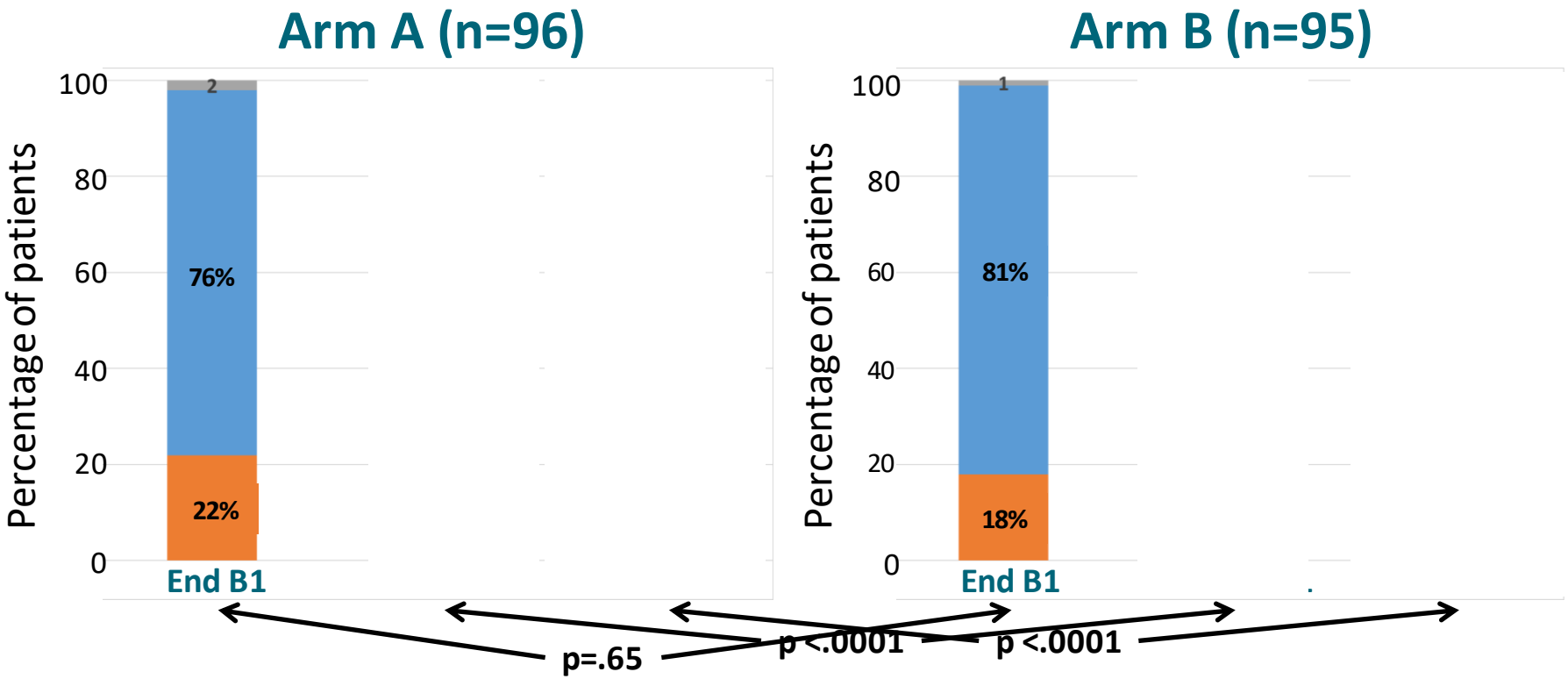
Brown PA, et al., *Blood* 2019; 134 (Supplement_2): LBA-1.

Blinatumomab-Related AEs on Arm B

	Blina C1 (n=99)		Blina C2 (n=83)	
Blinatumomab-Related AEs	Any Grade (%)	Grade 3-4 (%)	Any Grade (%)	Grade 3-4 (%)
Cytokine release syndrome	22%	1%	1%	0%
Neurotoxicity	18%	3%	11%	2%
Seizure	4%	1%	0%	0%
Other (encephalopathic)	14%	2%	11%	2%

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

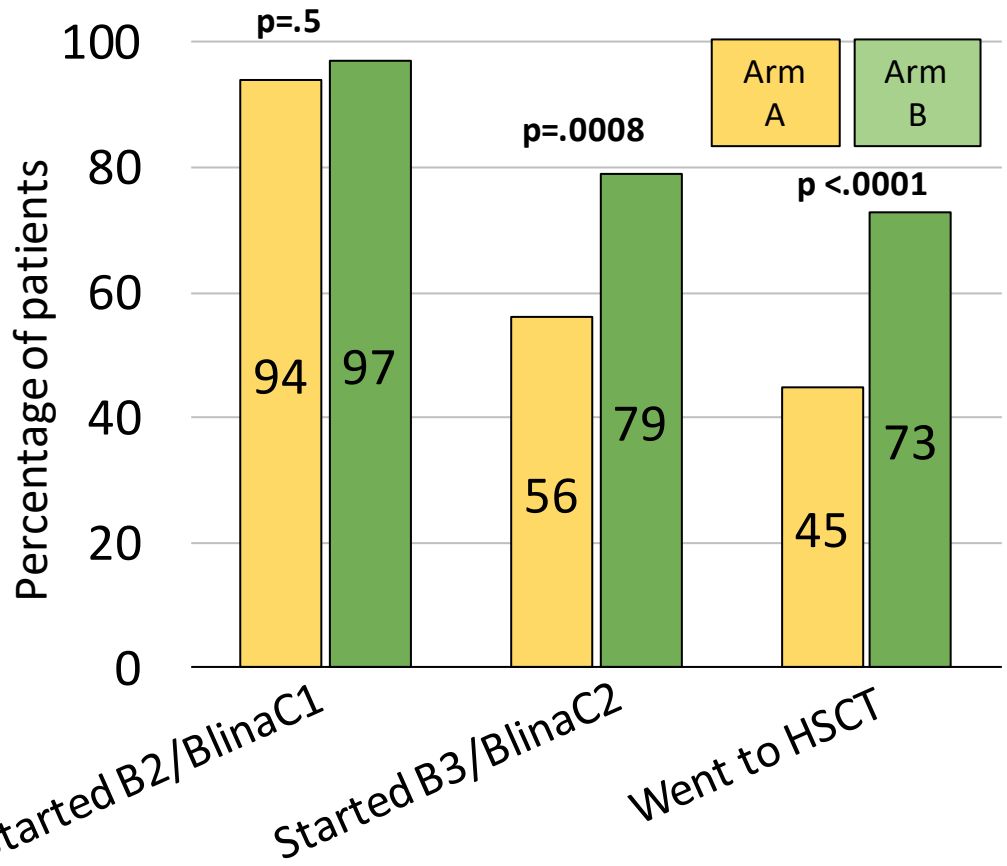
MRD Clearance (for iBM and BM+EM)



CHILDREN'S ONCOLOGY GROUP

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

Dropout/HSCT Rates: Arm A vs Arm B



A significant contributor to the improved outcomes for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may be the **ability of blinatumomab to successfully bridge to HSCT**

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

Conclusions

- For children and AYA patients with HR/IR first relapse of B-ALL, blinatumomab is superior to standard chemotherapy as post-reinduction consolidation prior to HSCT, resulting in
  - Fewer and less severe toxicities
  - Higher rates of MRD response
  - Greater likelihood of proceeding to HSCT
  - Improved disease-free and overall survival
- Blinatumomab constitutes a new standard of care in this setting
- Future: Optimizing immunotherapy in relapsed ALL
  - Combination of blinatumomab and checkpoint inhibitors
  - Immunotherapy to replace or augment reinduction chemotherapy
  - CAR T cells to replace or augment HSCT

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

AALL1331 Study Committee

- **Chair**: Pat Brown
- **Vice Chair**: Jim Whitlock
- **Stats**: Lingyun Ji, Mini Devidas
- **Heme/Onc**
  - Lia Gore
  - Laura Hogan
  - Terzah Horton
  - Stevie “Nix” Hunger
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- **Pharmacy**
  - Brooke Bernhardt
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- **Nursing**
  - Deb Schissel
  - Susan Zupanec
- **Research Coordinator**: Susan Conway, Don Sortillon, Naira Setrakian
- **Protocol Coordinator**: Rachel Vasquez

CHILDREN'S ONCOLOGY GROUP

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

Funding

- NCTN Operations Center Grant U10CA180886
- NCTN Statistics & Data Center Grant U10CA180899
- St. Baldrick's Foundation
- Blinatumomab provided by Amgen via Collaborative Research and Development Agreement (CRADA) with NCI/CTEP

Questions?

Multiple-Choice Question 1

Which of the following is NOT true of blinatumomab relative to chemotherapy as post-reinduction therapy for HR/IR first relapse of pediatric ALL?

A. **Lower rate of clearance of residual disease**

B. Lower rate of serious adverse events

C. Lower rate of relapse

D. Higher rate of proceeding to HSCT

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Genetic Variants in ALL – Ph+ and Ph-Like

Andre Schuh

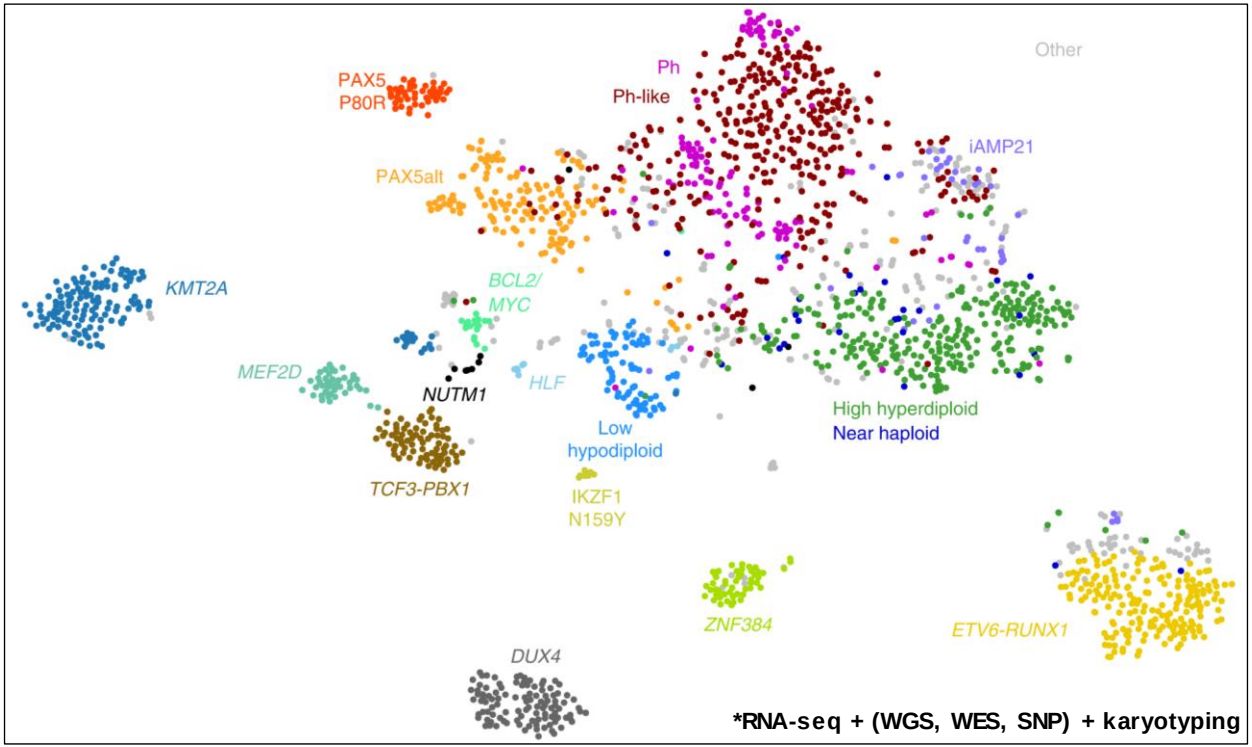
APTITUDE HEALTH

Genetic Variants in ALL: Ph+ ALL and Ph-Like ALL

Andre Schuh
Princess Margaret Cancer Centre
Toronto

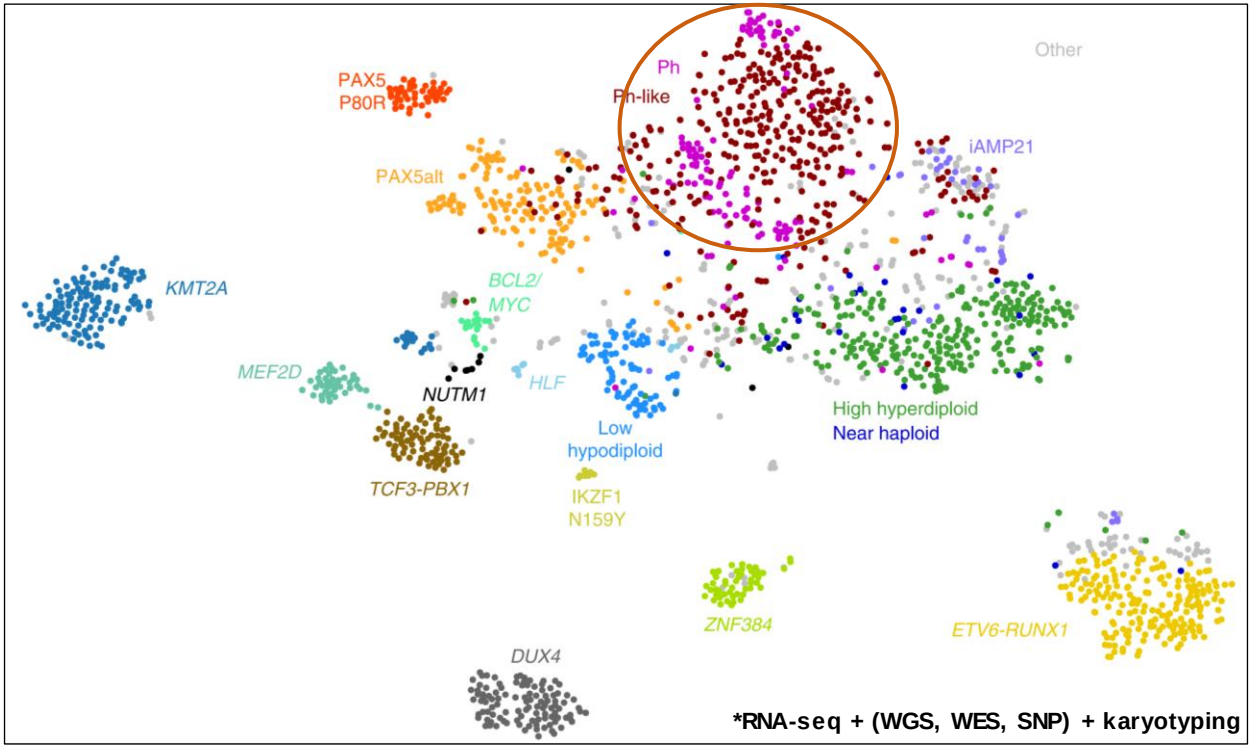
July 8, 2020

Integrative Genetic Profiling* Defines 23 Subtypes of ALL



Gu Z. *et al., Nature Genetics* 2019; 51: 296-307

Integrative Genetic Profiling* Defines 23 Subtypes of ALL



- **Genetic subtype/phenocopy relationships, eg, Ph+ and Ph-like**

Gu Z. *et al., Nature Genetics* 2019; 51: 296-307

Ph+ ALL

- Carries the Philadelphia (Ph) chromosome
- t(9;22)(q34.1; q11.2); *BCR-ABL1*
- Dysregulated activation of ABL1 kinase
- Known since 1970s
- Confers higher risk

Ph-like ALL

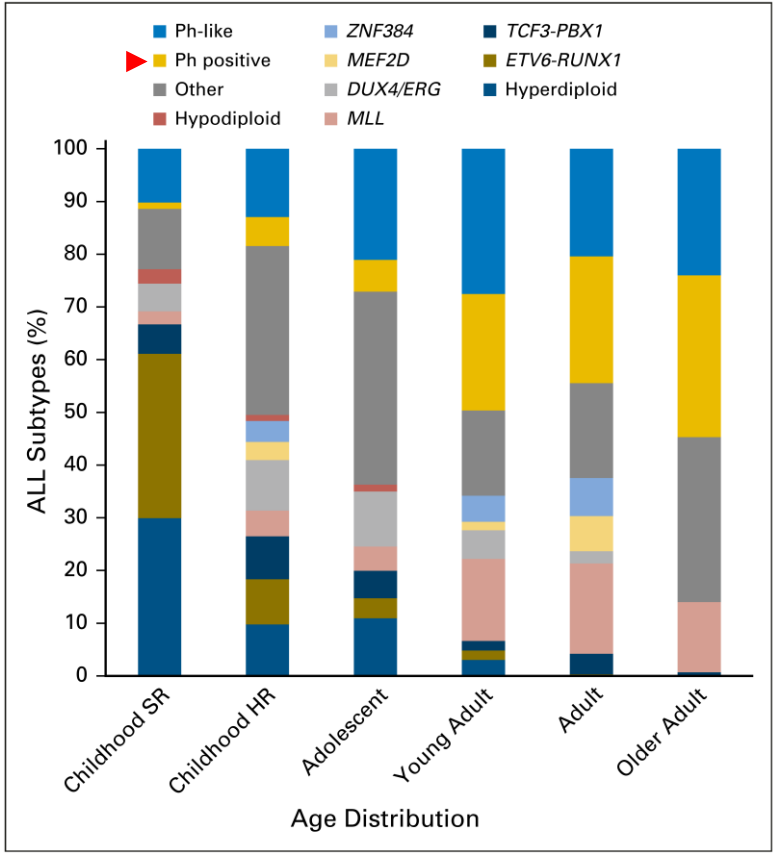
- Ph- ALL subtype with a gene expression profile similar to that of Ph+ ALL, but not carrying the Ph chromosome
- Can carry a variety of alternative kinase-activating rearrangements and mutations, falling largely into ABL and JAK/STAT classes
- First described by 2 groups in 2009
- Confers higher risk?

WHO Classification (2001, 2008, 2016)

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Ph+ ALL

Ph+ ALL Incidence Increases With Age



Iacobucci, I, and Mullighan, CG. *J Clin Oncol* 2017; 35:975-983

Treatment?

Pre-TKI Era

Longstanding "Truths"

- High risk
- Inferior outcomes with conventional ALL chemotherapy
- AlloSCT for all eligible patients

TKI Era

New Questions . . . New Trends

- Which TKI?
- Older patients
- Less intensive or chemo-free strategies, especially in the elderly
- Diminishing role of alloSCT
- Newer approaches to R/R disease
- Bring upfront the drugs that are effective in R/R disease

Pre-TKIs . . .

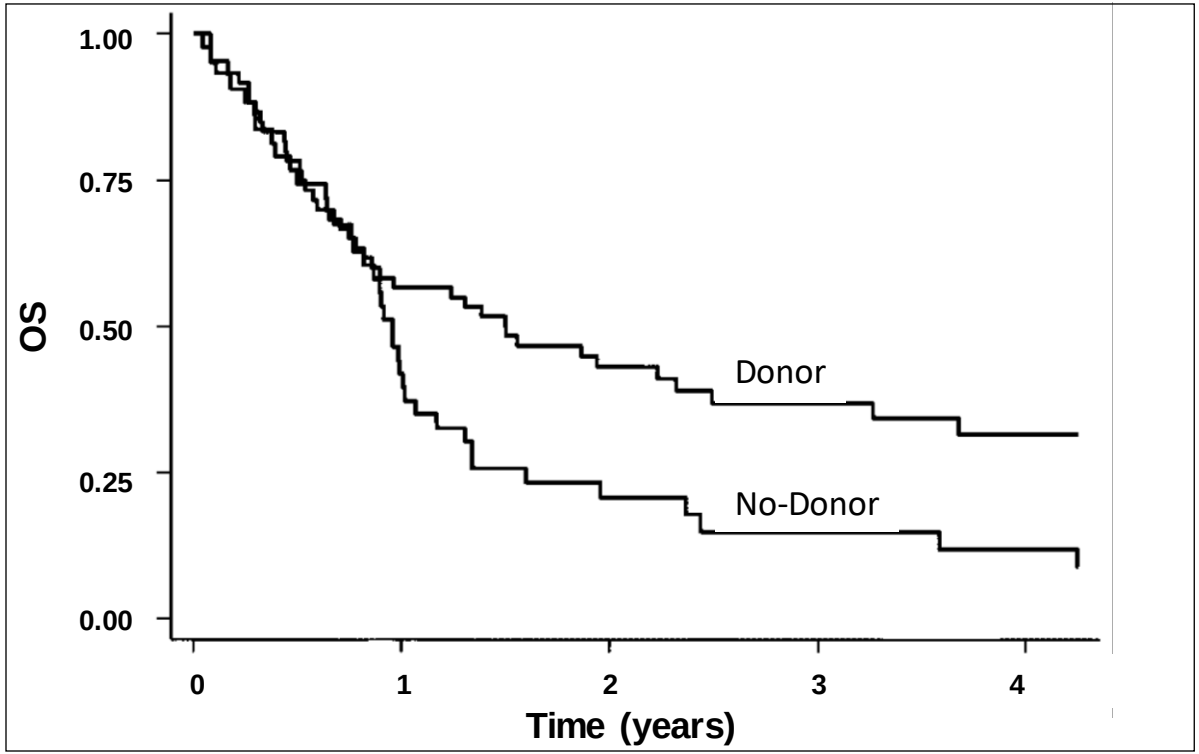
Ph+ ALL associated with an inferior outcome using conventional ALL chemotherapy

Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy Only

Clinical Trial (year)	N	Median Age, [range]	Chemotherapy	CR, %	SCT in CR1, %	OS, %
Gotz (1992)[53]	25	44 [21-74]	BFM	76	8	6 at 40 mo
Larson (1995)[54]	30	32 [16-80]	CALGB	70	NA	16 at 36 mo
Thomas (2001)[6]	51	35 [14-89][a]	LALA	NA	16	10 at 60 mo
Gleissner (2002)[55]	175	45 [15-65]	GMALL	68	NA	15 at 36 mo
Takeuchi (2002)[3]	51	31 [15-59][a]	JALSG	51	NA	5 at 72 mo
Kantarjian (2004)[4]	48	40 [15-92][a]	HyperCVAD	92	23	12 at 60 mo
Pullarkat (2008)[5]	36	47 [17-64]	SWOG	67	NA	8 at 60 mo

Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

Role of AlloSCT, Ph+ ALL, Pre-TKI



Dombret, H. *et al*., *Blood* 2002; 100: 2357-2366

TKI Era . . .

- Imatinib
- Dasatinib
- Ponatinib

Which TKI?

Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy Plus Imatinib

Clinical Trial (year)	N	Median Age, [range]	Chemo-therapy	TKI, mg/d	CR, %	CMR, %	SCT in CR1, %	OS, %
Imatinib								
Yanada (2006)[56]	80	48 [15-63]	JALSG ALL202	IM 600	96	26 at CR	49	76 at 12 mo
Wassmann (2006)[9]	45	41 [19-63]	GMALL	IM 400	96	27 at CR	80	43 at 24 mo
Fielding (2014)[10]	175	42 [16-64]	UKALLXII/ ECOG2993	IM 400-600	92	NA	46	38 at 48 mo
Chalandon (2015)[13]	135	49 [18-59]	Low-int induction	IM 800	98	29 at ~3 mo	74	48 at 60 mo
	133	45 [21-59]	High-int induction	IM 800	91	23 at ~3 mo	79	43 at 60 mo
Bassan (2010)[57]	59	45 [20-66]	NILG	IM 600	92	40 at ~3 mo	72	38 at 60 mo
Daver (2015)[11]	54	51 [17-84]	HyperCVAD	IM 400-800	93	45 at ~3 mo	30	43 at 60 mo
De Labarthe (2007)[58]	45	45 [16-59]	GRAAPH 2003	IM 600-800	96	NA	49	51 at 18 mo
Lim (2015)[12]	87	41 [16-71]	Multiagent chemo	IM 600	94	NA	64	33 at 60 mo

Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

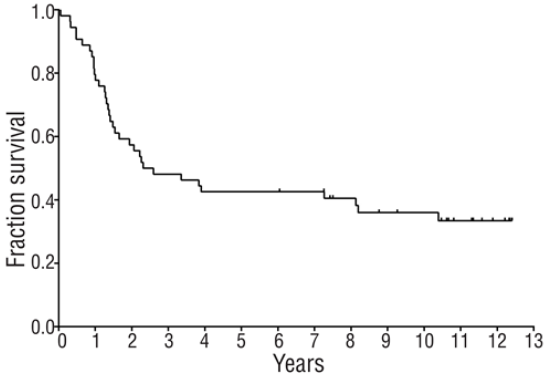
Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy Plus Nilotinib, Dasatinib, or Ponatinib

Clinical Trial (year)	N	Median Age, [range]	Chemo-therapy	TKI, mg/d	CR, %	CMR, %	SCT in CR1, %	OS, %
Nilotinib								
Kim (2015)[23]	90	47 [17-71]	Multiagent chemo	NIL 800	91	77 at ~3 mo	63	72 at 24 mo
Dasatinib								
Foa (2011)[31]	53	54 [24-76]	Prednisone	DAS 100-140	93	22 at CR	NA	69 at 20 mo
Ravandi (2015)[30]	72	55 [21-80]	HyperCVAD	DAS 100	96	65 at ~3 mo	17	46 at 60 mo
Ravandi (2016)[59]	94	44 [20-60]	HyperCVAD	DAS 70-100	88	NA	47	69 at 36 mo
Ponatinib								
Jabbour (2015)[36,37]	64	48 [21-80]	HyperCVAD	PON 30-45	100	77 at ~3 mo	16	78 at 36 mo

Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

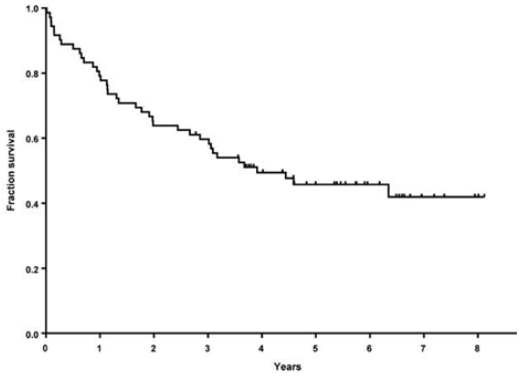
OS, HyperCVAD Plus Imatinib, Dasatinib, or Ponatinib

Imatinib: 5-yr OS, 43%



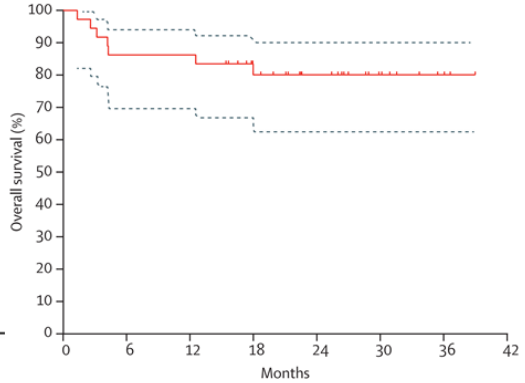
2001-2006
n=54
51 (17-84)

Dasatinib: 5-yr OS, 46%



2006-2012
n=72
55 (21-80)

Ponatinib: 3-yr OS, 79%*



2011-2013
n=53
54 (25-80)

***Estimated 5-yr OS, 71%**

Daver, N. *et al. Haematologica* 2015; 100:653-61
Ravandi, F. *et al. Cancer* 2015; 121:4158-64
Jabbour, E. *et al. Lancet Hematology* 2015; 16:1547-55
Jabbour, E. *et al. Clin Lymph Myel Leuk* 2018; 18:257-65

OS, by Molecular Response, HyperCVAD Plus TKI

Univariate analysis, RFS and OS

Characteristic	Risk of relapse or death			Risk of death		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (y)	1.01	0.99-1.04	.27	1.02	0.99-1.04	.15
Log WBC	1.56	0.95-2.56	.08	1.43	0.85-2.38	.18
Platelets	1.00	1.00-1.00	.89	1.00	1.00-1.01	.75
Absolute PB blasts	1.00	1.00-1.01	.15	1.00	0.99-1.00	.68
BM blasts (%)	0.99	0.98-1.00	.18	0.99	0.97-1.00	.05
Performance status ≥2	3.22	1.31-7.90	.01	1.97	0.75-5.13	.17
CD20 expression ≥20%	1.31	0.68-2.53	.42	1.46	0.71-3.00	.30
CNS leukemia	1.96	0.81-4.70	.13	1.24	0.43-3.56	.69
p190 *BCR-ABL1* transcript	1.02	0.49-2.16	.95	1.03	0.47-2.27	.95
Cytogenetics: Ph alone vs Ph^+ other	0.42	0.19-0.93	.03	0.46	0.20-1.06	.07
TKI: ponatinib vs dasatinib vs imatinib	0.59	0.37-0.94	.03	0.52	0.31-0.88	.02
CMR at 3 mo	0.43	0.21-0.78	.01	0.42	0.21-0.82	.01

WBC, white blood cell; PB, peripheral blood; BM, bone marrow; CNS, central nervous system.

Short, N. *et al. Blood* 2016; 128: 504-7

Meta-analysis:
Ponatinib vs 1st/2nd-Generation TKIs in Ph+ ALL

Table 2 Meta-analysis Results

Outcomes	All (n = 26 Studies)	Ponatinib (n = 1 Study)	First- and Second-Generation TKIs (n = 25 Studies)
Response			
CMR	34 (26-43)	79 (66-89)[a]	32 (25-40)
Survival			
2-y OS	59 (53-65)	83 (70-92)[a]	58 (53-63)
3-y OS	52 (43-60)	79 (66-89)[a]	50 (42-58)

Data presented as % (95% confidence interval).
Abbreviations: CMR = complete molecular response; OS = overall survival; TKI = tyrosine kinase inhibitor.
[a]For subgroups with only 1 observation, 95% CIs were calculated assuming a binomial distribution.

Jabbour, E. *et al. Clin Lymph Myel Leuk* 2018; 18:257-65

Why Is Ponatinib Superior to Other TKIs?

- Deeper and more rapid molecular response; a larger proportion of patients achieve MMR and CMR
- Relapse after treatment with imatinib, dasatinib, and nilotinib is often associated with the outgrowth of (pre-existing?) leukemic clones bearing *BCR-ABL1* KD mutations conferring TKI resistance
- By NGS, these resistance mutations are often present well before overt hematologic relapse, and may be present at the time of diagnosis

Pfeifer, H. *et al. Blood* 2007; 110: 727-34
Soverini, S. *et al. Leukemia* 2016; 30:1615-19
Rousselot, P. *et al. Blood* 2016; 128:774-82
DeBoer, R. *et al. Leuk Lymph* 2016; 57: 2298-2306

Why Less Intensive Approaches?

Baseline facts

- Aging population and increasing incidence of Ph+ ALL
- Increasing toxicity of chemotherapy in the elderly (especially if “pediatric-inspired” protocols are used)
- Increased toxicity when TKIs added to conventional chemotherapy regimens

Taken together with

- Dramatically improved outcomes when TKIs added

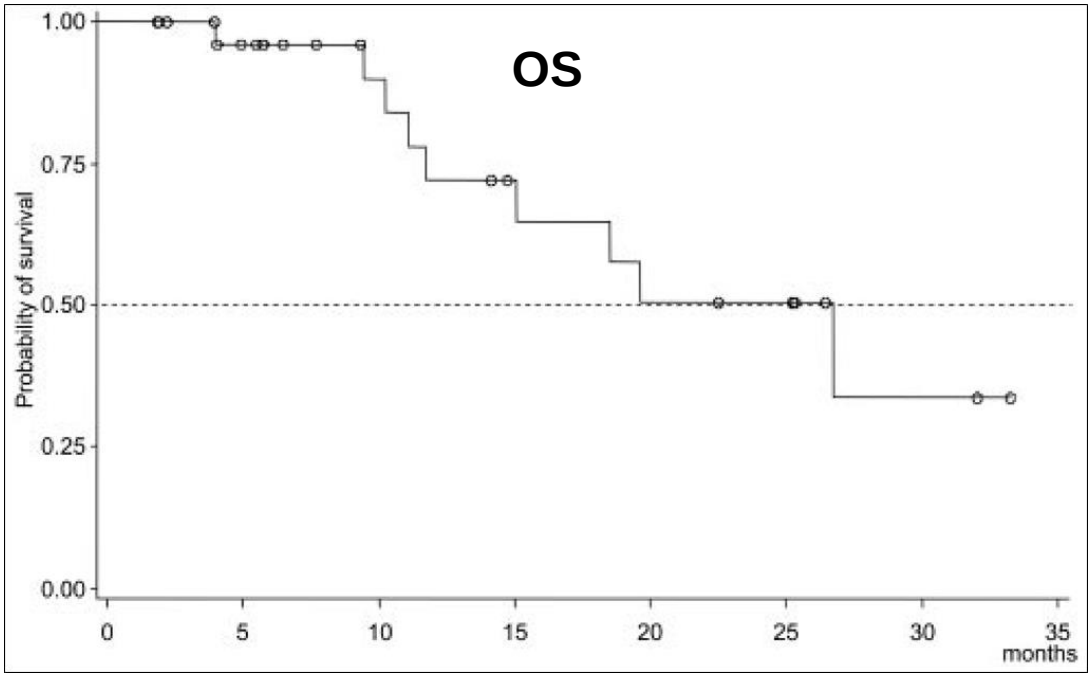
Opportunities for less-toxic, chemo- or steroid-sparing approaches?

Reduced-Intensity Approaches to Ph+ ALL: Low-Intensity Chemotherapy/Steroids Plus TKI

Clinical Trial (year)	N	Age, median [Range]	Chemotherapy	TKI, mg/d	CR, %	SCT in CR1, %	OS, %
Ottmann (2007)[15]	28	66 [54-79]	GMALL	IM 400	96	0	42 at 24 mo
Vignetti (2007)[14]	30	69 [61-83]	Prednisone	IM 800	100	0	50 at 24 mo
Delannoy (2006)[60]	29	66 [58-78]	GRALL-AFR09	IM 600	72	0	66 at 12 mo
Rousselot (2016)[32]	71	69 [59-83]	EWALL-Ph-01	DAS 100-140	96	10	36 at 60 mo
Ottmann (2014)[24]	47	65 [55-85]	EWALL-Ph-02	NIL 800	87	20	67 at 24 mo

Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

Imatinib Plus Prednisone Only



GIMEMA LAL0201-B Study: n=30, median age 69 (range 61-83)
Imatinib 800 mg/day plus prednisone 40 mg/m^2/day × 45 days
CR rate 97%; well tolerated; mostly done as OP; median OS ~20m

Vignetti, M. *et al. Blood* 2007; 109:3676-78

- Less intensive induction regimens containing a TKI are feasible, less toxic, and associated with very high CR rates

- In absence of subsequent (or simultaneous) chemotherapy, however, molecular responses and OS are inferior

- Simultaneous or subsequent chemotherapy results in better CMR rates and improved OS, similar to that obtained with more-intensive chemotherapy

Vignetti, M. *et al. Blood* 2007; 109:3676-78
Ottmann, O. *et al. Cancer* 2007; 109:2068-76
Chalandon, Y. *et al. Blood* 2015; 125:3711-3719

Relapsed Disease . . .

Ph+ ALL

- CR rates only moderate; outcomes post-relapse poor

Traditionally . . .

- Salvage chemotherapy
- Alternative TKI on the basis of *BCR-ABL1* KD mutation analysis
- AlloSCT

More recently . . .

- Blinatumomab, inotuzumab, CAR T cells
- Alternative TKI on the basis of *BCR-ABL1* KD mutation analysis
- AlloSCT

Blinatumomab vs Inotuzumab vs CAR T Cells for R/R Ph+ ALL

Blinatumomab

ALCANTARA study (Martinelli G, *et al. JCO* 2017: 35: 1795-1802)

- Open-label, single-arm, multicenter, phase II study, at 19 European and US centres
- Adult (age ≥18) Ph+ BCP-ALL relapsed after, or refractory to, at least 1 second-generation or later TKI, or intolerant to second-generation or later TKIs, and intolerant or refractory to imatinib
- 45 very heavily pretreated patients
  - 46% *ABL1* KD mutations (27% T315I)
  - 44% prior alloSCT
  - 38% ≥3 prior TKIs (51% prior ponatinib)

Blinatumomab

ALCANTARA study (Martinelli G, *et al. JCO* 2017: 35: 1795-1802)

- CR/CRh within 2 cycles: 36%
- CR/CRh in patients with
  - *ABL1* KD mutation: 35%
  - *T315I* mutation: 40%
  - ≥3 prior TKIs: 47%
  - Prior ponatinib: 35%
- Complete MRD response: 88%
- AlloSCT realization: 25%

Inotuzumab

INO-VATE study (Kantarjian H, *et al. N Engl J Med* 2016; 375: 740-53)

- Phase III multicenter (18 countries), randomized study of R/R B-ALL (both Ph+ and –), randomized from 2012-2014 to inotuzumab vs SOC salvage chemotherapy
- n=279 overall; of the first 109 patients in each group . . .
  14/109 (13%) Ph+ inotuzumab
  18/109 (17%) Ph+ SOC
- CR/CRi: 78.6% vs 44.4%, but PFS only ~4 months

Blinatumomab vs Inotuzumab, R/R Ph+ B-ALL

	Blinatumomab*,#	Inotuzumab^
No. treated	45	38
CR/marrow CR (%)	16 (36)	25 (66)
MRD- in CR, %	88	63
Median OS, months	7.1	8.1
Proceeding to alloSCT, %	44	32

*From ALCANTARA study.
^From 1010 and 1022 (INO-VATE) studies.
#More heavily pretreated.

Kantarjian, H. *et al. N Engl J Med* 2016; 375: 740-53
Martinelli, G. *et al. JCO* 2017: 35: 1795-1802
Stock, W. *et al. JCO* 2018; 36: (2018 suppl. abstr. 7030)

Phase I study, MSKCC, patients with heavily pretreated R/R B-ALL treated with autologous 19-28z CAR T cells

2010-2016, 83 patients enrolled;
53 patients infused (64%)

~1/2 of patients had low tumor burden (<5% marrow blasts)

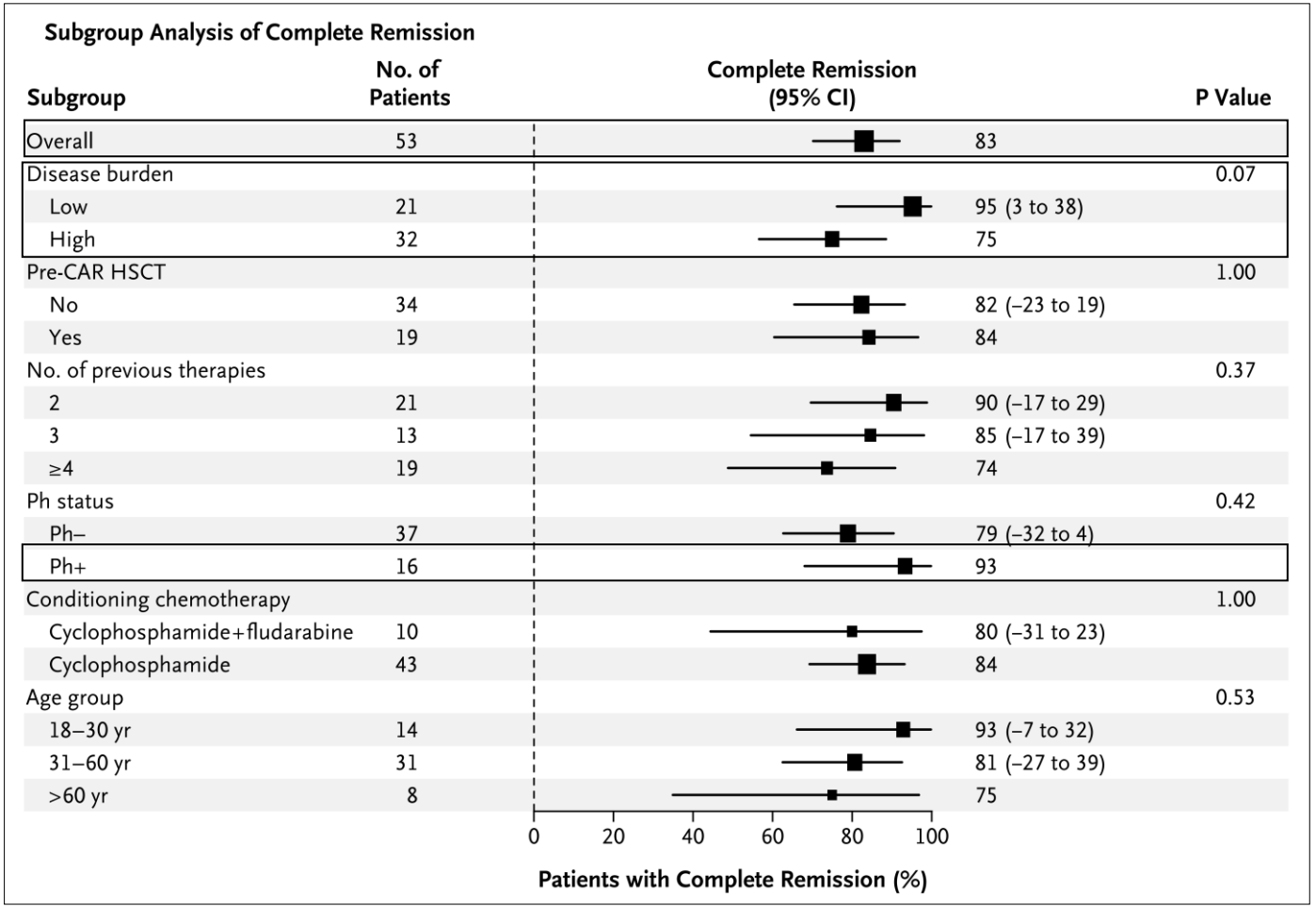
Of 53 treated patients, 16 (30%) were Ph+

- **Median no. prior TKIs: 2.5 (range 1-4)**
- **5 patients with *T315I* mutation**
- **10/16 patients refractory to ponatinib**

Table 1. Characteristics of the 53 Patients at Baseline.*

Characteristic	Value
Age	
Median (range) — yr	44 (23–74)
Distribution — no. (%)	
18–30 yr	14 (26)
31–60 yr	31 (58)
>60 yr	8 (15)
No. of previous therapies — no. (%)	
2	21 (40)
3	13 (25)
≥4	19 (36)
Primary refractory disease — no. (%)	
Yes	12 (23)
No	41 (77)
Previous allogeneic HSCT — no. (%)	
Yes	19 (36)
No	34 (64)
Previous treatment with blinatumomab — no. (%)	
Yes	13 (25)
No	40 (75)
Pretreatment disease burden†	
Median bone marrow blasts (range) — %	63 (5–97)
Bone marrow blasts — no. (%)	
≥5%	27 (51)
<5% with extramedullary disease	5 (9)
≥0.01% and <5%	15 (28)
<0.01%	6 (11)
Philadelphia chromosome–positive — no. (%)	
Yes	16 (30)
No	37 (70)

Park, J. *et al. N Engl J M*ed 2018; 378:449-59



Park, J. *et al. N Engl J Med* 2018; 378:449-59

Blinatumomab vs Inotuzumab vs CAR T?

- Availability
- CR rates by ITT
- MRD negativity
- Relative toxicity
- Tumor burden considerations
- Need for subsequent alloSCT?
- First vs subsequent relapse
- Infrastructure and training requirements
- FACT/IEC accreditation requirements
- Cost

Going forward . . .

- Several studies evaluating upfront use of blinatumomab or inotuzumab +/– chemo plus TKIs . . .

Numerous questions remain

- Intensive chemotherapy, vs less-intensive chemo vs chemo-free approaches?
- Which TKI (dasatinib vs ponatinib)?
- Optimizing TKI plus blinatumomab etc for relapsed disease (we and others use both drugs simultaneously)
- Sequencing of blinatumomab and inotuzumab in the same patient?
- Role of blinatumomab in MRD+, Ph+ ALL in CR?
- Ongoing role of alloSCT in TKI/immunotherapy era?
- Optimized molecular monitoring strategy and when to switch TKIs
- Role of CAR T cells?

How Do I Treat?

Untreated Ph+ B-ALL . . .

- At PM, all ALLs receive the pediatric DFCI 01-175 ALL protocol, with PM modifications for age (<60, ≥60) and Ph status
- Ph+ ALLs receive modified DFCI plus imatinib (400 mg/600 mg) or dasatinib (100 mg)
- *BCR-ABL1* transcripts are measured by PCR at diagnosis and postinduction, and then every 3 months
- Aim for PCR negativity, or at least ~4-log reduction (or better) by 3-4 months
- AlloSCT offered only to patients not achieving molecular targets
- Hope to initiate upfront study of ponatinib plus blinatumomab

How Do I Treat?

Relapsed Disease . . .

- TKI defined by *BCR*-ABL1 KD mutation analysis
- TKI plus blinatumomab, followed by alloSCT in fit patients age ≤70-75
- In absence of alloSCT, lifelong TKI
- Inotuzumab is available, but is generally not used in this indication due to perceived VOD risk
- CAR T-cell therapy: Kymriah is approved in Canada and will be available soon (at selected centres) up to age 25
- In the meantime, and for older adults, CAR T-cell therapy is available via clinical trial

Ph-like (BCR-ABL like) ALL

Ph-like (BCR-ABL like) ALL

- Ph- subtype characterized by a gene expression profile similar to Ph+ ALL and a range of kinase-activating rearrangements and mutations, and associated with a poor outcome
- Frequently bear alterations of B-lymphoid transcription factor genes (most commonly *IKZF1*)
- ~1/2 are surface CRLF2+
- 10%–20% of standard- and high-risk childhood B-ALL, with an increasing prevalence with increasing age

Mullighan CG, *et al*., *NEJM*. 2009;360:470-480
Den Boer ML, *et al*., *Lancet Oncol*. 2009;10:125-134
Roberts KG, *et al*., *NEJM*. 2014; 371:1005–1015

Ph-Like (BCR-ABL like) ALL

Incidence

Prevalence and clinical outcomes of Ph-like ALL.

Clinical Trial	Age (yrs)	NCI Risk Group	Ph-like prediction	Ph-like ALL prevalence (%)	Total cases studied	Treatment Outcome
COG P9906	1–21	HR	PAM	20.5%	200	5 yr EFS 25.0%
COG AALL0232	1–30	HR	PAM	14.0%	572	5 yr EFS 62.6%
COG AALL0932	1–30	SR	LDA	17.0%	505	N/A
COG AALL1131	1–30	HR	LDA	22.4%	884	N/A
St. Jude Total XV	1–18	All	PAM	11.6%	344	5-yr EFS 90.0%
COALL 92/97	0–18	All	HC	19%	154	5 yr DFS 59.5%
DCOG ALL 8/9	0–18	All	HC	15%	92	5 yr DFS 57.1%
GMALL	16–84	All	PAM	12.6%	207	5-yr DFS 26%
HOVON	16–71	All	HC	16.5%	127	5-yr EFS ~25%
Multiple US	21–39	All	LDA	27.9%	344	5-yr EFS 24.1%
	40–59			20.4%	304	5-yr EFS 21.4%
	60–86			24.0%	150	3-yr EFS 8.0%
MDACC	15–49	All	PAM/LDA	42.0%	80	5-yr OS 23%
	40–84			24.0	68	
Multiple US	18–39	All	LDA	25.9%	27	N/A
	40–88			18.3%	60	

Roberts, K., *Best Pract & Res Clin Haem* 2017; 30:212-221

Baseline Characteristics of Ph-Like ALL, Categorized as *CRLF2*+ and Non-*CRLF2*

	Ph-like ALL, N = 56		
	CRLF2$^+$	Non-CRLF2	*P*
N	37	19	
Age, y, median (range)	35 (18-71)	26 (15-62)	.12
Sex, n (%)			
Female	10 (27)	9 (47)	.13
Male	27 (73)	10 (53)	
Ethnicity, n (%)			
White	8 (22)	5 (26)	
Hispanic	29 (78)	9 (48)	.008
African American	—	2 (10)	
Asian	—	3 (16)	
Cytogenetics, n = 49, n (%)			
Diploid	15 (45)	4 (25)	.49
Hyperdiploid	6 (18)	4 (25)	
Hypodiploid	3 (9)	1 (6)	
Miscellaneous	9 (28)	7 (44)	
Presenting features			
WBC, $\times 10^9$/L, median (range)	27.7 (1-603)	5.3 (1-81)	.001
Platelet count, $\times 10^9$/L, median (range)	36 (1-169)	41 (8-238)	.55
Hemoglobin, g/dL, median (range)	9.4 (6.5-13.7)	9.2 (5.7-15.1)	.19
Bone marrow blast %, median (range)	92 (62-98)	87 (17-99)	.17
CNS involvement at Dx, n (%)	5 (14)	3 (16)	.82
IKZF1 deleted, n = 41, n (%)	21/25 (84%)	7/16 (44%)	.014
Treatment received, n (%)			
Hyper-CVAD based	29 (78)	8 (42)	.007
Augmented BFM	8 (22)	11 (58)	

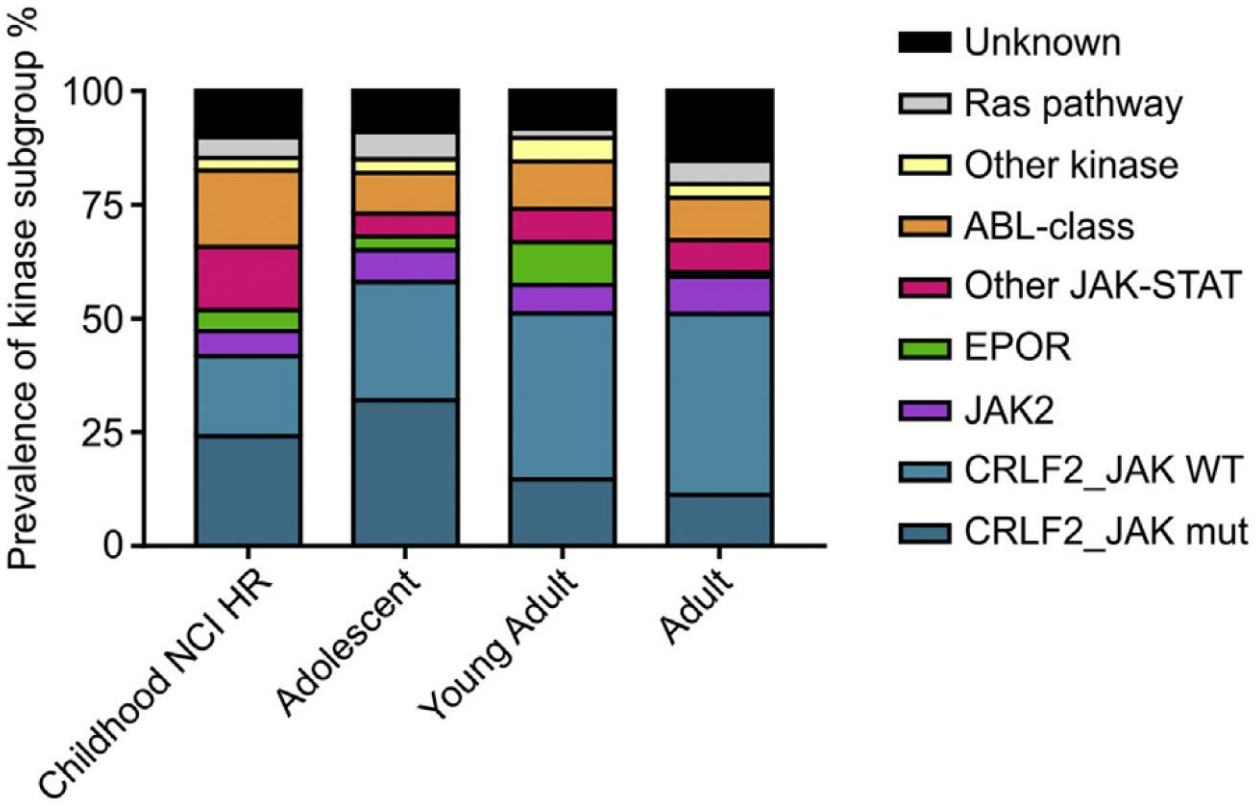
Jain, N *et al. Blood* 2017; 129:572-881

Ph-Like (BCR-ABL like) ALL

Chromosomal Rearrangements/Fusions

ABL Class	*ABL1* *ABL2* *CSF1R* *LYN* *PDGFRA* *PDGFRB*
JAK/STAT	*CRLF2* *JAK2* *EPOR* *TYK2* *IL2RB* *JAK1/3* *IL7R* *SH2B3*
Other	*NTRK3* *FLT3* *FGFR1* *BLNK*

Rearrangements Vary With Age



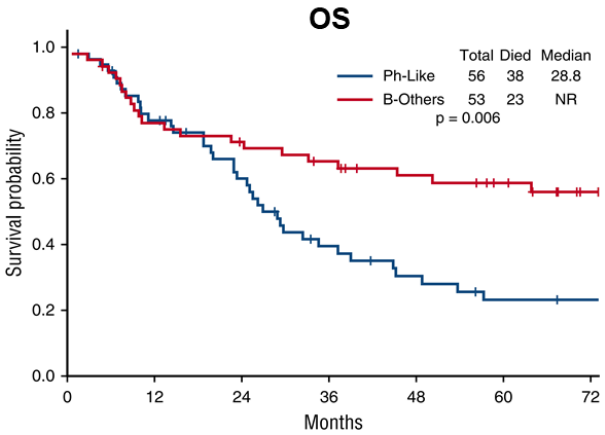
Roberts, K., *Best Pract & Res Clin Haem* 2017; 30:212-221

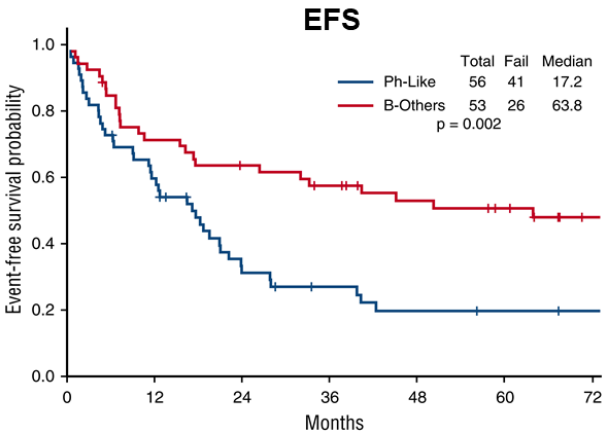
Responses in Ph-Like ALL, Ph+ ALL, and B-Other ALL

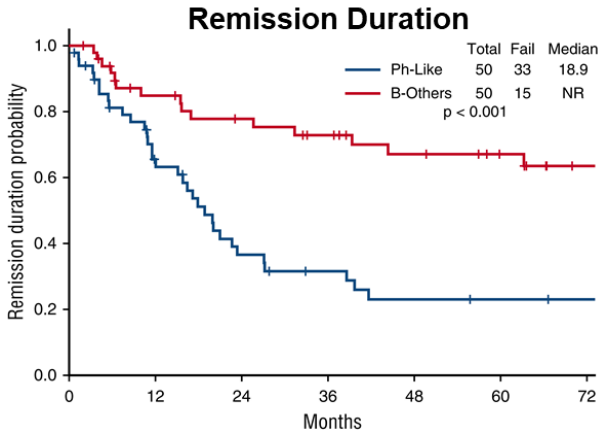
	B-ALL categories, N = 155				
	Ph-like	Ph$^+$	B-other	*P* (all 3 groups)	*P* (Ph-like vs B-other)
N	56 (33.5 [15-71])	46 (49 [22-84])	53 (38 [15-79])		
CR/CRp, n (%)	50 (89)	43 (93)	50 (94)	.57	.34
MRD assessed at CR, n = 98, n (%)	(33.5 [15-71])	(49 [22-84])	(38 [15-79])		
MRD$^+$	23 (70)	15 (44)	4 (13)	<.001	<.001
MRD$^-$	10 (30)	19 (56)	27 (87)		

Jain, N *et al. Blood* 2017; 129:572-881

OS, EFS, and Remission Duration, Ph-Like vs B-Other





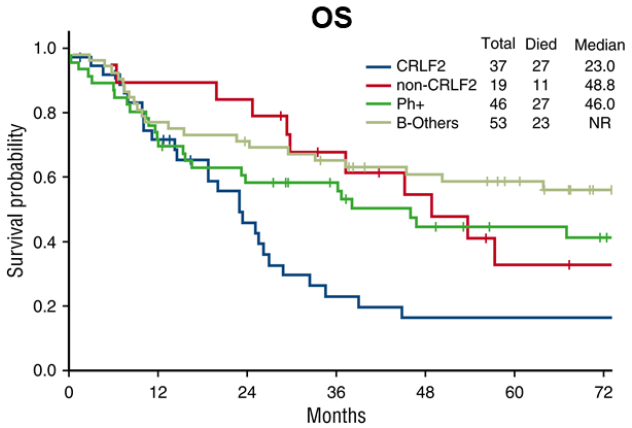


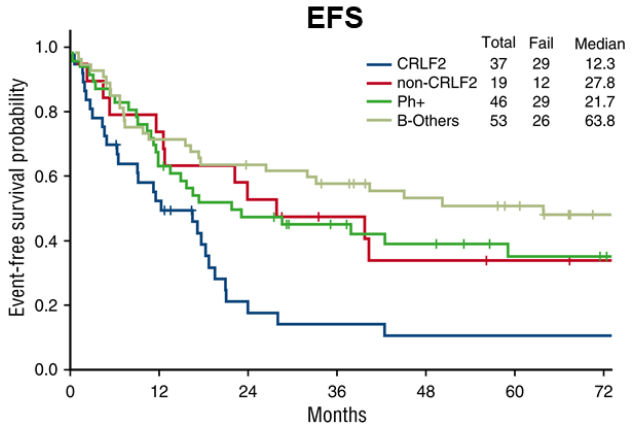
Ph-like
n=56; median age 33.5 (15-71)
HyperCVAD, 37 (66%)
Augmented BFM, 19 (34%)

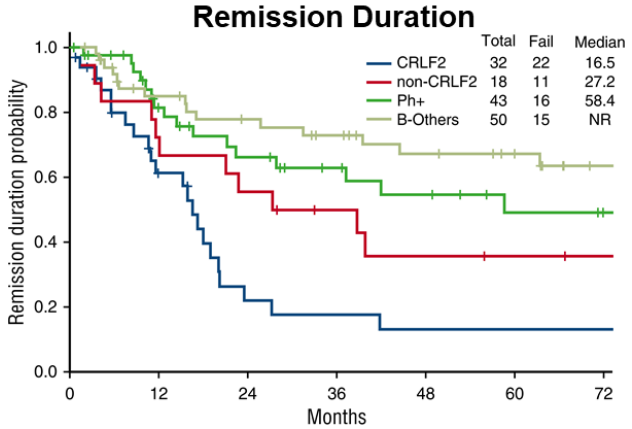
B-other
n=53; median age 38 (15-79)
HyperCVAD, 41 (77%)
Augmented BFM, 12 (23%)

Jain, N *et al. Blood* 2017; 129:572-881

OS, EFS, and Remission Duration, *CRLF2*/Non-*CRLF2* Ph-Like vs Others







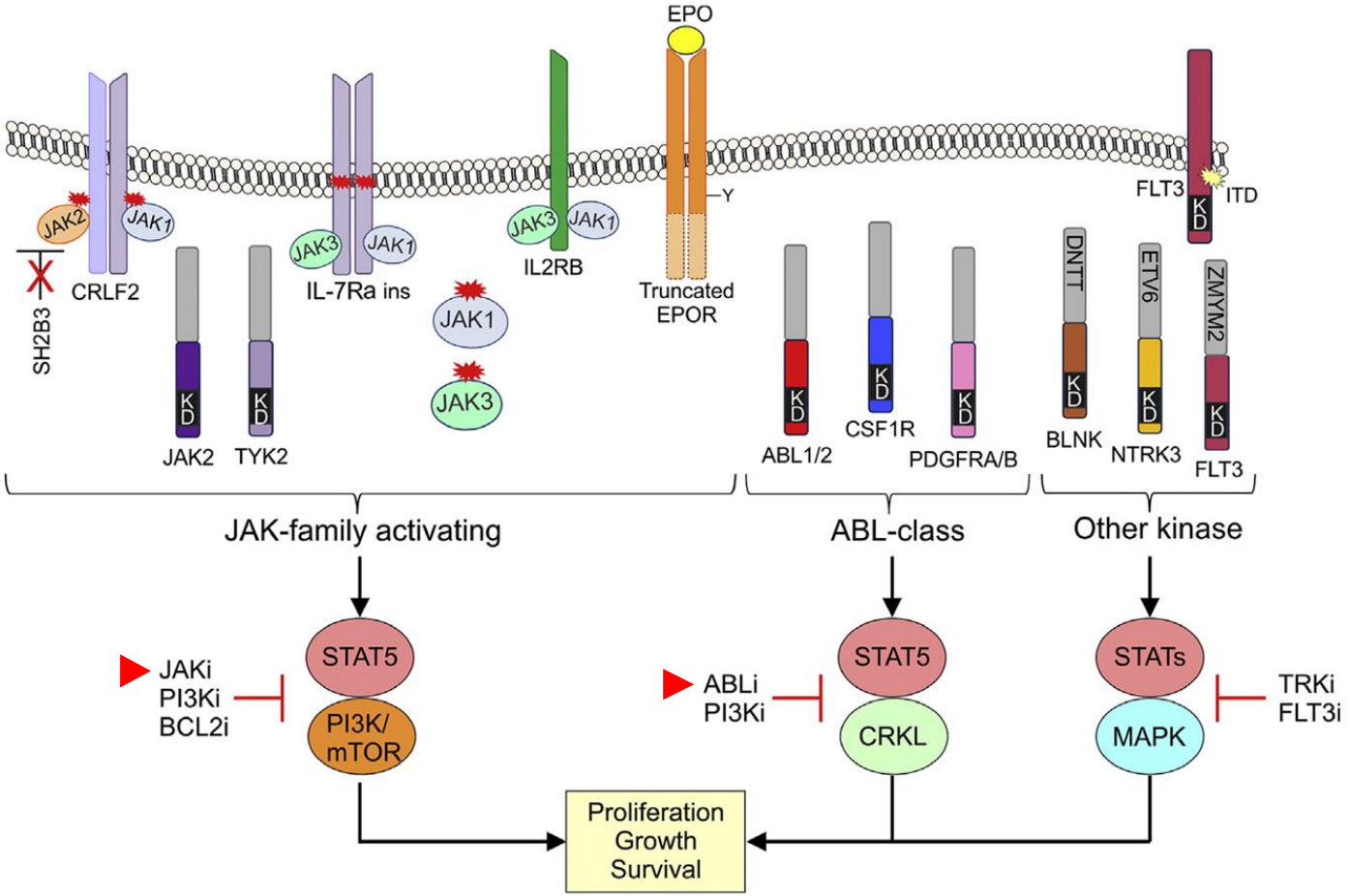
OS:
CRLF2 vs B-other, p=.001
CRLF2 vs non-*CRLF2*, p=.01

EFS:
CRLF2 vs B-other, p=.001
CRLF2 vs non-*CRLF2*, p=.01
CRLF2 vs Ph+, p=.02

Remission Duration:
CRLF2 vs B-other, p<.001
CRLF2 vs Ph+, p=.001
Non-*CRLF2* vs B-other, p=.03

Jain, N *et al*. *Blood* 2017; 129:572-881

Potential for Therapeutic Intervention



Roberts, K., *Best Pract & Res Clin Haem* 2017; 30:212-221

Does Intervention Change Outcome?

- Preclinical and isolated anecdotal reports
  Eg, Tanasi I, et al. *Blood* 2019; 134:1351-1355
- Numerous ongoing clinical trials
  - TKI
  - JAK inhibitor
  - Blinatumomab, etc
  - Others
- AlloSCT

Status at PM . . .

- *CRLF2* flow cytometry routine
- Other testing is not available outside of clinical trial
- Both PM/UHN and HSC are developing algorithms; Canada-wide initiative
- RNA-Seq possible on a research basis at PM/UHN and HSC
- No clinical intervention guidelines (ruxolitinib, dasatinib, alloSCT) formalized yet
- *CRLF2*+ patients are currently being referred to alloSCT in CR1
- Anecdotal use of imatinib or of ruxolitinib

Question 1:

Regarding Ph+ve ALL in adults, which of the following is true?

1. patients in CR should proceed to alloSCT, if at all possible
2. MRD positivity at the post induction time-point is most predictive of outcome
3. incidence increases with age
4. all TKIs are essentially equal
5. concurrent use of blinatumomab and a TKI is excessively toxic

Question 2:

Regarding Ph-like ALL in adults, which of the following is true?

1. in contrast to Ph+ve ALL, the incidence of Ph-like ALL decreases with age
2. CRLF2+ and non-CRLF2 cases have similar presentations
3. CRLF2+ cases are less likely to carry JAK mutations
4. the OS of non-CRLF2 Ph-like cases is similar to that of Ph+ ALL
5. achievement of CR and post-induction MRD negativity is similar in Ph-like and Ph+ ALL

Thank You!
Questions?
Comments?

Global Leukemia Academy

Panel Discussion on the Role of HSCT

APTITUDE HEALTH®

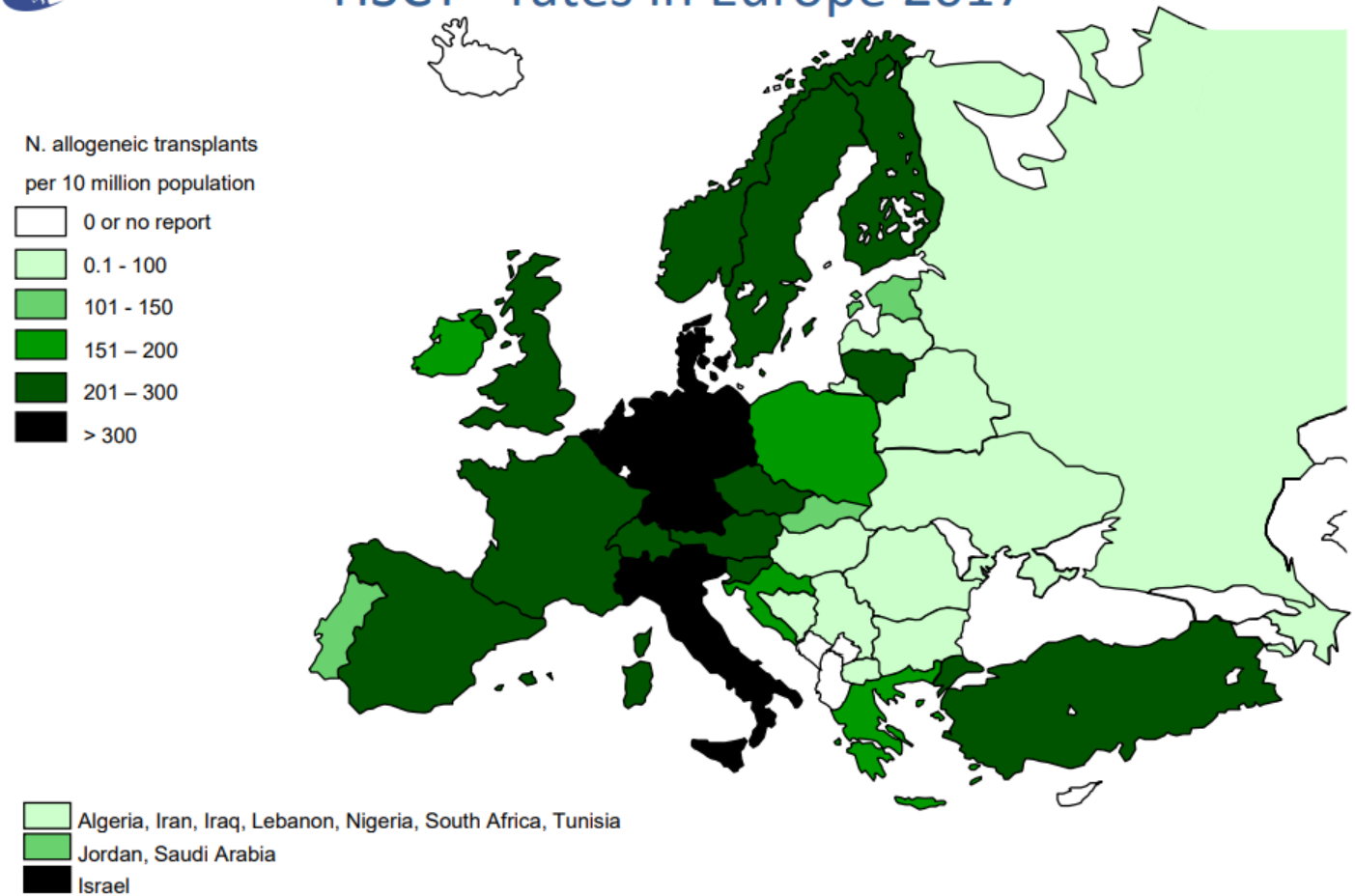
Global Leukemia Academy

Experience of HSCT in the Region

Fatih Demirkan

APTITUDE HEALTH®

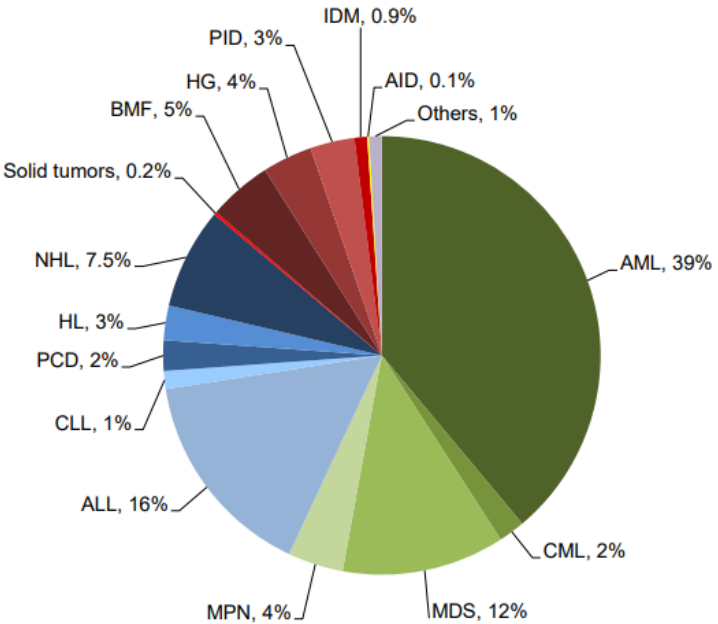
HSCT - rates in Europe 2017



EBMT Activity Survey 2017 https://www.ebmt.org/sites/default/files/2019-09/Transplant%20Activity%20Survey%202017%20Summary.pdf

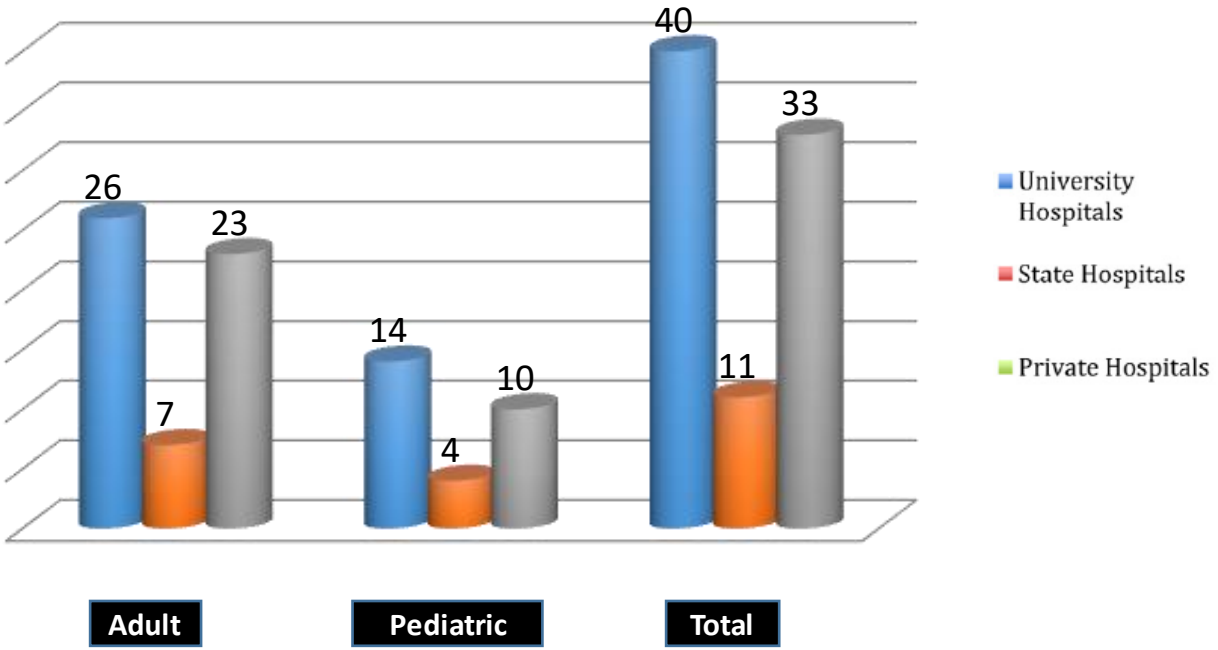
EBMT 2017: alloSCT

Allogeneic HSCT in Europe 2017
1st HSCT



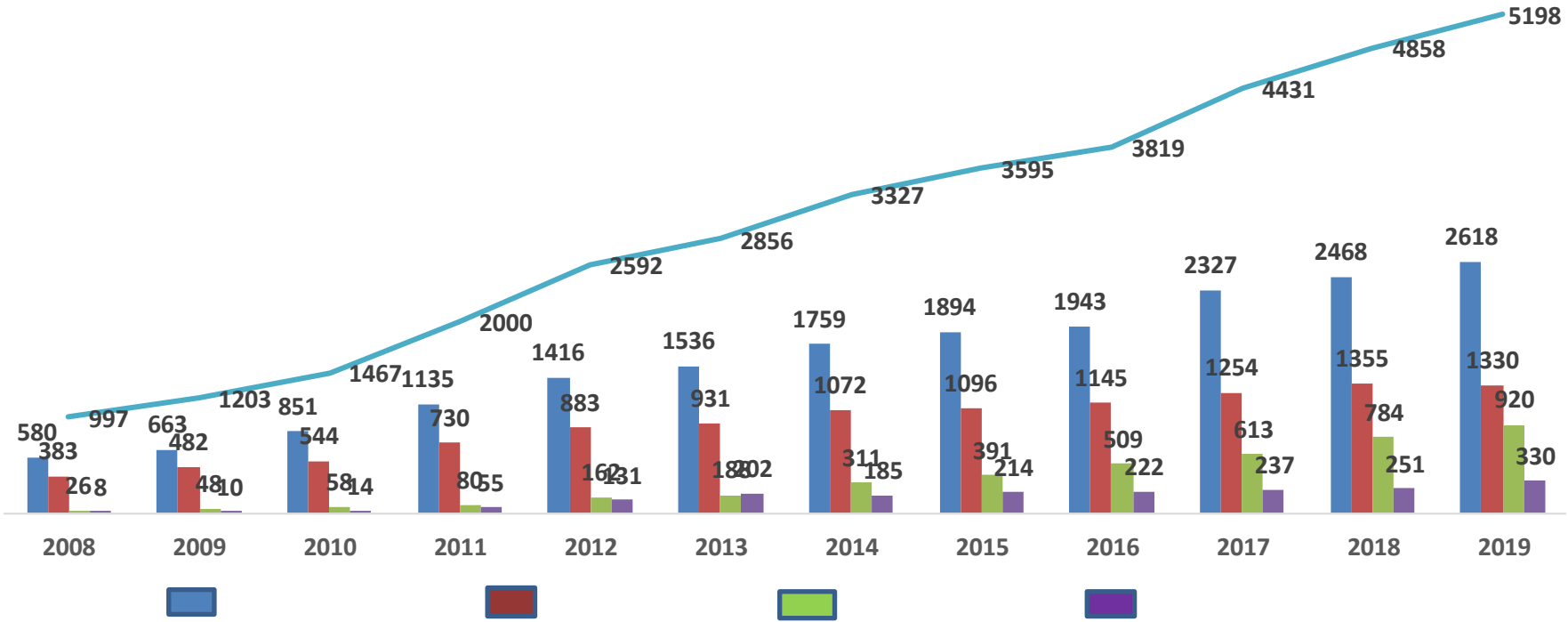
EBMT Activity Survey 2017 https://www.ebmt.org/sites/default/files/2019-09/Transplant%20Activity%20Survey%202017%20Summary.pdf

Turkey: Distribution of transplant centers according to type of institution – 2017



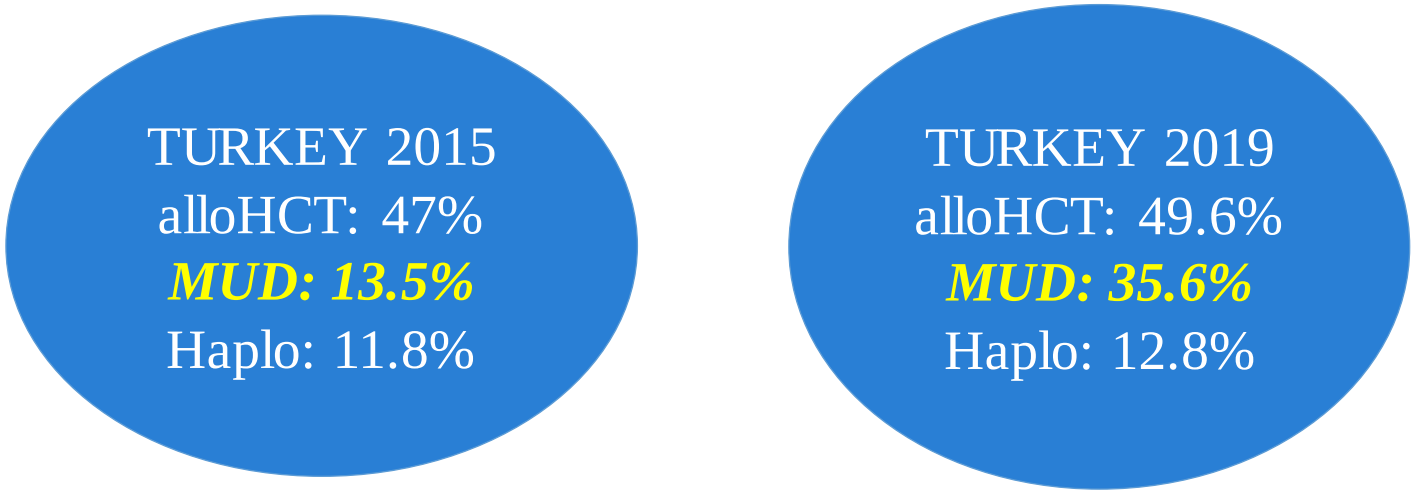
Personal communication from Dr Demirkan.

Turkey: HSCT activity compared with HLA compatibility (2008–2019)



Personal communication from Dr Demirkan.

HSCT: Matched unrelated donor (2014 vs 2019)



Personal communication from Dr Demirkan.

Turkish National Donor Registry (TÜRKÖK)

- Established April 2015
- DONOR POOL: 590,000
- Donor candidates between 18 and 25 years old: 25.8%

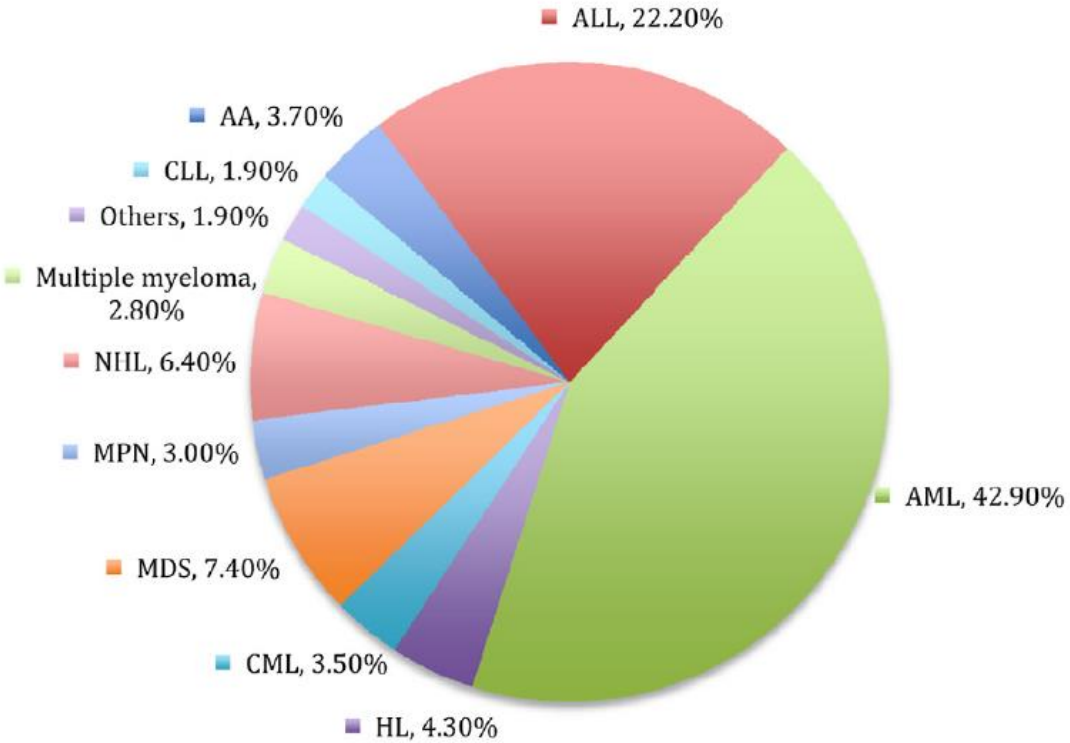
➢2015–2020 FEB

  ➢1850 TRANSPLANTATIONS

- 2019 YEAR– 864 TRANSPLANTATIONS

Personal communication from Dr Demirkan.

Indications for alloHSCT in Turkey



Tekgündüz E, et al. *Transfus Apher Sci*. 2016;54:53-59.

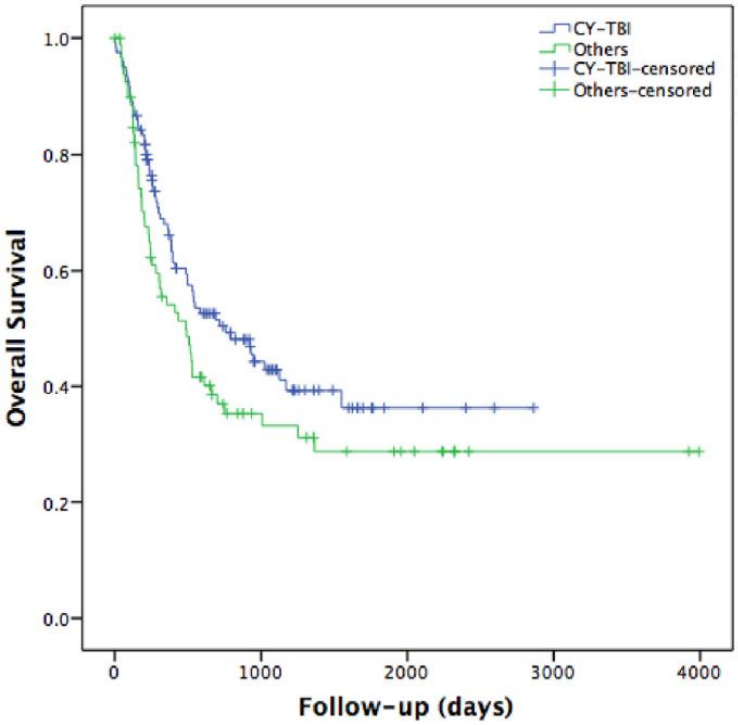
Retrospective analysis of adult patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic cell transplantation: A multicenter experience of daily practice

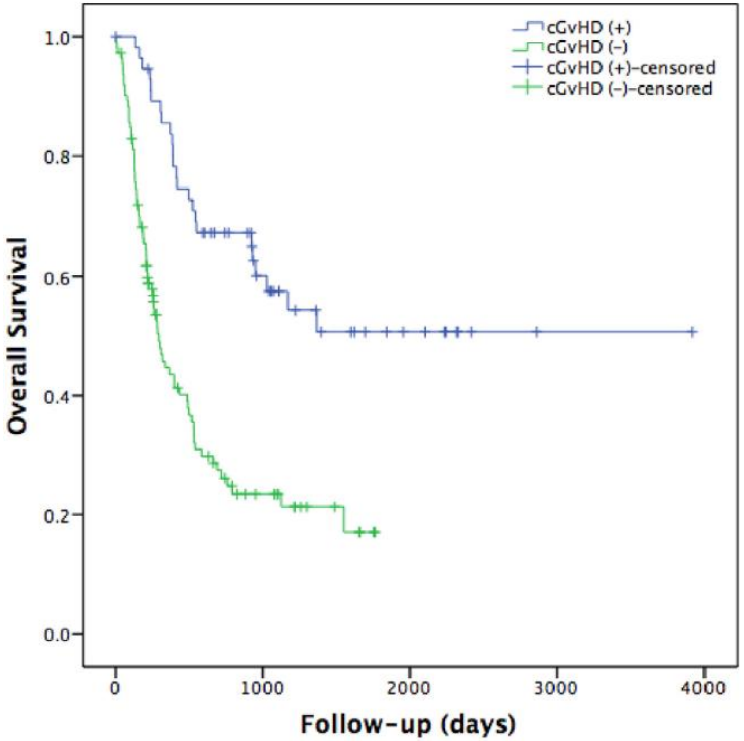
Variable	Results	Available data (n)
Gender (male/female)	122/83	205
Age (median; range)	28 (18–59)	205
Lineage (n; %)		205
B-ALL	133 (64.9%)	
T-ALL	72 (35.1%)	
Ph+ ALL (n; %)	52 (25.4%)	205
Risk group (n; %)		169
High risk	133 (78.7%)	
Standard risk	36 (21.3)	

Variable	Results	Available data (n)
Remission status before HCT		203
CR1	130 (64%)	
CR2	40 (19.7)	
Beyond CR2 and/or active disease	33 (16.3%)	
Conditioning regimen		205
Cy-TBI	124 (60.5%)	
Bu-Cy	24 (11.7%)	
Bu-Flu-ATG	26 (12.7%)	
Flu-Mel	9 (4.4%)	
Flu-TT-Mel-ATG	6 (2.9%)	
Others	16 (7.8%)	
Conditioning intensity		205
MA	154 (75.1%)	
RIC	41 (20%)	
NMA	10 (4.9%)	

Tekgündüz E, et al. *Transfus Apher Sci*. 2016;54(1):41-47.

CR1, TBI-based conditioning and development of cGvHD are important parameters predicting OS





Tekgündüz E, et al. *Transfus Apher Sci*. 2016;54(1):41-47.

Which allo donor type increased in the past 5 years in Turkey?

a) Matched related

b) Matched unrelated

c) Haploidentical

d) Autologous

What is the approximate percentage of ALL indication among all alloHSCTs in Turkey?

a) 40%–50%

b) 7%– 10%

c) 20%–25%

d) 3%–5%

Global Leukemia Academy

Pros and Cons of HSCT

Fatih Demirkan and Andre Schuh

APTITUDE HEALTH®

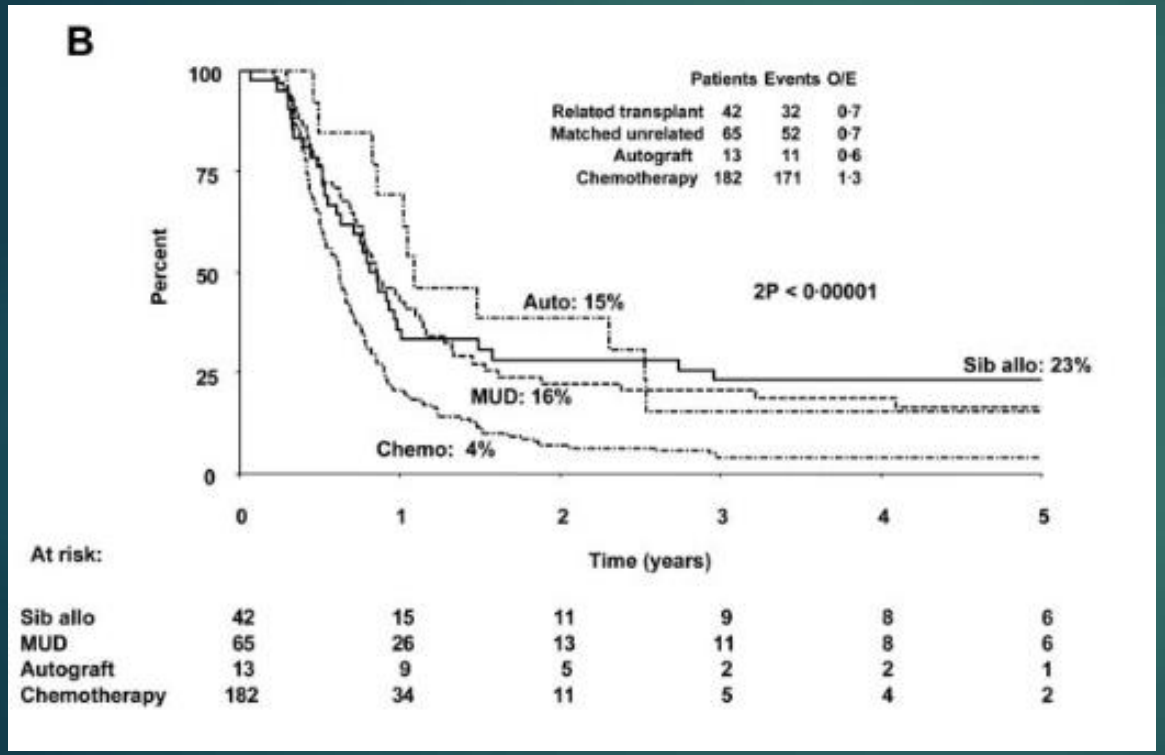
Global Leukemia Academy

Pros of HSCT

Fatih Demirkan

APTITUDE HEALTH®

HSCT in relapsed ALL



MRC UKALL12/ECOG 2993 trial

- Survival postrelapse stratified according to therapy given in relapse. Patients who died within 100 days of relapse and those who were transplanted in CR1 were excluded from this analysis, for better comparison of the different therapeutic modalities

Fielding, et al. *Blood*. 2007;109(3):944-950.

Indications for HSCT at first CR

- Presence of the Philadelphia (Ph) chromosome
- High WBC count at the time of presentation WBC >30 × 10^9/L in B-ALL or WBC >100 × 10^9/L in T-ALL
- A slow response to induction therapy; no CR after first induction
- Adverse cytogenetics
- MRD ≥10^{-3} after induction or ≥10^{-4} after early consolidation

Giebel S, et al. *Bone Marrow Transplant*. 2019;54:798-809.

CR1: HSCT for whom?

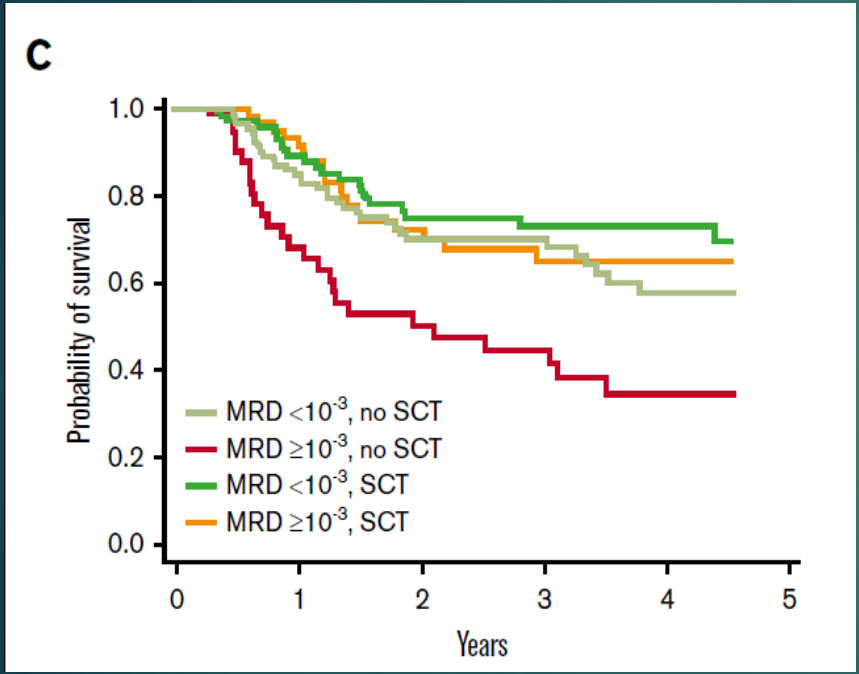
- For everyone
- For high-risk patients
- For MRD+ patients after induction therapy

MRC UKALL XII/ECOG EC2993: Ph– ALL

Group	n	OS (5), %	Relapse (5), %	NRM (2), %
High risk*	401			
Donor (+)	171	40 (*P* = .2)	39	39
Donor (-)	230	36	62	12
Standard risk†	512			
Donor (+)	218	63 (*P* = .02)	27	20
Donor (-)	294	51	50	7

*Age >35; WBC >30,000/mm^3 (B) – 100,000/mm^3 (T); time to CR >4 weeks.
†In standard-risk group 60% <30 years old.
Goldstone AH, et al. *Blood*. 2008;111:1827-1833.

HSCT may improve unfavorable impact of poor MRD response



GRAALL-2003 and GRAALL-2005 trials

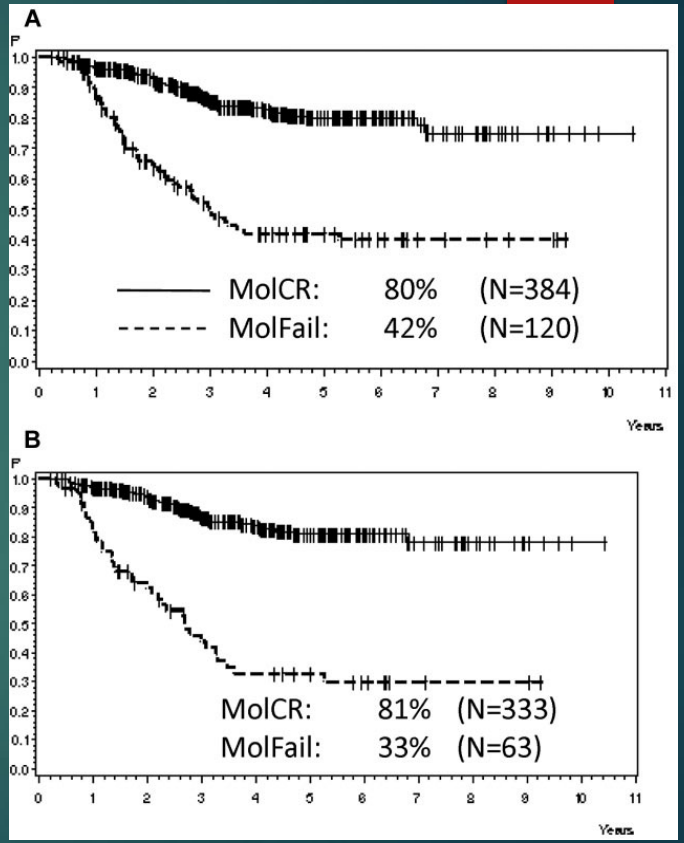
- 522 high-risk patients, 282 (54%) received SCT after 3 or 6 blocks of consolidation on the basis of the availability of a related or unrelated donor. Two hundred seventy-eight patients were studied for MRD after first induction (154 SCT and 124 non-SCT patients)
- SCT benefited patients with MRD levels $\geq 10^{-3}$ at week 6 (hazard ratio, 0.4) compared with nontransplantation patients, and SCT erased the unfavorable impact of poor MRD response in this cohort

Dhédin N, et al. *Blood*. 2015;125(16):2486-2496.

Effect of allogeneic SCT for patients with molecular failure

GMALL 06/99 and 07/03 trials

- CR was achieved in 89% of all patients
- Measurement of MRD found that 30% of the patients with cytologic CR did not achieve molecular CR
- In patients with molFail without allogeneic SCT in first CR, the median time from detection of molFail to cytologic relapse was 7.6 mo
- Probability of CCR after 5 years was significantly higher for patients with molFail and SCT in first CR than for those without SCT in first CR (66% vs 12%; *P* = .0001) and better survival for patients with SCT than for those without (54% vs 33%)



Probability of survival for patients in the SR and HR groups according to molecular response status in week 16, (A) overall (*P* = .0001) and (B) excluding SCT in first CR (*P* = .0001).

Gokbuget N, et al. *Blood*. 2012;120(10):2032-2041.

Restrictions of MRD-driven strategy in deciding HSCT

- MRD testing is not available
- If less-intensive regimens like hyperCVAD are commonly used, relevance of MRD negativity may not be strong
- The prognostic impact of MRD seems to be influenced by the disease status; best at first CR and then after first salvage treatment
- Presence of a matched sibling donor

Giebel S, et al. *Bone Marrow Transplant*. 2019;54:798-809; Jabbour E, et al. *Cancer*. 2017;123(2):294-302.

Summary

- HSCT cannot be replaced by other treatment options yet in relapsed/refractory ALL and in MRD+ high-risk patients at first CR
- No randomized trials comparing alloHSCT with consolidation chemotherapy for patients achieving MRD negativity after induction
- The use of monoclonal antibodies or bispecific antibodies for consolidation or maintenance is not definite

Q

What is the indication for alloHSCT at first CR?

a) High WBC count at the time of presentation

b) A slow response to induction therapy; no CR after first induction

c) Adverse cytogenetics

d) High MRD after induction or after early consolidation

e) All of the above

Q

According to the MRC UKALL12/ECOG 2993 trial alloHSCT in relapsed setting can offer a 5-year OS of ___?

a) 70%

b) 50%

c) 20%

d) 10%

e) 4%

Global Leukemia Academy

Cons of HSCT

Andre Schuh

APTITUDE HEALTH®

Allogeneic SCT for ALL - Con

Andre Schuh
Princess Margaret Cancer Centre
Toronto

July 8, 2020

Question:

Regarding ALL in adults, which of the following is true?

1. Ph+ patients in CR should proceed to alloSCT, if at all possible
2. MRD positivity at the post induction time-point is most predictive of outcome
3. improved outcomes in adults treated with pediatric or pediatric-inspired protocols may diminish the need for alloSCT
4. any strategy that defers up-front alloSCT requires ongoing, sensitive MRD testing

Traditional Approach to AlloSCT in ALL

- All eligible patients in CR2
- AutoSCT and alloSCT
- High-risk patients in CR1 (age, presentation WBC, time to CR, high-risk cytogenetics [Ph, 11q23 abnormalities], etc)
- Adults were generally treated with “adult” protocols, with poor outcomes compared with pediatric population

Strategies to Improve Outcomes in Adult ALL

- Adoption of pediatric or “pediatric-inspired” protocols
- TKIs in Ph+ ALL
- Trials to clarify the role of alloSCT
  - Mostly donor/no-donor
  - Multiple systematic reviews, meta-analyses, etc
- More recently
  - Molecularly defined risk
  - Identification of new high-risk ALL subtypes
  - Role of MRD

Numerous Trials (mostly donor/no-donor)

- Most predate the use of pediatric protocols in adults
- Many predate the use of MRD
- Varying definitions of “high-risk”; inclusion/exclusion of Ph+
- Variable effects; sometimes confusing or contradictory results and conclusions, eg, alloSCT improves OS only in standard-risk patients, or only in high-risk patients
- Most have found an alloSCT effect primarily in high-risk patients, and this is a common recommendation . . .

- But see the **MRC UKALL XII/ECOG E2993** study
  (Goldstone, AH et al. *Blood* 2008;111:1827-1833)

Multiple Systematic Reviews, Meta-analyses, etc

- Most studies analyzed predate the use of pediatric protocols in adults
- Contradictory data using the same studies

For Example

Yanada N, et al. *Cancer.* 2006;106:2657-2663

- 7 studies; 1274 patients; donor/no-donor; Ph+ included
- Donor group had better OS (HR=1.29), with effect most marked in high-risk group (HR=1.42)

Pidala J, et al. *Cochrane Database of Systematic Reviews.* 2011 #11; pp 1-49

- 14 trials; 3157 patients; donor vs no-donor; Ph+ included
- Overall OS advantage in donor group (HR=0.86; p=0.01 but not OS advantage when standard-risk and high-risk groups analyzed separately
- Increased DFS and TRM, and decreased relapse, in donor group
- Conclude that alloSCT is the optimal therapy in ALL patients in remission

Gupta V, et al. *Blood*. 2013;121:339-350

- Individual patient data meta-analysis; 13 studies; 2962 patients; Ph+ excluded
- Survival advantage in donor group in patients age <35 (OR 0.79; p=0.0003)
- No survival in donor group in patients age ≥35 (OR 1.01; p=0.9)
- AlloSCT provides a survival advantage in younger patients of ~10% at 5 years

What If One Focuses on Adults Treated With a Pediatric-Inspired Protocol?

For example

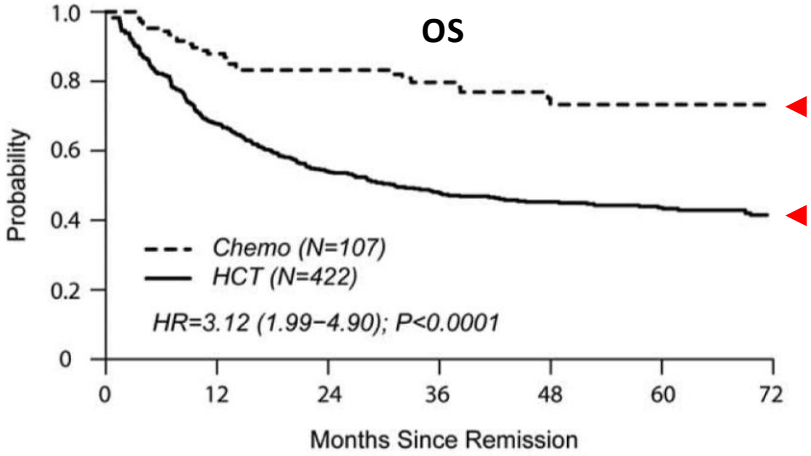
Seftel, MD et al. *AJH* 2016;91;322-329

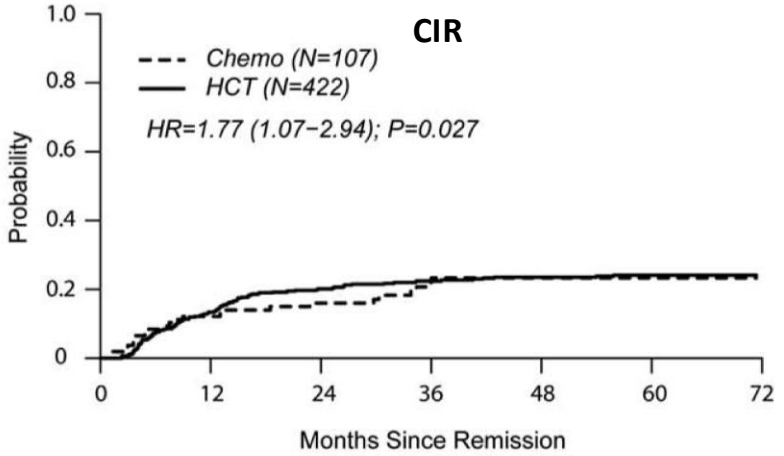
- Compared 108 concurrent Ph- ALL patients aged 18-50 in CR1 on successive Dana-Farber ALL Consortium pediatric-inspired protocols DFCI 01-0175 and DFCI 06-254, with 422 age-, disease-, and transplant variable- matched CR1 alloSCT recipients (CIBMTR)
- At 4 years of follow-up

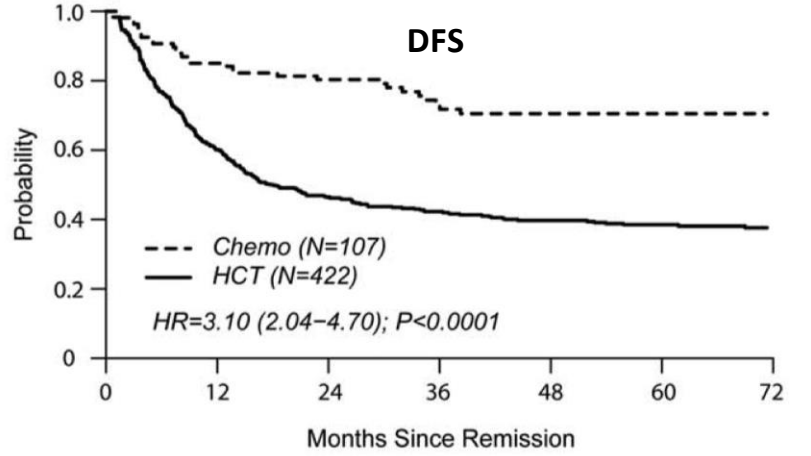
	alloSCT	Chemo	*P* value
Relapse	24%	23%	0.97
TRM	37%	6%	<0.0001
DFS	40%	71%	<0.0001
OS	45%	73%	<0.0001

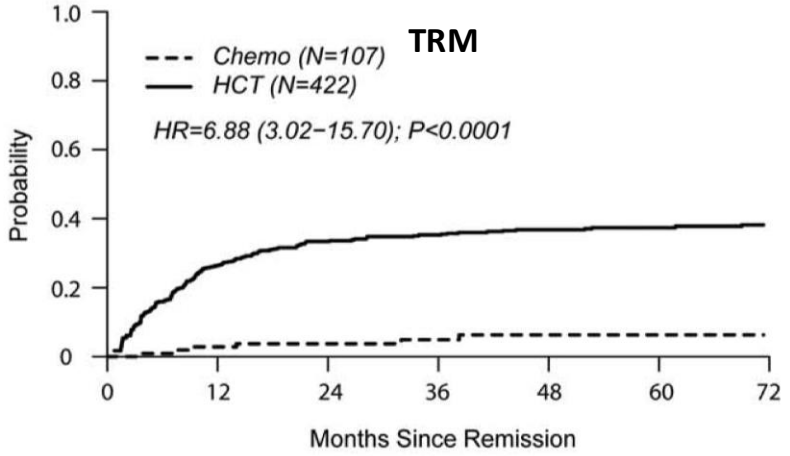
- In multivariable analysis, only alloSCT was predictive of shorter OS (HR 3.12; *P* <.0001)

Seftel, MD *et al*. *AJH* 2016; 91; 322-329









Seftel, MD *et al. AJH* 2016; 91; 322-329

What If One Focuses on MRD?

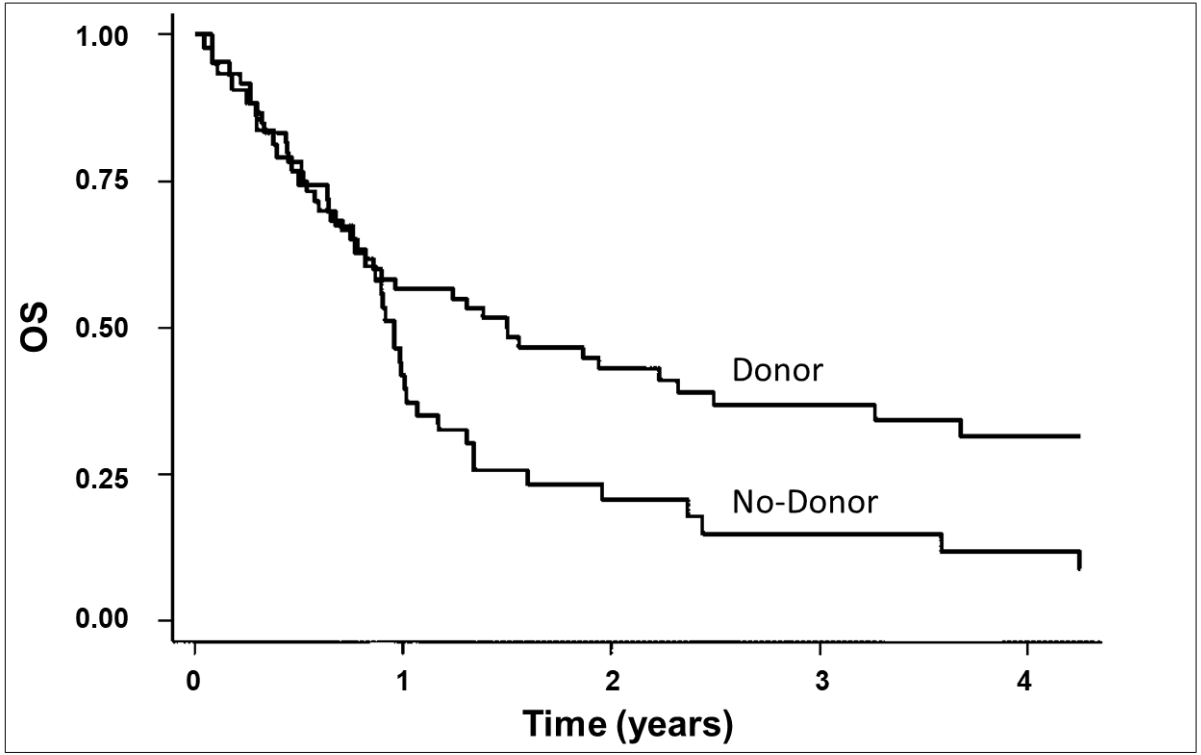
- Not measured in the majority of older studies
- Numerous studies indicate a worse RFS/OS in MRD+ patients
- Numerous studies and guidelines suggest alloSCT if still MRD+ by 12-16 weeks
- Post-alloSCT outcomes are inferior in patients MRD+ pretransplant
- OS is improved in MRD+ patients undergoing alloSCT (relative to no alloSCT)
- MRD status in CR may trump pretreatment risk-stratification
- It is not known whether pretransplant interventions to reduce/eliminate MRD improve OS post-alloSCT

see . . .

Bassan R, et al. *Blood Cancer J* 2014:4:e225
Gökbuget N, et al. *Hematology* 2019;24:337-348
Bassan R, et al. *Haematologica* 2109;104:2028-2039

What About Ph+ ALL?

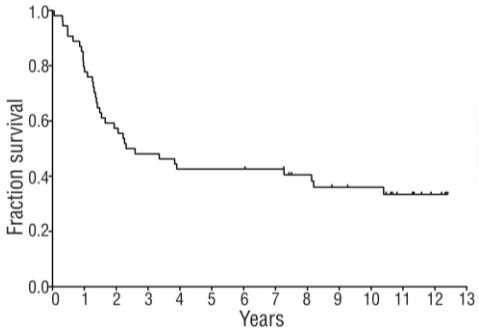
Role of alloSCT, Ph+ ALL, Pre-TKI



Dombret, H. *et al.*, *Blood* 2002; 100: 2357-2366

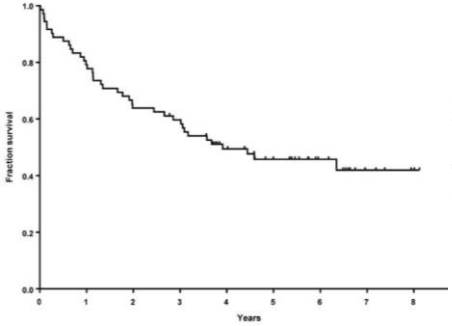
OS, HyperCVAD + Imatinib, Dasatinib, or Ponatinib

Imatinib: 5-yr OS, 43%



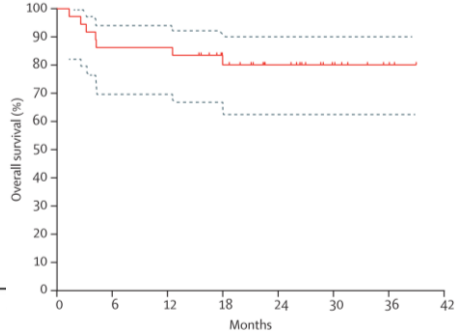
2001-2006
n=54
51 (17-84)

Dasatinib: 5-yr OS, 46%



2006-2012
n=72
55 (21-80)

Ponatinib: 3-yr OS, 79%*



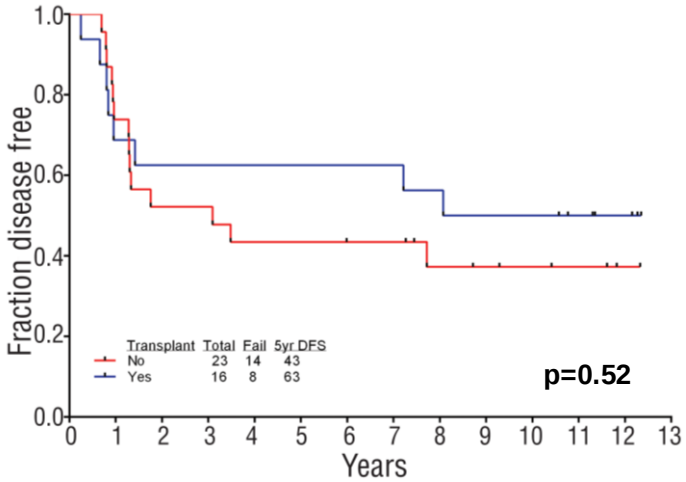
2011-2013
n=53
54 (25-80)

***Estimated 5-yr OS, 71%.**

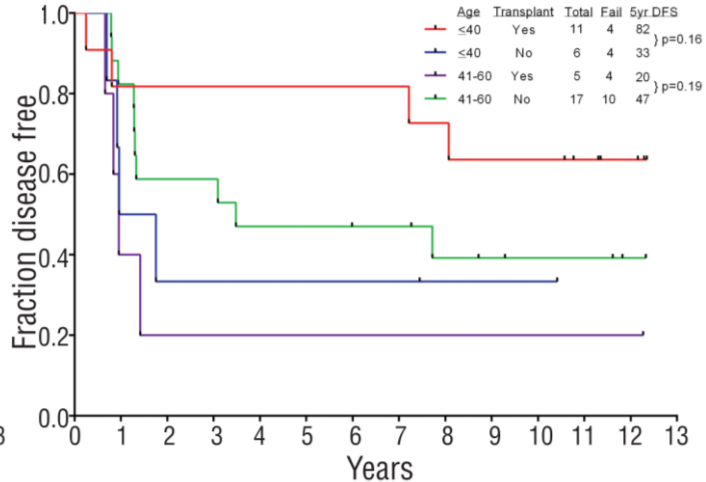
Daver, N. *et al. Haematologica* 2015; 100:653-61
Ravandi, F. *et al. Cancer* 2015; 121:4158-64
Jabbour, E. *et al. Lancet Hematology* 2015; 16:1547-55
Jabbour, E. *et al. Clin Lymph Myel Leuk* 2018; 18:257-65

HyperCVAD + Imatinib +/– AlloSCT

DFS, by alloSCT



DFS, alloSCT, by age



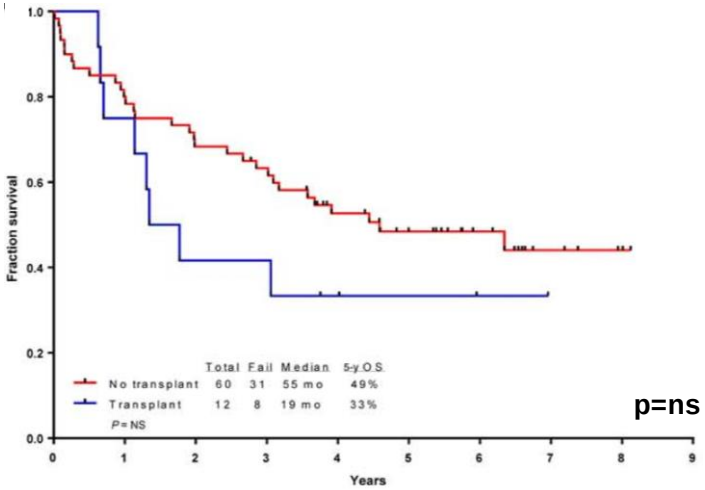
Overall 5-yr OS, 43%

But, in 41-60 age group, OS better without alloSCT

Daver, N. *et al. Haematologica* 2015; 100:653-61

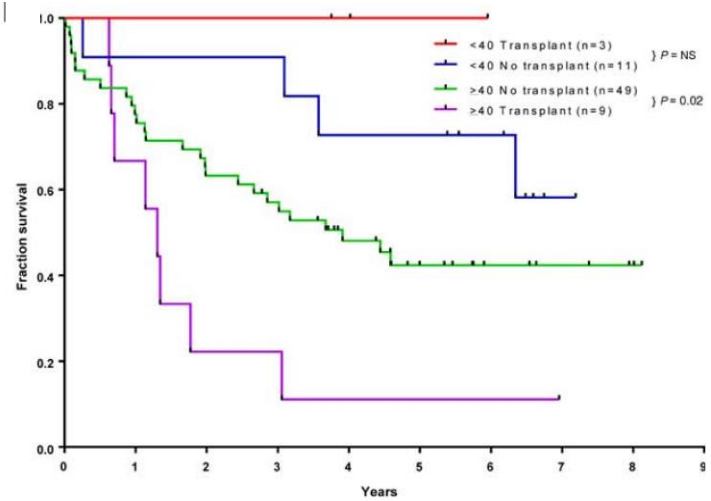
HyperCVAD + Dasatinib +/– AlloSCT

OS, by alloSCT



p=ns

OS, alloSCT, by age

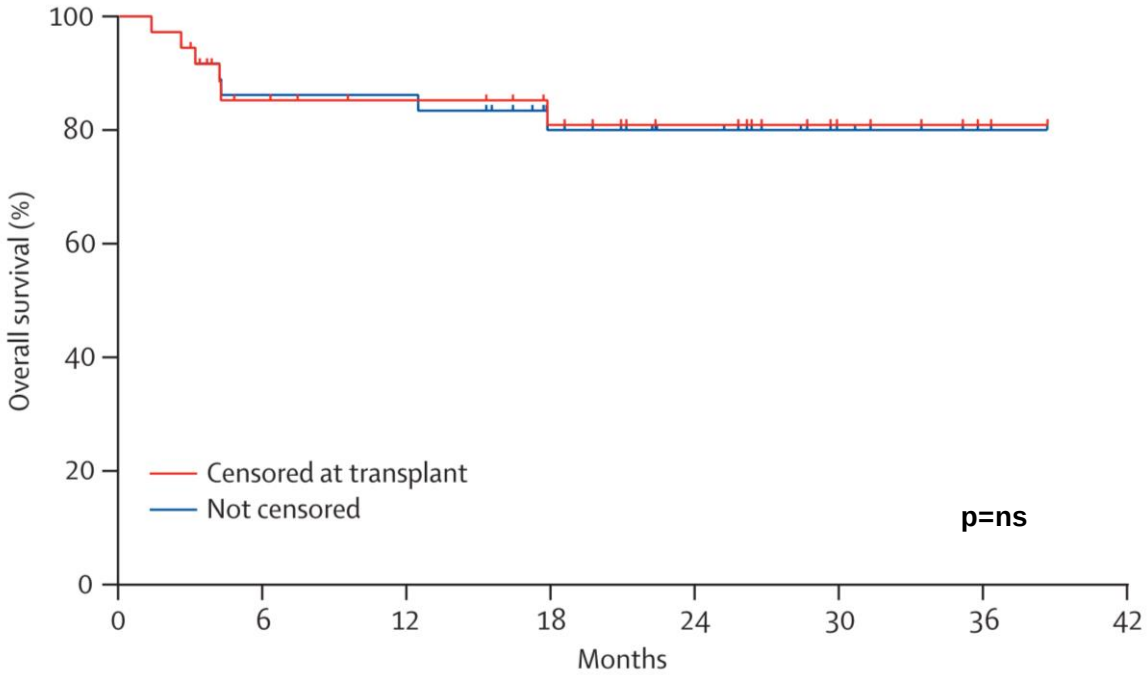


Overall 5-yr OS, 46%
But, in ≥40 age group OS better without alloSCT

Ravandi, F. *et al*. *Cancer* 2015; 121:4158-64

HyperCVAD + Ponatinib +/– AlloSCT

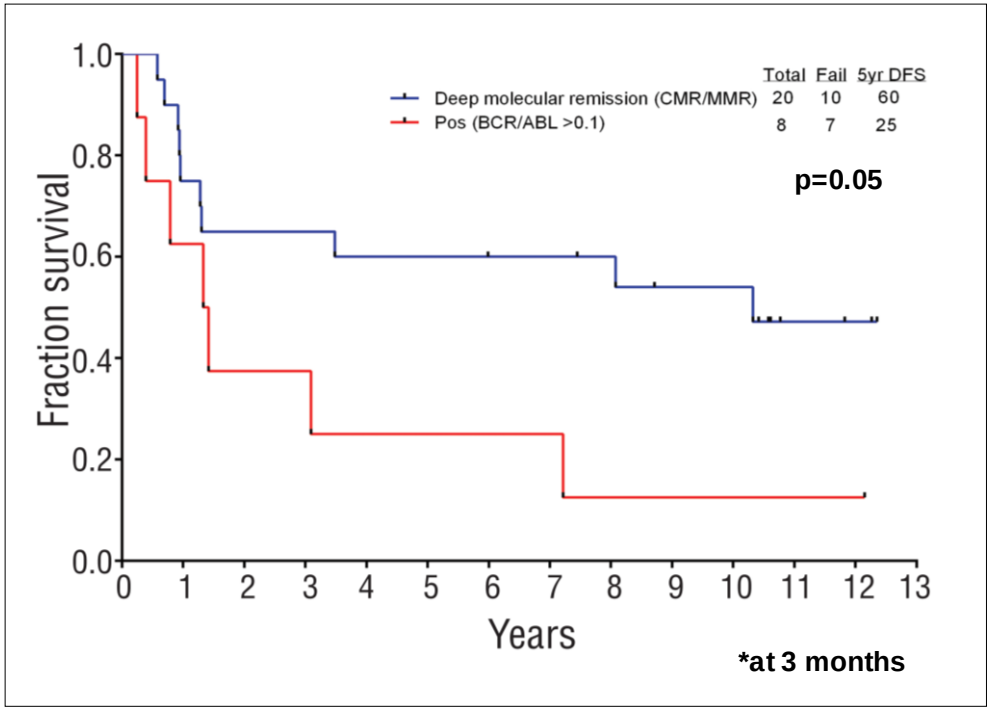
OS, by alloSCT



Overall 3-yr OS, 79%

Jabbour, E. *et al. Lancet Hematology* 2015; 16:1547-55
Jabbour, E. *et al. Clin Lymph Myel Leuk* 2018; 18:257-65

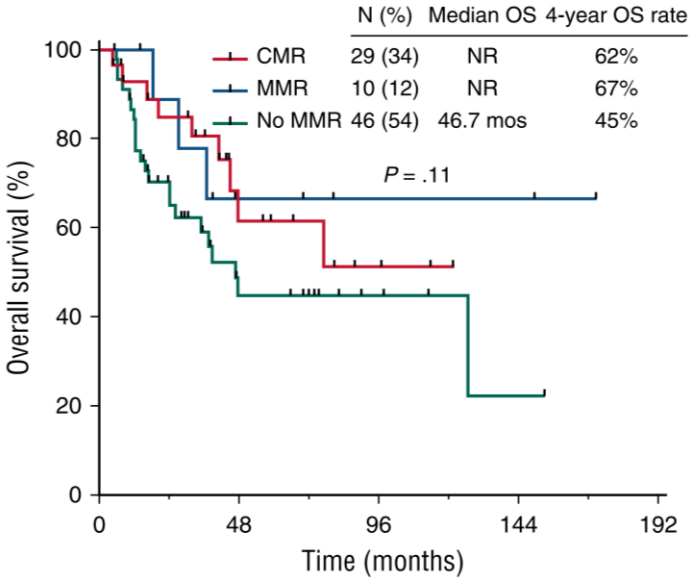
OS, HyperCVAD + Imatinib, by CMR/MMR*



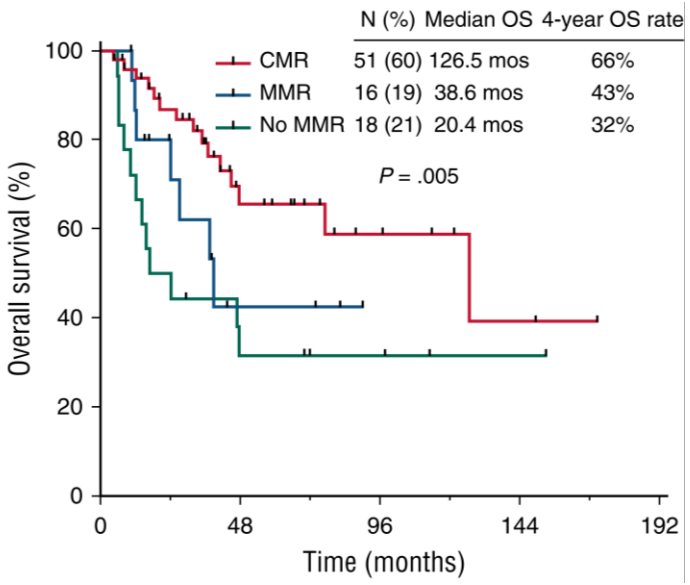
Daver, N. *et al. Haematologica* 2015; 100:653-61

OS, by Molecular Response, HyperCVAD + TKI

At CR



At 3 Months



Short, N. *et al. Blood* 2016; 128: 504-7

OS, by Molecular Response, HyperCVAD + TKI

Univariate analysis, RFS and OS

Characteristic	Risk of relapse or death			Risk of death		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (y)	1.01	0.99-1.04	.27	1.02	0.99-1.04	.15
Log WBC	1.56	0.95-2.56	.08	1.43	0.85-2.38	.18
Platelets	1.00	1.00-1.00	.89	1.00	1.00-1.01	.75
Absolute PB blasts	1.00	1.00-1.01	.15	1.00	0.99-1.00	.68
BM blasts (%)	0.99	0.98-1.00	.18	0.99	0.97-1.00	.05
Performance status ≥2	3.22	1.31-7.90	.01	1.97	0.75-5.13	.17
CD20 expression ≥20%	1.31	0.68-2.53	.42	1.46	0.71-3.00	.30
CNS leukemia	1.96	0.81-4.70	.13	1.24	0.43-3.56	.69
p190 *BCR-ABL1* transcript	1.02	0.49-2.16	.95	1.03	0.47-2.27	.95
Cytogenetics: Ph alone vs Ph^+ other	0.42	0.19-0.93	.03	0.46	0.20-1.06	.07
TKI: ponatinib vs dasatinib vs imatinib	0.59	0.37-0.94	.03	0.52	0.31-0.88	.02
CMR at 3 mo	0.43	0.21-0.78	.01	0.42	0.21-0.82	.01

WBC, white blood cell; PB, peripheral blood; BM, bone marrow; CNS, central nervous system.

Short, N. *et al. Blood* 2016; 128: 504-7

AlloSCT in Ph+ ALL in CR1 in Post-TKI Era?

If only overall OS is considered . . .

- Imatinib YES
- Dasatinib YES
- Ponatinib LIKELY NO

But when CMR/MMR and age are considered . . .

- Imatinib MAYBE
- Dasatinib MAYBE
- Ponatinib LIKELY NO

But . . .

- Frequent follow-up for MRD required
- Availability of NGS helpful, especially if MRD+

At PM . . .

Ph–

- AlloSCT for
- All in CR2
- In CR1 for 11q23, Ph-like
- Maybe for complex, hypodiploid
- MRD+ after 2nd intensification cycle (~13-14 weeks)

Ph+

- AlloSCT for all in CR2
- In CR1 for poor molecular response (>~3.5 log reduction) at ~13-14 weeks, and after tweaking TKI
- If alloSCT is deferred, regular, accurate MRD is required

Question:

Regarding ALL in adults, which of the following is true?

1. Ph+ patients in CR should proceed to alloSCT, if at all possible
2. MRD positivity at the post induction time-point is most predictive of outcome
3. improved outcomes in adults treated with pediatric or pediatric-inspired protocols may diminish the need for alloSCT
4. any strategy that defers up-front alloSCT requires ongoing, sensitive MRD testing

Thank You!
Questions?
Comments?

Global Leukemia Academy

Panel Discussion on the Role of HSCT: Discussion and Voting

APTITUDE HEALTH®

Question 1

In your practice, what is the most important factor for deciding ineligibility for HSCT?

a) Age ≥65 years
b) Frailty
c) Comorbidities

Question 2

Do you think that MRD can guide your decision on HSCT?

a) Yes, as patients who achieve MRD negativity are on the way to cure and do not require HSCT

b) No, as HSCT is the SOC today and should be part of the treatment algorithm of patients independently of MRD

c) I do not know

Question 3

What are the factors influencing the increased probability of relapse post-HSCT?

a) Disease status
b) Chemosensitivity at the time of transplantation
c) Development of graft-versus-host disease
d) All of the above
e) None of the above

Global Leukemia Academy

Debate on CD19-Targeted Approaches

APTITUDE HEALTH®

Question 1

What is your preferred ALL treatment choice in salvage if all these therapies are available in your country?

a) CAR T therapies

b) Monoclonal antibodies or bispecifics

Question 2

Do you think that children and young adults with active non-bulky CNS disease can safely be treated with CD19 CAR T cells?

a) Yes

b) No

c) I do not know

Question 3

What advantages do you see in bispecific antibodies vs CAR T cells?

a) Readily available off the shelf
b) Dosing can be easily interrupted in case of toxicity
c) Can be combined with chemotherapy
d) I do not know

Global Leukemia Academy

Debate on CD19-Targeted Approaches: CAR T

Josep-Maria Ribera

APTITUDE HEALTH

CD19 CAR T: Main results in R/R ALL

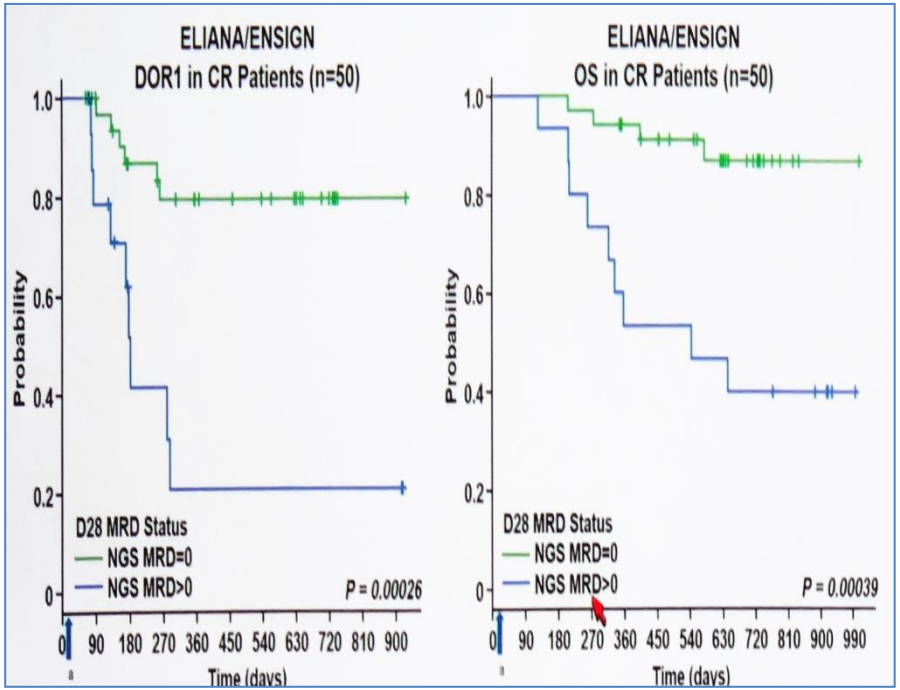
Author, reference	Institution	Costimulatory domain	Age (median, range)	Infused N	ORR %	CRS, %	Neurotoxicity, %	OS
Maude *et al.*[15]	UPenn	4-1BB	14 years (5–60)	30	90%	100% (severe, 27%)	43%	78% at 6 months
Davila *et al.*[16]	MSKCC	CD28	50 years (NA)	16	88%	severe, 44%	Gr 3/4, 25%	NA
Lee *et al.*[17]	NCI	CD28	15 years (5–27)	21	67%	76% (Gr 3/4, 29%)	29% (Gr 3/4, 5%)	52% at 12 months
Turtle *et al.*[18]	FHCRC	4-1BB	40 years (20–73)	30	93%	83%	50% (Gr 3/4, 50%)	NA
Gardner *et al.*[19]	SCRI	4-1BB	12 years (1–25)	43	93%	93% (Gr 3/4, 23%)	49% (Gr 3/4, 21%)	69.5% at 12 months
Maude *et al.*[20]	Novartis	4-1BB	11 years (3–23)	75[1]	81%	77%	40% (Gr 3/4, 13%)	76% at 12 months
Park *et al.*[21]	MSKCC	CD28	44 years (23–74)	53[2]	83%	85% (Gr 3/4, 26%)	48% (Gr 3/4, 42%)	median, 12.5 months

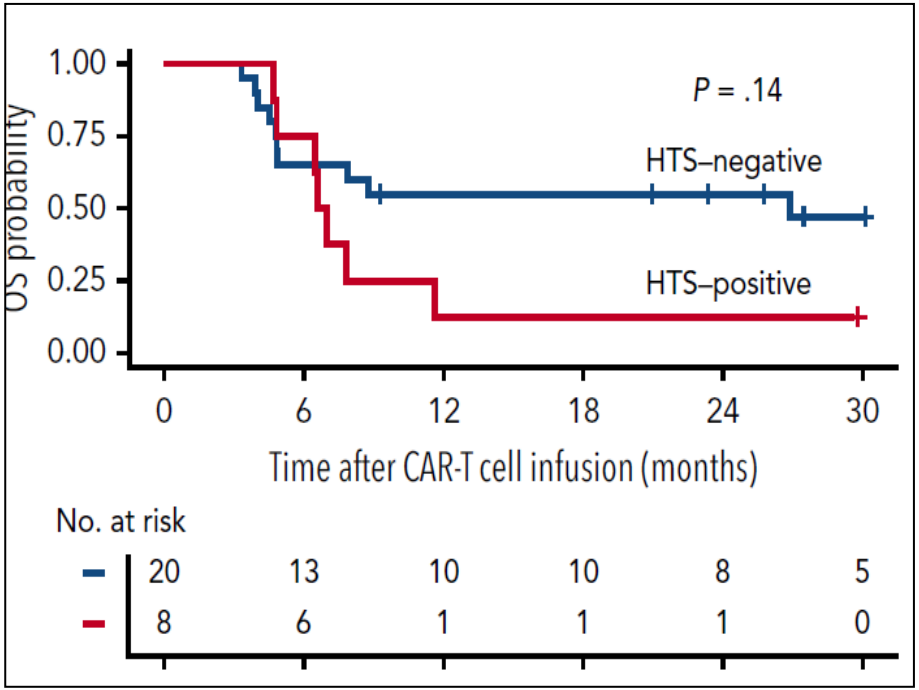
Ribera JM, et al. *Ther Adv Hematol.* 2020;11:1-15.

Second-generation CD19 CAR T in R/R adult ALL: Facts

- Limited experience, short-term results
- High CR rate (80%–90%), MRD– in 60%–80%
- Short duration of response (median 8–18 mo)
- Better results in patients with low tumor mass, promising in MRD+ patients
- Need for subsequent alloHSCT unclear, with good results in some series
- Early MRD assessment by high-throughput sequencing predicts outcome
- Prognostic factors in MRD–neg CR patients identified
- Major concerns: durability, CD19–neg relapses

Early clearance of the leukemic clone by HTS associated with better outcome





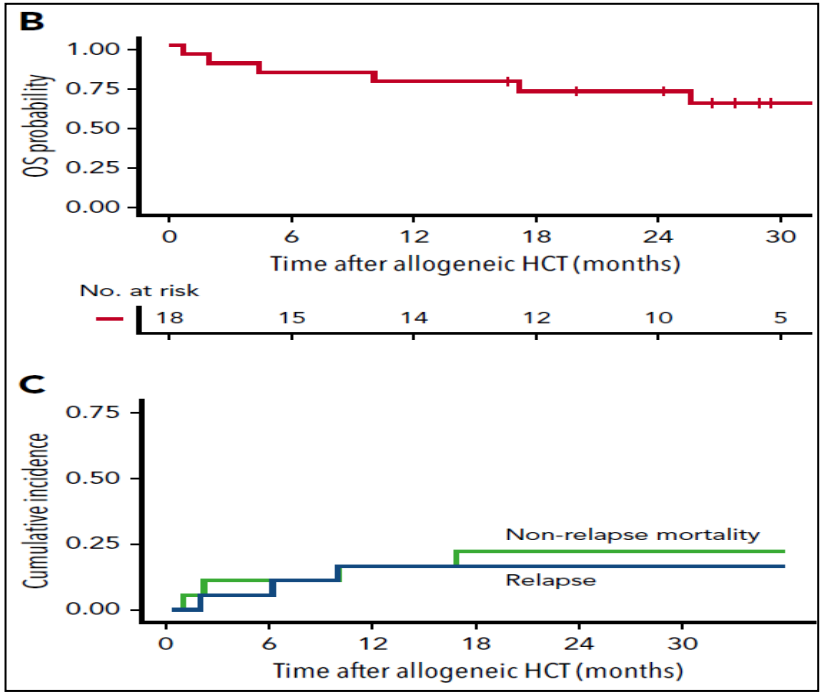
Median OS 26.9 vs 6.8 months

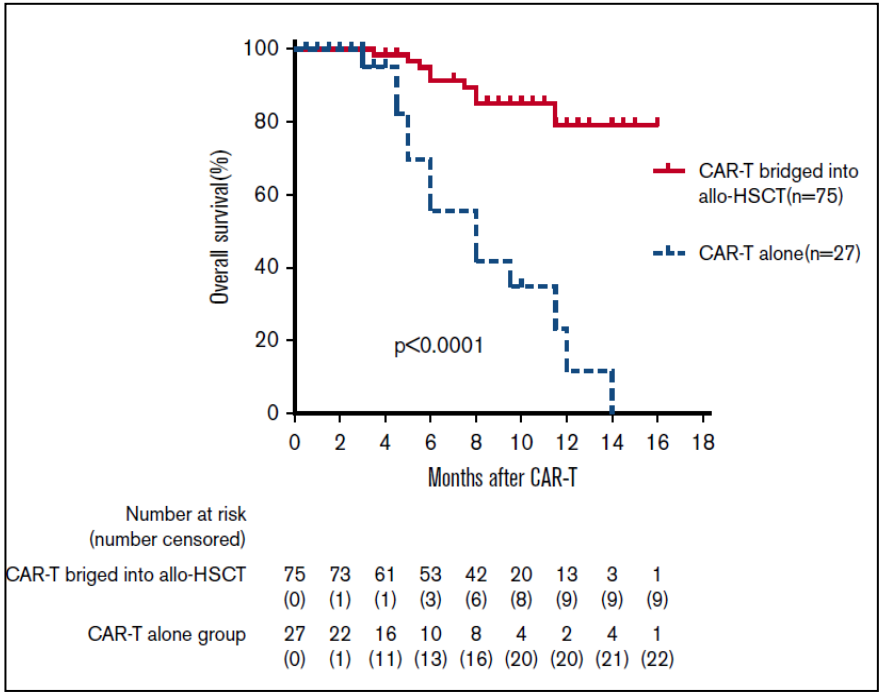
Pulsipher et al. ASH 2018. Abstract 1551.

Hay K, et al. *Blood.* 2019;133:1652-1663.

HSCT after CAR T

AlloHSCT in MRD– patients after CAR T





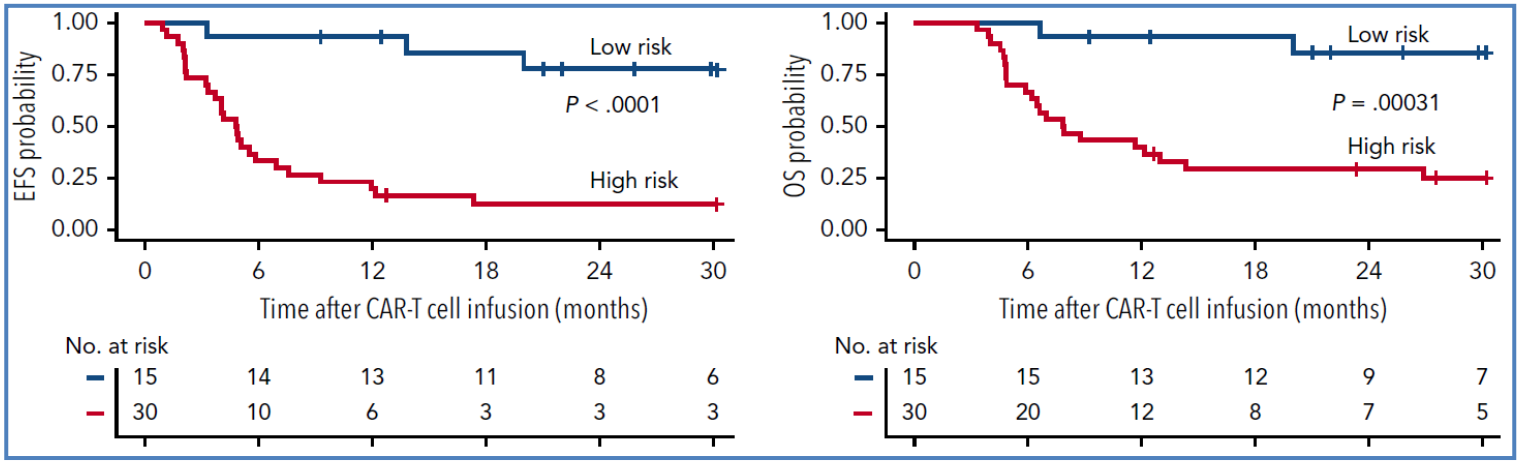
Hay K, et al. *Blood.* 2019;133(15):1652-1663.

Zhang X, et al. *Blood Adv.* 2020;4: 2325-2338.

D28 landmark multivariable analysis for DFS in MRD– CR patients (n = 45)*

Variable	HR (95% CI)	*P* value
LDH prior to lymphodepletion†	1.39 (1.12–1.74)	.003
Platelets prior to lymphodepletion‡	0.65 (0.47–0.88)	.006
Fludarabine in lymphodepletion	0.34 (0.15–0.78)	.011

†Per 100 U/L increment; ‡Per 50,000/µL increment.



Hay K, et al. *Blood.* 2019;133(15):1652-1663.

*40% of patients with MRD– CR were transplanted.

Strategies to improve outcomes after CD19 CAR T-cell therapy

- Beyond CD19 target – prevent CD19–neg relapse
  - CD22
  - CD19+CD22
  - CD19+CD20+CD22
- Improve CAR T-cell persistence
  - Fully human/humanized scFv to prevent immune rejection
  - Combination with checkpoint inhibitors (eg, tisagenlecleucel + pembro/nivolumab)
- Improve availability
  - Off-the-shelf CAR T
- Expand indications
  - CAR T (CD7, CD1a) or NK for R/R T-ALL

Global Leukemia Academy

Debate on CD19-Targeted Approaches: Monoclonal Antibodies and Bispecifics

Elias Jabbour

APTITUDE HEALTH®

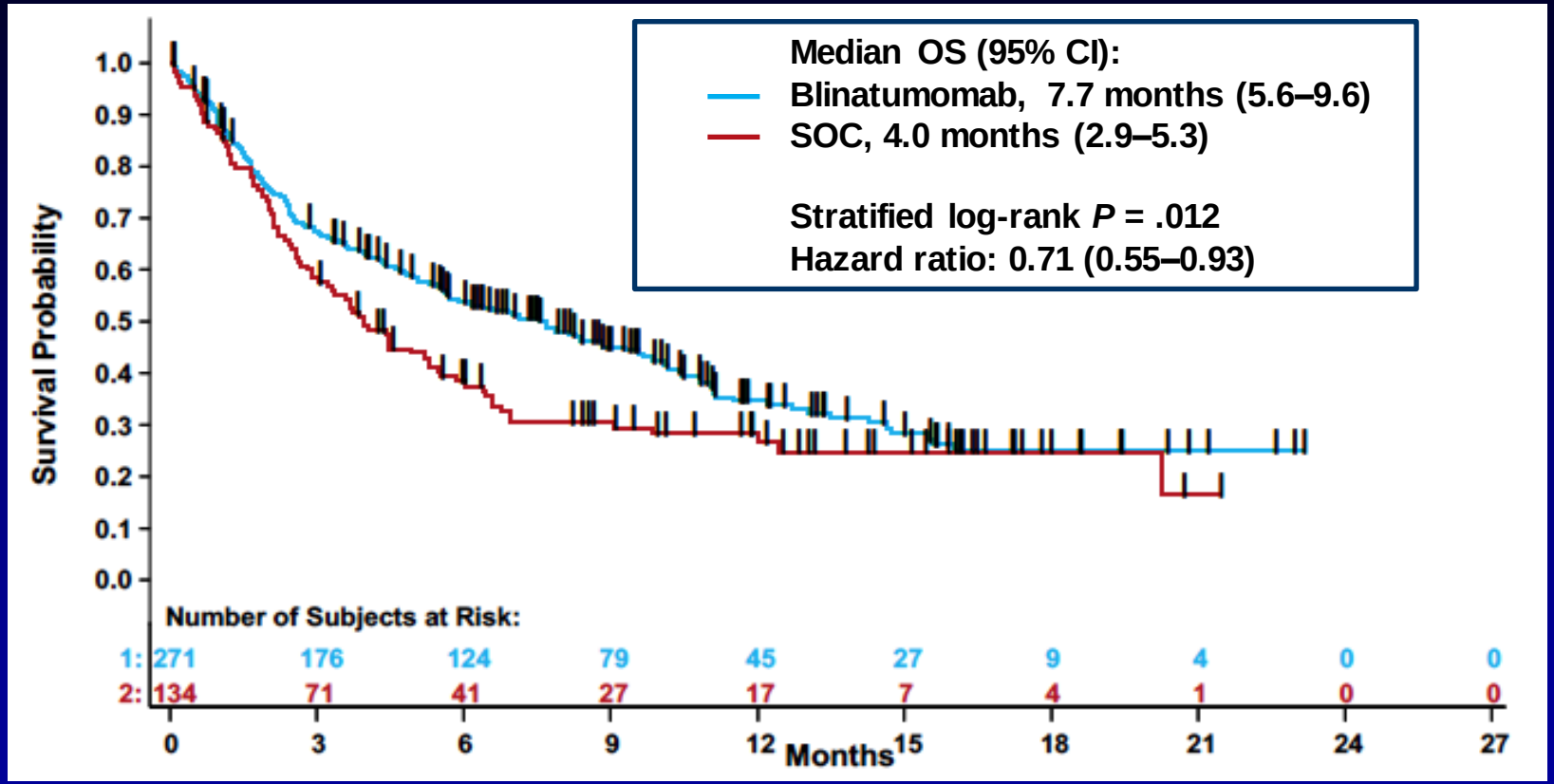
Historical Results in R-R ALL

- Poor prognosis in R-R ALL Rx with standard of care (SOC) chemotherapy

Rate (95% CI)	No Prior Salvage (S1)	1 Prior Salvage (S2)	≥2 Prior Salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

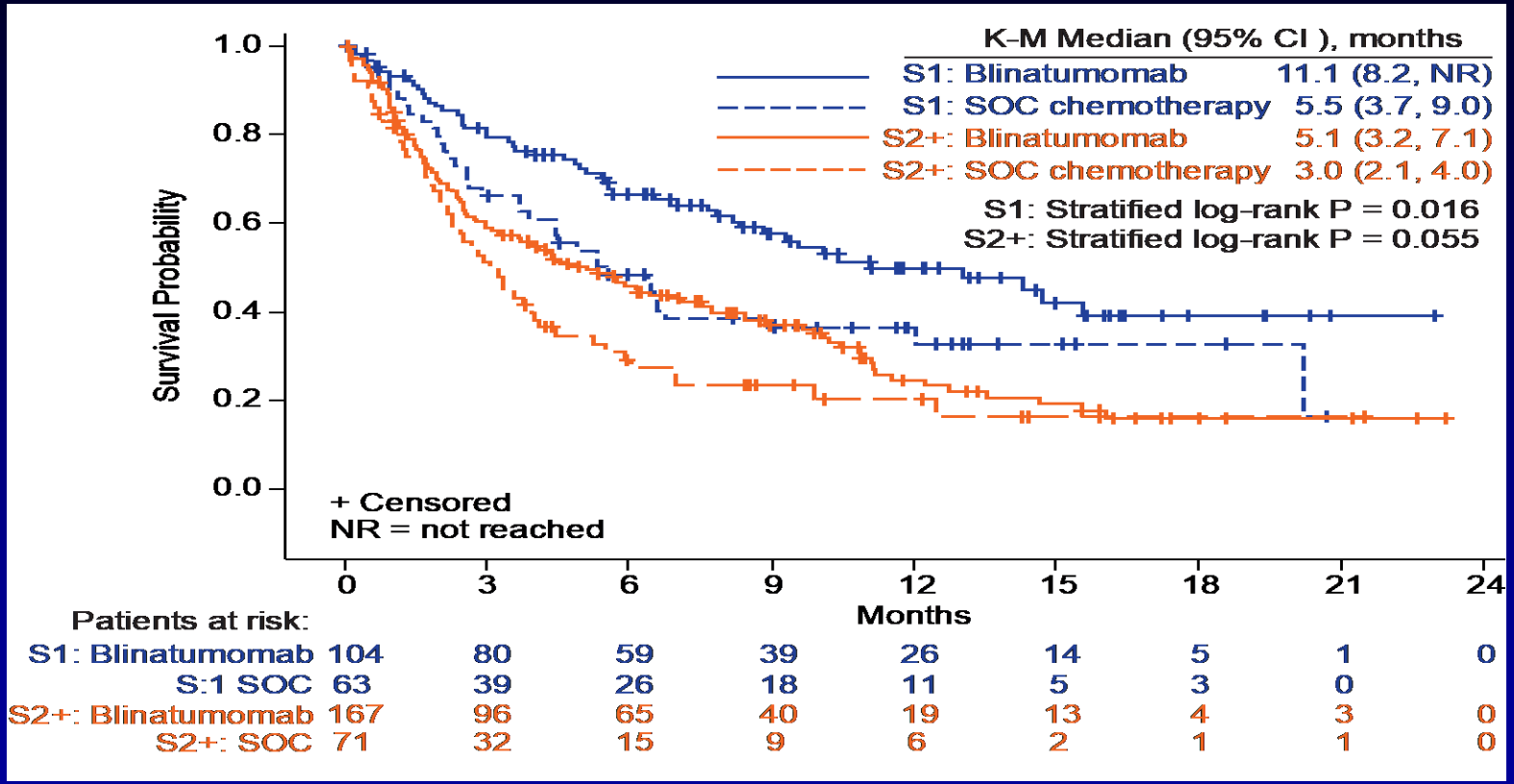
Gökbuget N, et al. *Haematologica*. 2016;101:1524-1533.

Blinatumomab vs Chemotherapy in R/R ALL



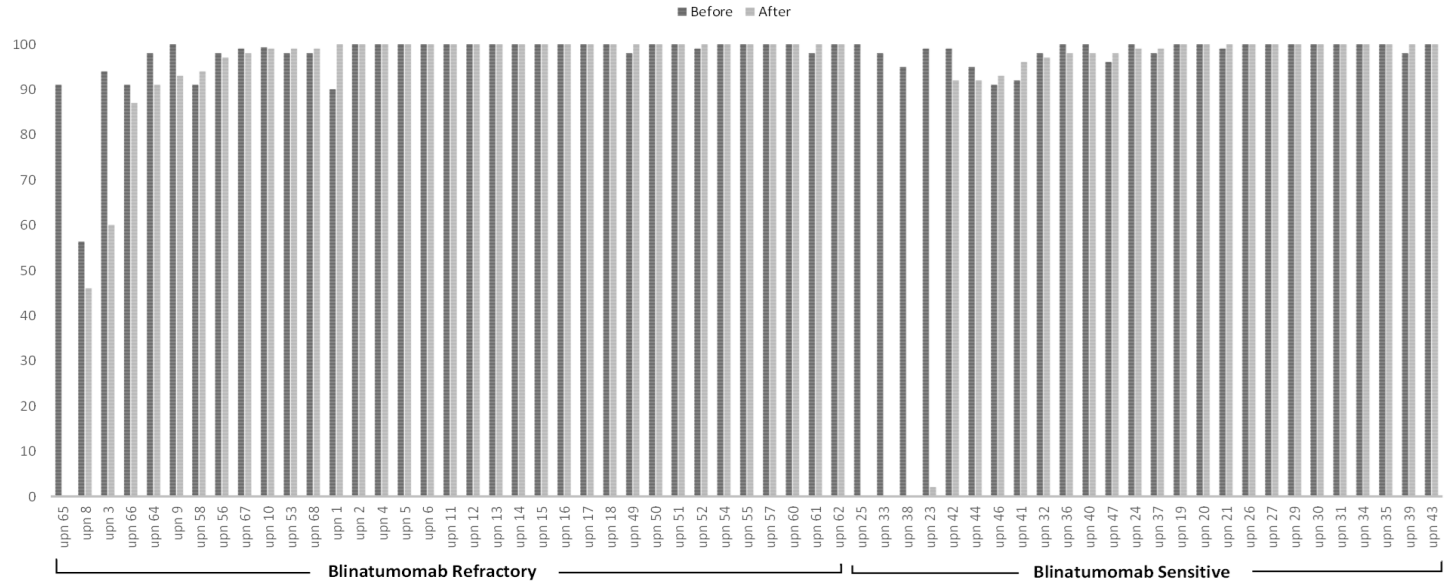
Kantarjian. *N Engl J Med.* 2017;376:836-847.

Phase III TOWER Study: Survival by Salvage



Dombret. *Leuk Lymphoma*. April 2019.

CD19 (%) Expression Before and After Blinatumomab Therapy

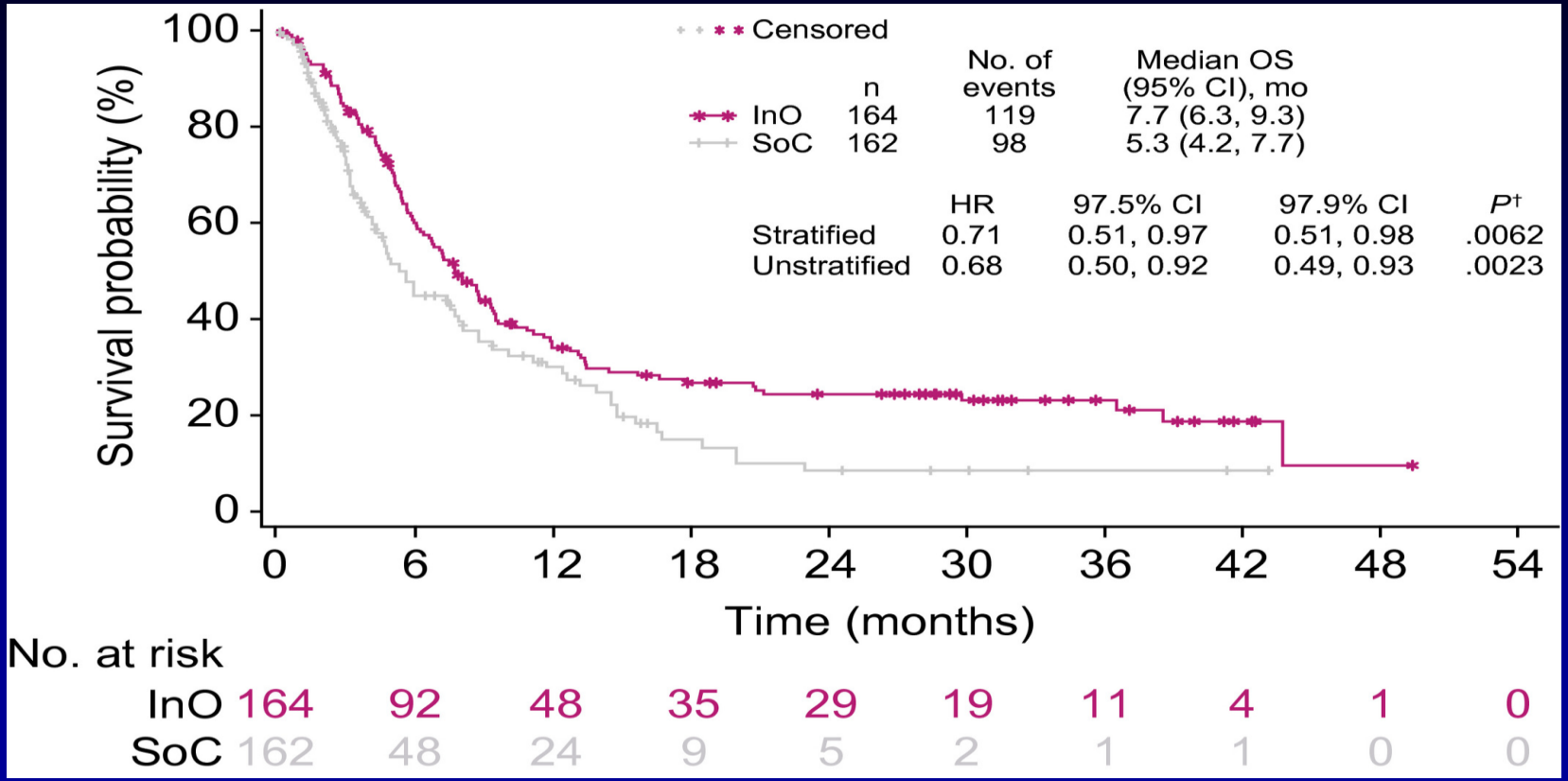


61 patients evaluated for immunophenotype; 56 (92%) had CD19+ disease

- **5 (8%) had ALL recurrence with CD19– disease**
- **2 patients progressed with lower CD19+ disease**

Jabbour. *Am J Hematol.* 2018;376:836-847.

OS After Censoring



Kantarjian H, et al. *Cancer*. 2019;125(14):2474-2487.

AlloSCT Post-inotuzumab in R/R ALL

- 236 pts Rx with inotuzumab; 103 (43%) alloSCT
- Ino as S1 in 62%; prior SCT 15%
- Median OS post-SCT 9.2 mo; 2-yr OS 46%
- 73 pts had alloSCT in CR post-Ino: 2-yr OS 51%
- VOD 19/101 = 20%
- Lower risk of mortality post-HSCT associated with MRD negativity and no prior HSCT

Kebriaei, et al. *Blood.* 2017;130:abstract 886.

Phase II Study of Inotuzumab in R-R Children-AYA ALL (COG ALL0232)

- 48 pts; median age 9 yr (1–21). S2+ 67%. Prior blina 29%; prior allo-SCT 23%; prior CAR T 23%
- Inotuzumab weekly × 3: 0.8–0.5 mg/m^2 D1, 0.5 mg/m^2 D8 and D15. Total 1.8–1.5 mg/m^2/course, up to 6 courses
- CR/CRi 30/48 (62%), MRD– 19/29 (65%)
- 12-mo EFS 36%; 12-mo OS 40%
- 19 pts (39%) received allo-SCT
- 5 VOD (10.4%): all post-SCT: 5/19 (26%)

O'Brien. *Blood.* 2019;134:abstract 741.

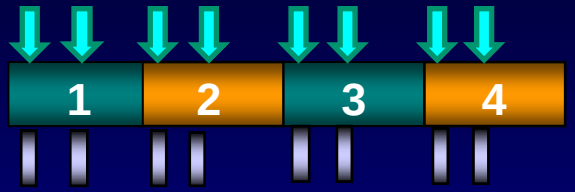
Mini-HCVD–Ino–Blina in ALL: Design

- Dose-reduced hyper-CVD for 4–8 courses
  - Cyclophosphamide (150 mg/m^2 × 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 × 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1 and 8) and 0.6 mg/m^2 C2–4 (0.3 and 0.3 on D1 and 8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055.

Mini-HCVD + Ino ± Blinatumomab in R-R ALL: Modified Design

Intensive phase



Mini-HCVD

Mini-MTX–cytarabine

IT MTX, ara-C

Blinatumomab

POMP

Consolidation phase

Ino	Total Dose (mg/m²)	Dose per Day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2–4	0.6	0.3 D1 and D8

Total ino dose = 2.7 mg/m²

Maintenance phase

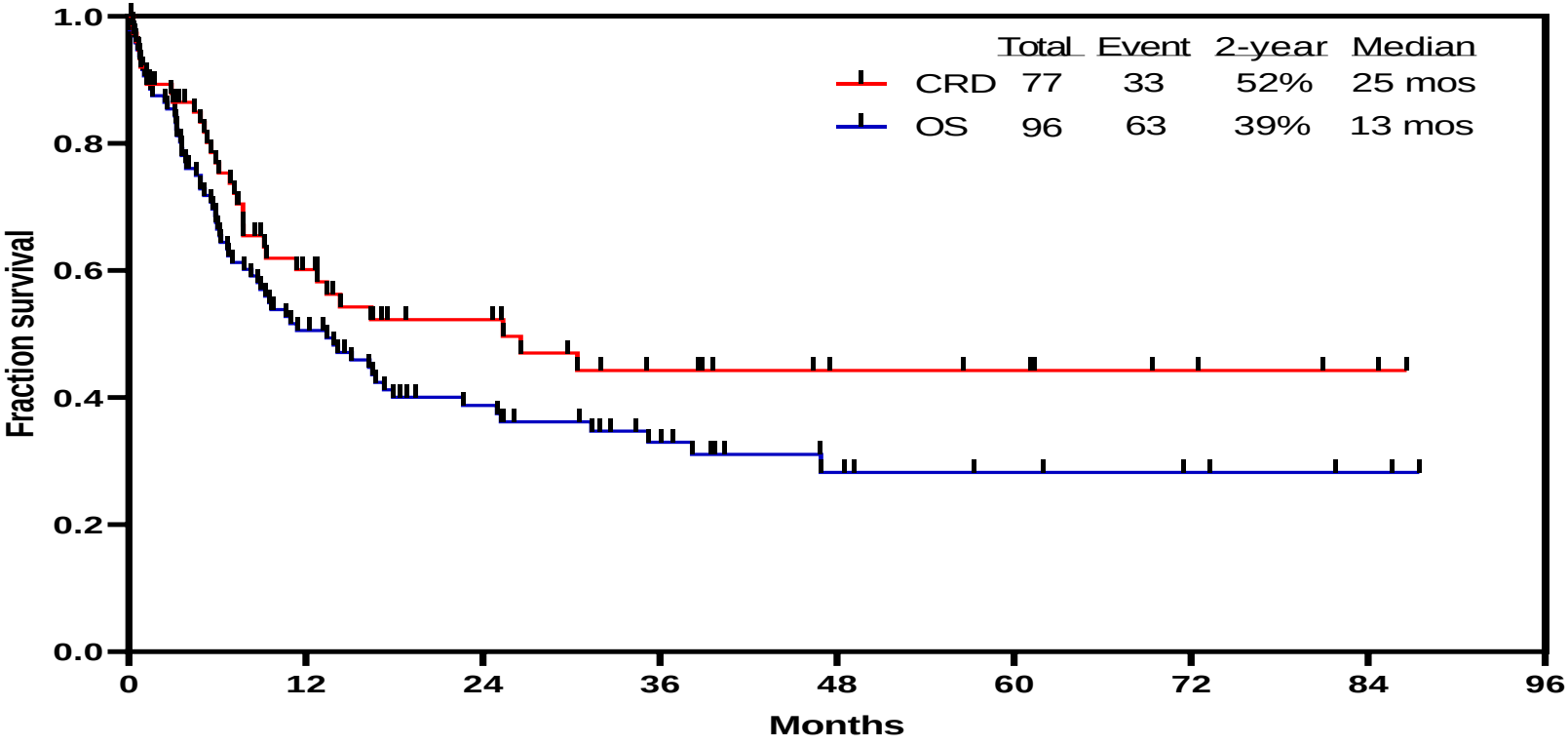
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Sasaki K, et al. *Blood.* 2018;132:abstract 553.

Mini-HCVD + Ino ± Blinatumomab in R-R ALL: Response by Salvage (N = 96)

Response	N	Percentage
Salvage 1	58/64	**91**
S1, primary refractory	8	100
S1, CRD1 <12 mo	21	84
S1, CRD1 ≥12 mo	29	94
Salvage 2	11	61
Salvage ≥3	8	57
Overall	**77**	**80**
MRD–	62/75	83
Salvage 1	**50/56**	**89**
Salvage ≥2	12/19	63
Early death	7	7

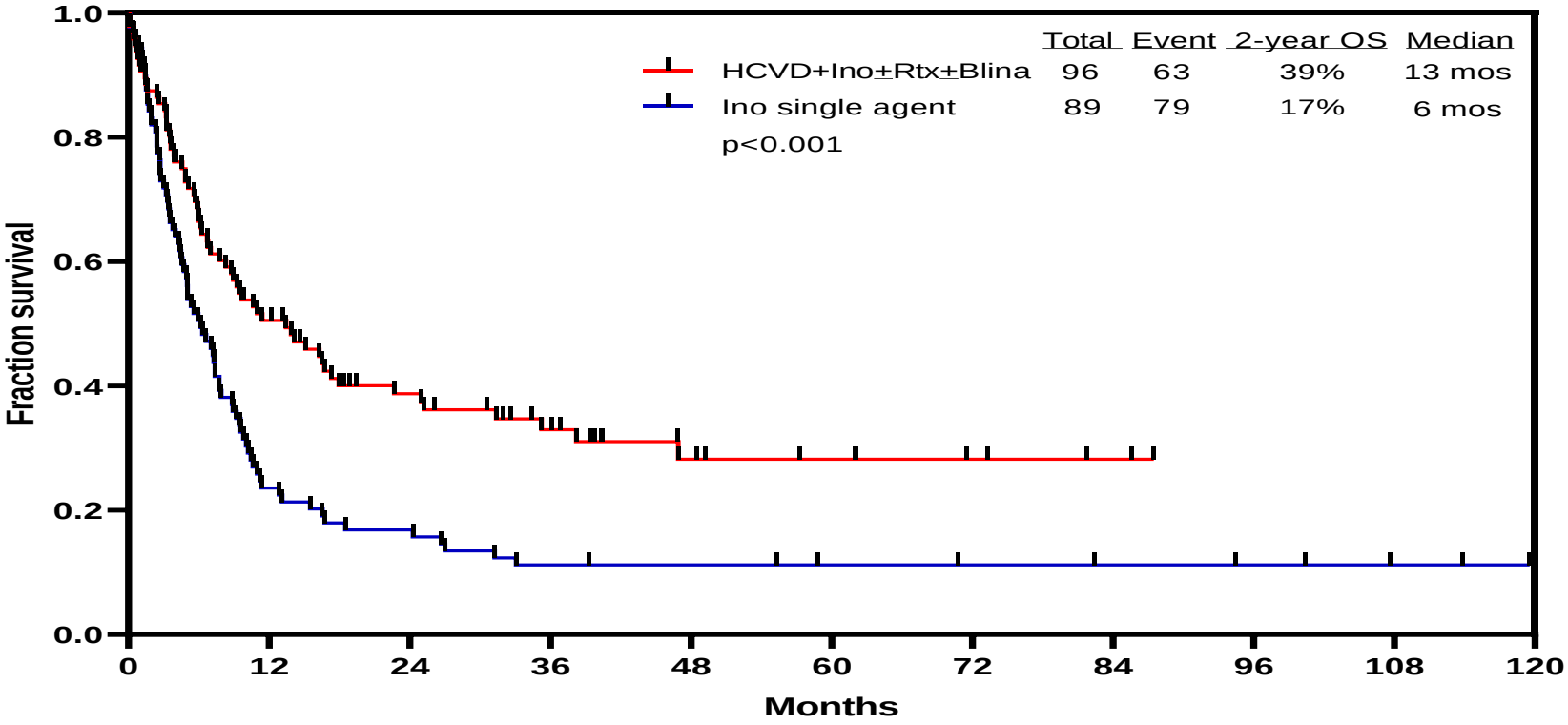
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055.

Mini-HCVD + Ino ± Blinatumomab in R/R ALL: CR Duration and OS (median F/U 48 months)



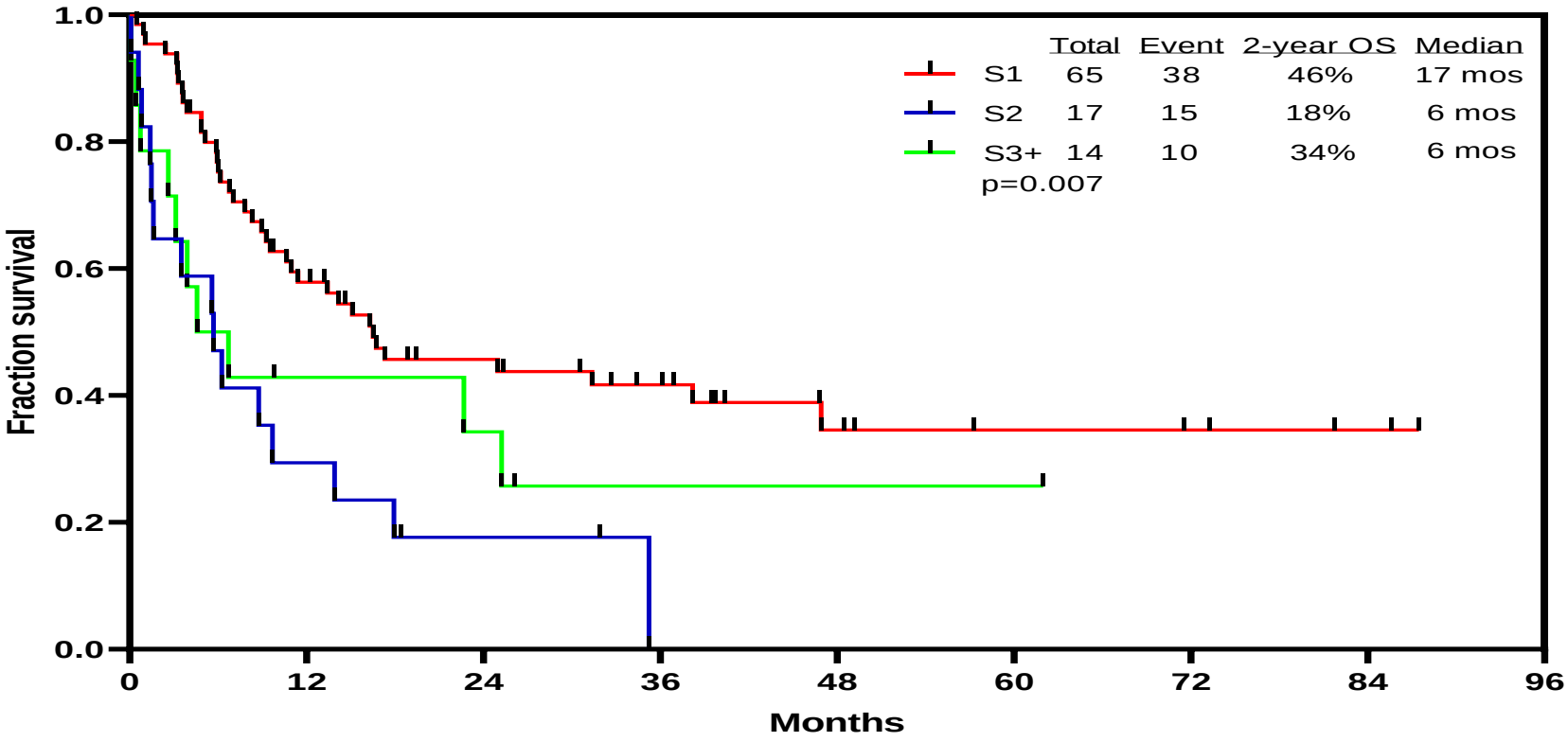
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Sasaki K, et al. *Blood*. 2018;132(suppl):553.

Mini-HCVD + Ino ± Blinatumomab in R/R ALL: Historical Comparison



Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Sasaki K, et al. *Blood*. 2018;132(suppl):553.

Mini-HCVD + Ino ± Blinatumomab in R/R ALL: OS by Salvage Status

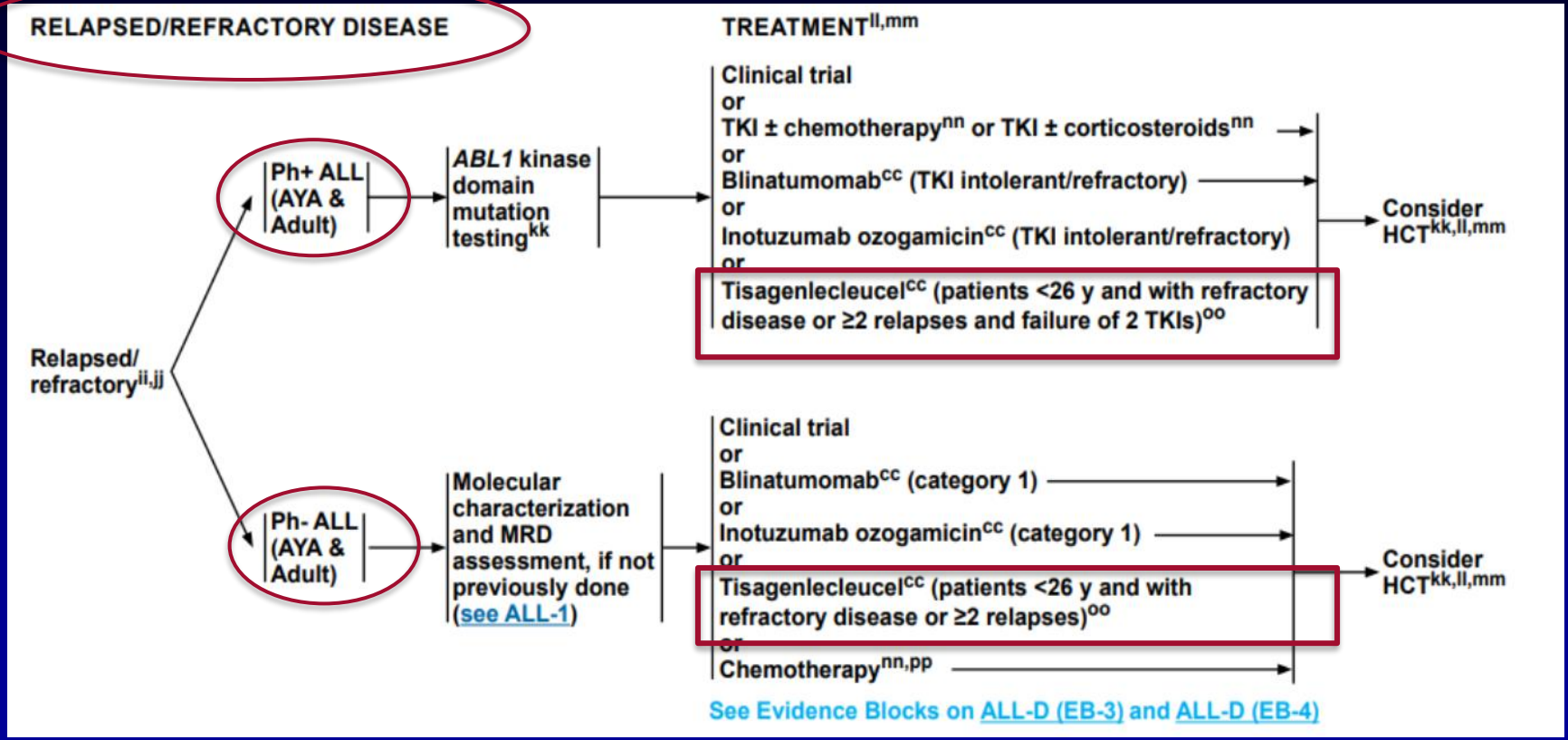


Sasaki. *Blood.* 2018;132:abstract 553; Jabbour E. *JAMA Oncol.* 2018;4:230.

Mini-HCVD + Ino ± Blina in ALL: VOD

- N = 96 pts
  - 67 pts Rx monthly InO; of them, 22 (33%) received subsequent alloSCT
  - 29 pts Rx weekly low-dose InO followed by Blina; of them, 15 (52%) received subsequent alloSCT
- VOD = 9 (9%); all had at least 1 alloSCT, 3 had 2 alloSCT
  - 9/67 (single; 13%) vs 0/29 (weekly LD; 0%)

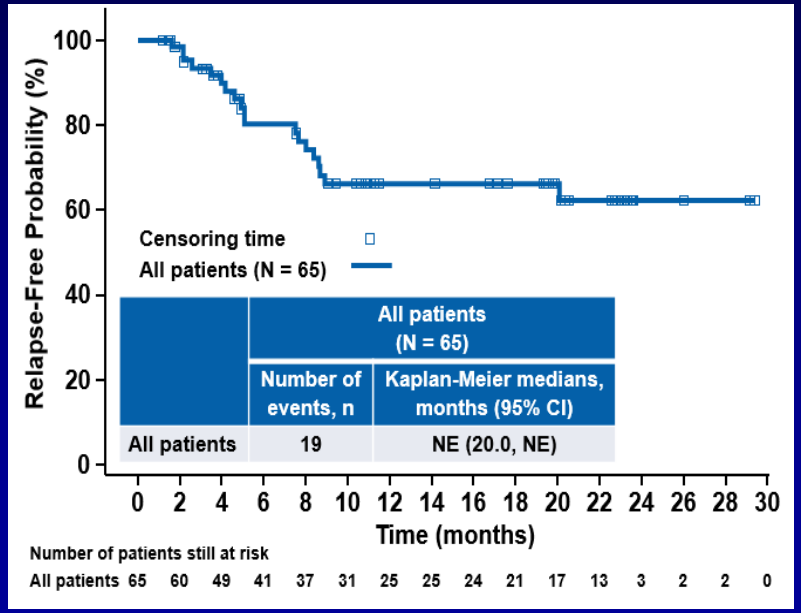
Where Does CAR T-Cell Therapy Stand?

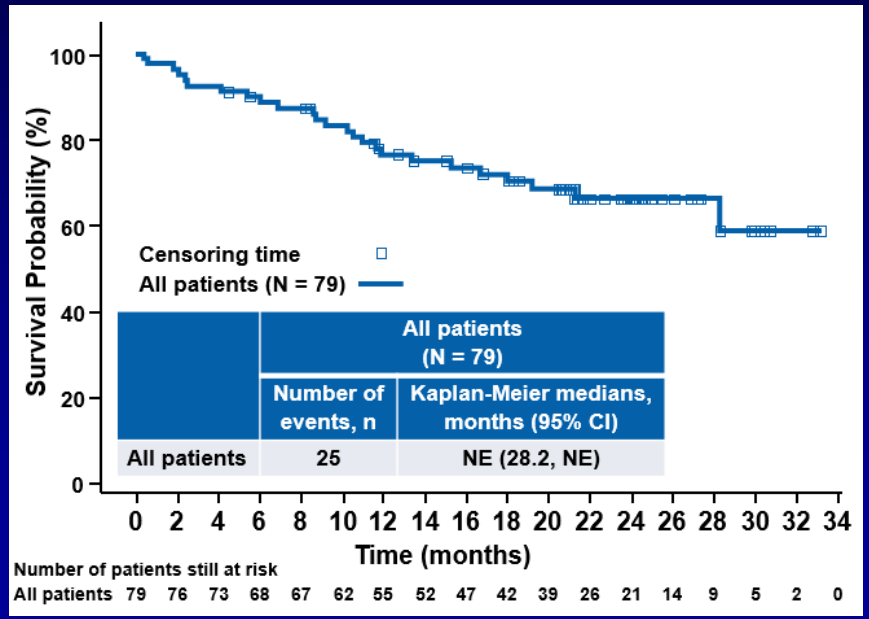


NCCN Guidelines ALL version 1.2020: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

ELIANA Trial Update

- 113 screened, 97 enrolled, 79 infused
- 3-mo CR 65/79 = 82%, or 65/97 = 67%
- 24-mo OS 66%; RFS 62%. G 3–4 CRS 49%. ICU 48%

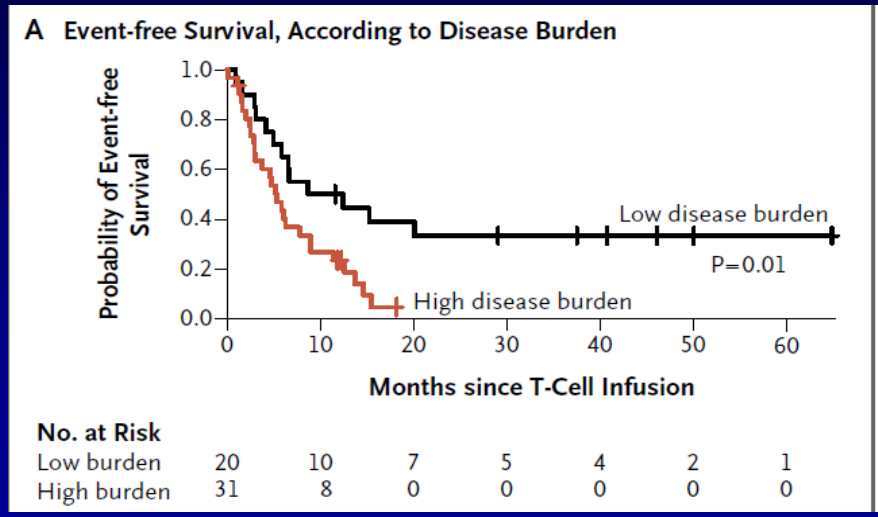


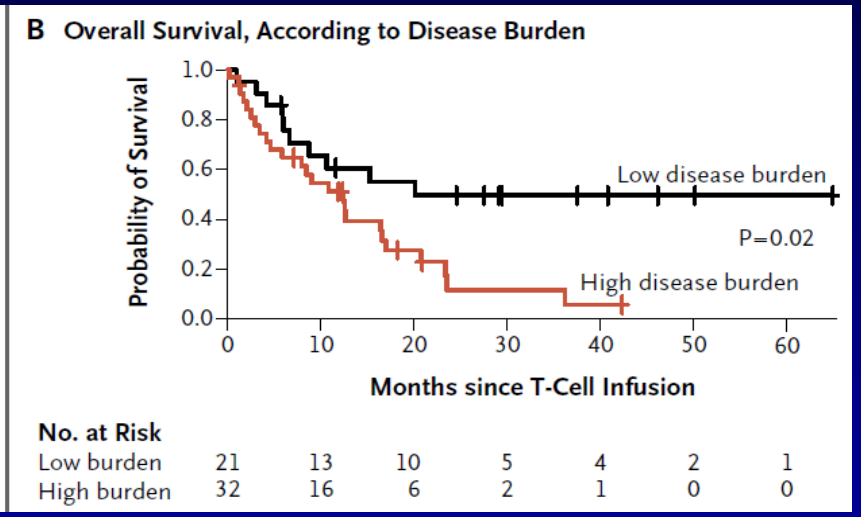


Grupp. EHA 2019. Abstract S1618.

CD19-CD28z CAR (MSKCC): Outcome by Tumor Burden

- High tumor burden
  - Bone marrow blasts ≥5% (n = 27)
  - Bone marrow blasts <5% + extramedullary disease (n = 5)
- Low tumor burden (MRD+ disease; n = 21)





Median EFS
Low tumor burden (MRD+): 10.6 mo
High tumor burden: 5.3 mo

Median OS
Low tumor burden (MRD+): 20.1 mo
High tumor burden: 12.4 mo

Park. *N Engl J Med.* 2018;378:449-459.

Adult R-R ALL: CAR T vs MoAb

Parameter	HCVD-Ino-Blina	MSKCC (R-R)	MSKCC (MRD)	Blina (MRD)
N	ITT	Evaluable		ITT
ORR, %	78	75	95	NA
MRD–, %	83	67		78
Median OS, mo	**14**	**12.4**	**20.1**	**36**
Salvage 1, mo	**25**	**Not reported**	Not reported	40
Toxicities	VOD (10%)	G3–4 CRS (26%); NE (42%)		G3–4 CRS (2%); NE (13%)

Personal communication from Dr Jabbour.

Venetoclax + Navitoclax in R/R ALL

- Navitoclax inhibits BCL2, BCL-XL, and BCL-W
- Venetoclax-navitoclax synergistic antitumor activity
- Rx with Ven/Nav + chemoRx (PEG-ASP, VCR, Dex)
- 47 pts (25 B-ALL + 19 T-ALL + 3 LL), median age 29
- Median 4 prior therapies; 28% post-ASCT, 13% post-CAR T
- ORR 28/47 (60%); MRD negativity 15/26 (58%)
- 4/32 (13%) CR/CRi/CRp at D8 after Ven/Nav
- Median OS 7.8 mo; 9.7 mo (B-ALL) and 6.6 mo (T-ALL)
- Preliminary BH3 profiling analysis revealed a trend in BCL2 dependence at baseline in T-ALL cells vs both BCL2 and BCL-XL dependence in B-ALL cells

Jabbour E, et al. EHA 2020. Abstract 144.

Salvage Therapies in ALL: Conclusions

- Very effective salvage therapy in R/R ALL
  - High MRD negativity rate
  - Best outcome in salvage 1
- Combination with low-dose chemotherapy
  - Safe and effective
  - Median survival 14 months
  - Salvage 1: 24 months (2-year OS rate >50%)
- AEs better controlled
  - CRS: debulk with sequential chemotherapy
  - VOD lower doses explored
- CAR T-cell Rx offered post-blinatumomab and -inotuzumab failure
  - Salvage 2 and high-risk salvage 1 (eg, MLL)
  - Consolidation in high-risk patients (replacing alloSCT)
- Better "blinatumomab" and "inotuzumab" needed
  - Better "Blina": long half-life; SQ; no neurotoxicities
  - Better "InO": no VOD

Global Leukemia Academy

Debate on CD19-Targeted Approaches: Discussion and Voting

APTITUDE HEALTH®

Question 1

What is your preferred ALL treatment choice in salvage, after the debate?

a) CAR T therapies

b) Monoclonal antibodies or bispecifics

Question 2

Do you think that children and young adults with active non-bulky CNS disease can safely be treated with CD19 CAR T cells?

a) Yes

b) No

c) I do not know

Question 3

What advantages do you see in bispecific antibodies vs CAR T cells?

a) Readily available off the shelf
b) Dosing can be easily interrupted in case of toxicity
c) Can be combined with chemotherapy
d) I do not know

Global Leukemia Academy

Emerging Data and the Management of ALL Patients During COVID-19

Elias Jabbour

APTITUDE HEALTH®

Question 1

Has the COVID-19 pandemic impacted the number of new cancer patients you are seeing in your clinic?

- **No, I am seeing about the same number of new cancer patients per month**
- **Yes, I am seeing fewer new cancer patients per month**
- **Yes, I am seeing more new cancer patients per month**

Question 2

Do you feel that associations like NCCN, ASCO, or ASH have provided sufficient guidance on caring for cancer patients during the COVID-19 pandemic?

- **Yes**
- **No**

Treating Leukemia in the Time of COVID-19

- Clinical infection <1%–2% worldwide
  - ✓ Mortality rate of 1%–5% in COVID-infected patients in the general population
  - ✓ Potentially ≥30% in patients with cancer

- Careful consideration to the risk of COVID-19 in leukemia vs
  - ✓ Reducing access of patients to specialized cancer centers
  - ✓ Modifying therapies to those with unproven curative benefit

Treating Leukemia in the Time of COVID-19

- **Patients with leukemia have uniquely higher risk of COVID-19 infection for multiple reasons associated with**
  - ✓ **Underlying disease**
  - ✓ **Treatment**
  - ✓ **Patient-specific factors**

Risk Factors	Cause		
	Leukemia Diagnosis	Treatment	Patient Specific
Neutropenia	X	X	
Leukopenia	X	X	
Hypogammaglobulinemia	X	X	
Depressed immune function	X	X	
Hypercoagulable state	X	X	
Organ dysfunction (cardiac, renal, liver, pulmonary)	X	X	X
Comorbid conditions			X
Age			X

Paul S, el at. *Acta Haematol.* 2020;1-13.

Treating Leukemia in the Time of COVID-19

	Possible Risk Factors
ALL	• Myelosuppression due to underlying disease and treatment • Hypogammaglobulinemia • Impaired B-cell function due to CD20-targeted monoclonal antibodies • Prolonged steroid exposure • Pulmonary and renal impairment due to methotrexate therapy • Cardiac dysfunction due to anthracycline exposure • Increased risk of COVID-19–associated thrombosis with asparaginase
AML	• Myelosuppression due to underlying disease and treatment • Cardiac dysfunction due to anthracycline exposure • Pulmonary injury due to midostaurin
CML	• Cardiac injury due to dasatinib, nilotinib, ponatinib • Pulmonary injury due to dasatinib • Increased risk of COVID-19–associated thrombosis with ponatinib and nilotinib
CLL	• Hypogammaglobulinemia • Impaired B-cell function due to CD20-targeted monoclonal antibodies • Impaired innate immune response as well as B-cell and T-cell function with Bruton's tyrosine kinase (BTK) inhibitors

Paul S, et al. *Acta Haematol.* 2020;1-13.

Treating Leukemia in the Time of COVID-19

- Weigh the treatment of a lethal, acute illness requiring aggressive therapy against the systemic limitations of inpatient stays, frequent clinic visits, and increasingly restricted blood product supply
- Development of several targeted therapies to treat acute leukemia may allow a reduction of dose-intensity while preserving the efficacy and the potential for cure
- Patients who are candidate for intensive Rx to be tested upfront

Treating Leukemia in the Time of COVID-19

- **Patients with leukemia have uniquely higher risk of COVID-19 infection for multiple reasons associated with**
  - ✓ **Underlying disease**
  - ✓ **Treatment**
  - ✓ **Patient-specific factors**

Risk Factors	Cause		
	Leukemia Diagnosis	Treatment	Patient Specific
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Leukopenia	X	X	
Hypogammaglobulinemia	X	X	
Depressed immune function	X	X	
Hypercoagulable state	X	X	
Organ dysfunction (cardiac, renal, liver, pulmonary)	X	X	X
Comorbid conditions			X
Age			X

Paul S, el at. *Acta Haematol.* 2020;1-13.

Treating Leukemia in the Time of COVID-19

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Paul S, et al. *Acta Haematol.* 2020;1-13.

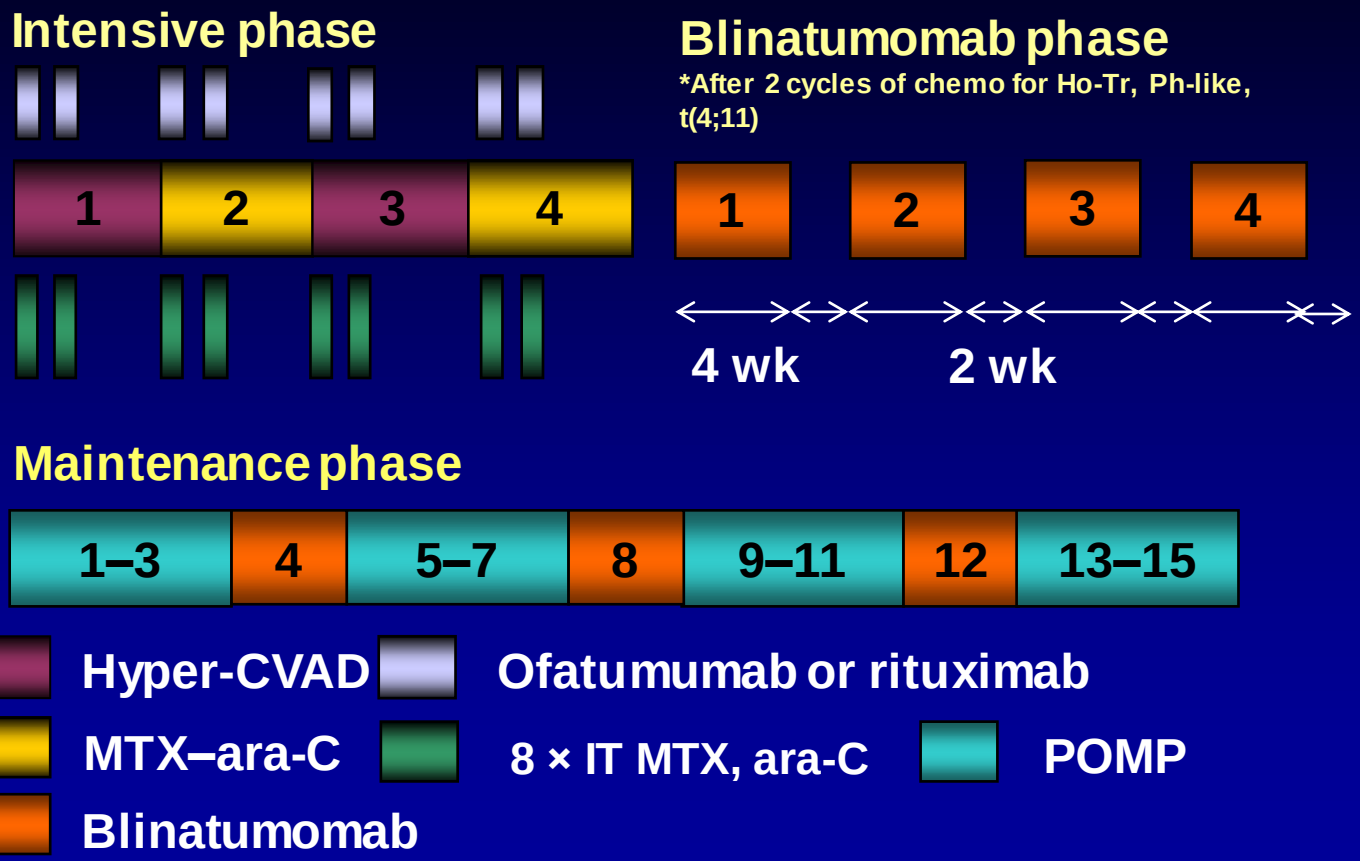
Treating ALL in the Time of COVID-19

Type				
ALL	Induction/ Consolidation	Ph negative	<60 y.o.	• HCVAD × 4 cycles followed by Blina × 4 cycles
			≥60 y.o.	• Mini-HCVD + Ino × 4 cycles followed by Blina × 4 cycles
			≥70 y.o.	• Mini-HCVD + Ino × 2 cycles followed by Blina × 8 cycles
			MRD positive	• Move to Blina early after 2 cycles of HCVAD or mini-HCVD + Ino or clinical trial for MRD positivity • Allogeneic SCT can be considered if benefit outweighs risks
		Ph positive		• Blina + TKI or Ino + TKI • Blinatumomab + ponatinib preferred
	Maintenance			• Important to still give maintenance • May omit vincristine to reduce clinic visits and reduce steroids • May transition to maintenance early if MRD negativity achieved and administering HCVAD or mini-HCVD is logistically difficult • Incorporate Blina or low-dose Ino in late intensification

- **Asparaginase possibly increases the thrombotic risk: complication of COVID-19**
- **If necessary, peg-asparaginase recommended**

Paul S, el at. *Acta Haematol.* 2020;1-13.

Hyper-CVAD + Blinatumomab in B-ALL (Ph– B-ALL <60 years): Treatment Schedule

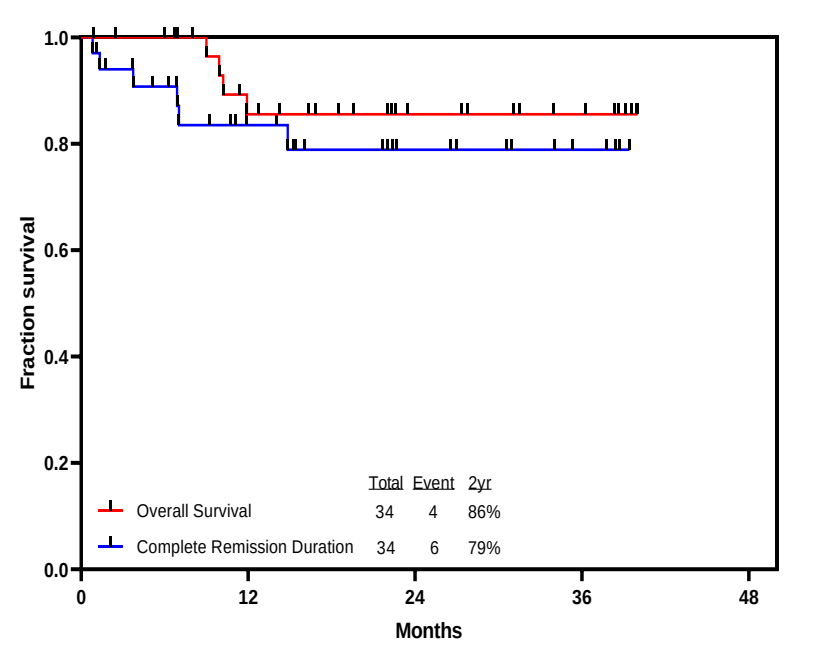


Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

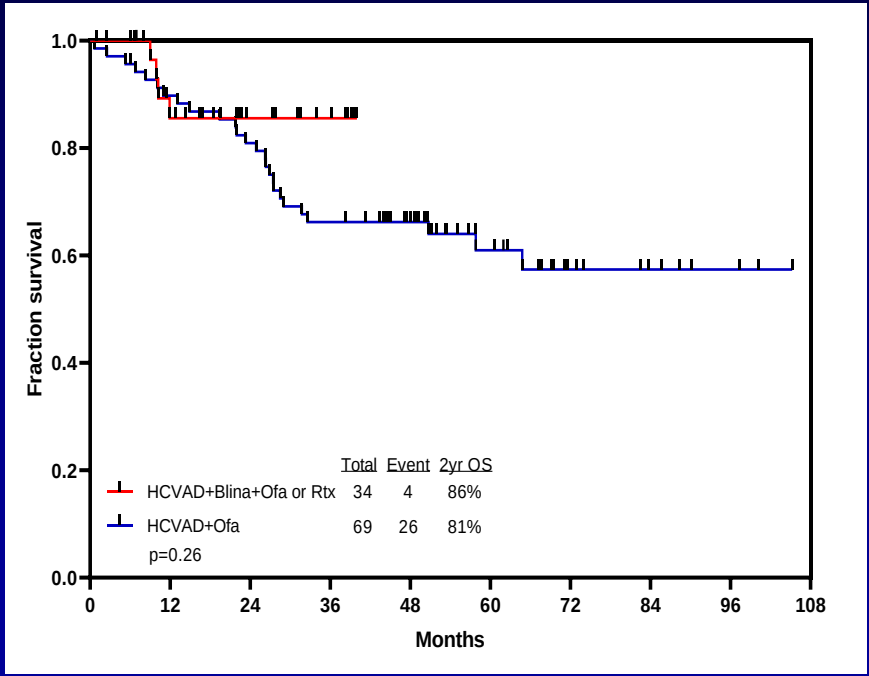
Hyper-CVAD + Blinatumomab in FL B-ALL (N = 34)

- CR 100%, MRD negativity 97% (at CR 87%), early death 0%

CRD and OS Overall

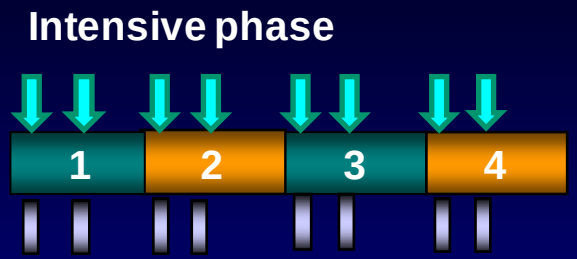


OS – HCVAD-Blina vs O-HCVAD



Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

Mini-HCVD + Ino ± Blina in Older ALL: Modified Design (pts 50+)



Mini-HCVD

Mini-MTX–cytarabine

IT MTX, ara-C

Blinatumomab

POMP

Ino*	Total Dose (mg/m^2)	Dose per Day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total ino dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Kantarjian H, et al. *Lancet Oncol.* 2018;19:240.

Mini-HCVD + Ino ± Blina in Older ALL (N = 64)

Characteristic	Category	N (%)/Median [range]
Age (years)	**≥70**	**68 [60-81]** **27 (42)**
Performance status	≥2	9 (14)
WBC (× 10^9/L)		3.0 [0.6-111.0]
Karyotype	Diploid HeH **Ho-Tr** **Tetraploidy** **Complex** **t(4;11)** Misc IM/ND	21 (33) 5 (8) **12 (19)** **3 (5)** **1 (2)** **1 (2)** 9 (14) 12(19)
CNS disease at diagnosis		4 (6)
CD19 expression, %		99.6 [30-100]
CD22 expression, %		96.6 [27-100]
CD20 expression	≥20%	32/58 (57)
CRLF2+ by flow		**6/31 (19)**
TP53 mutation		**17/45 (38)**

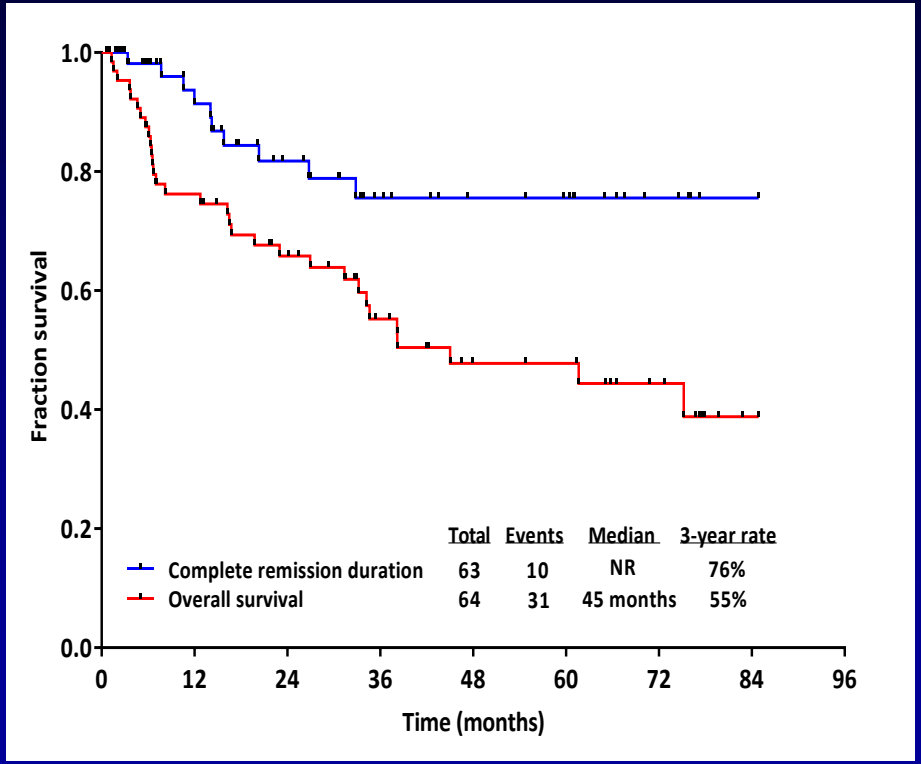
Response (N = 59)	N (%)
ORR	**58 (98)**
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	**0**

Flow MRD response	N (%)
D21	50/62 (81)
Overall	**60/63 (95)**

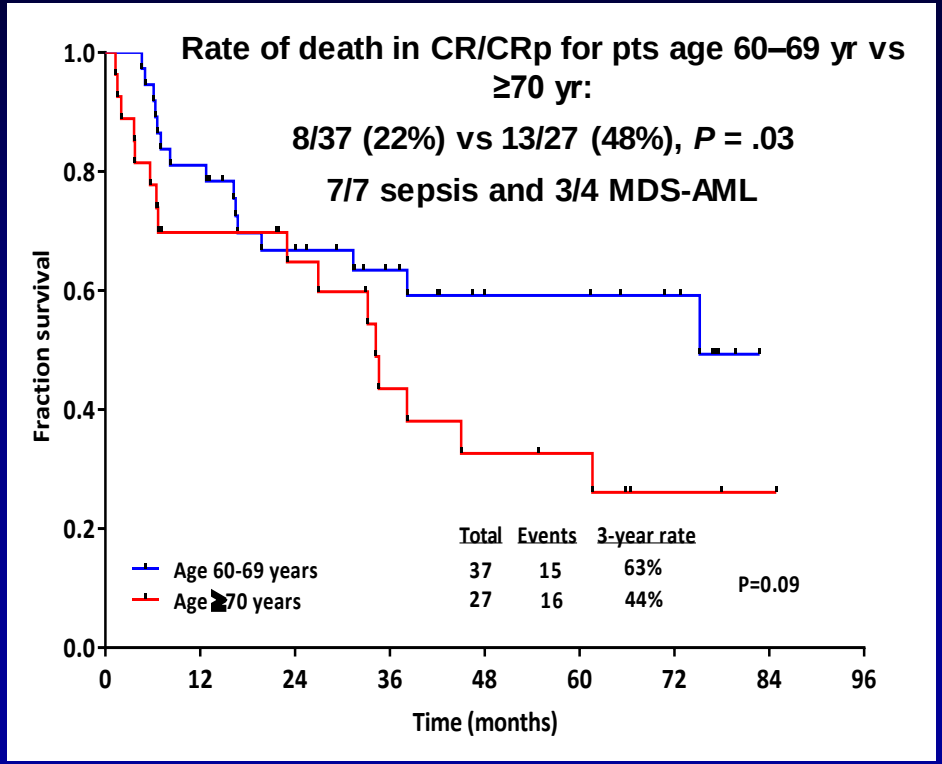
Short. *Blood.* 2019;134:abstract 823.

Mini-HCVD + Ino ± Blina in Older ALL: Outcome

CRD and OS overall



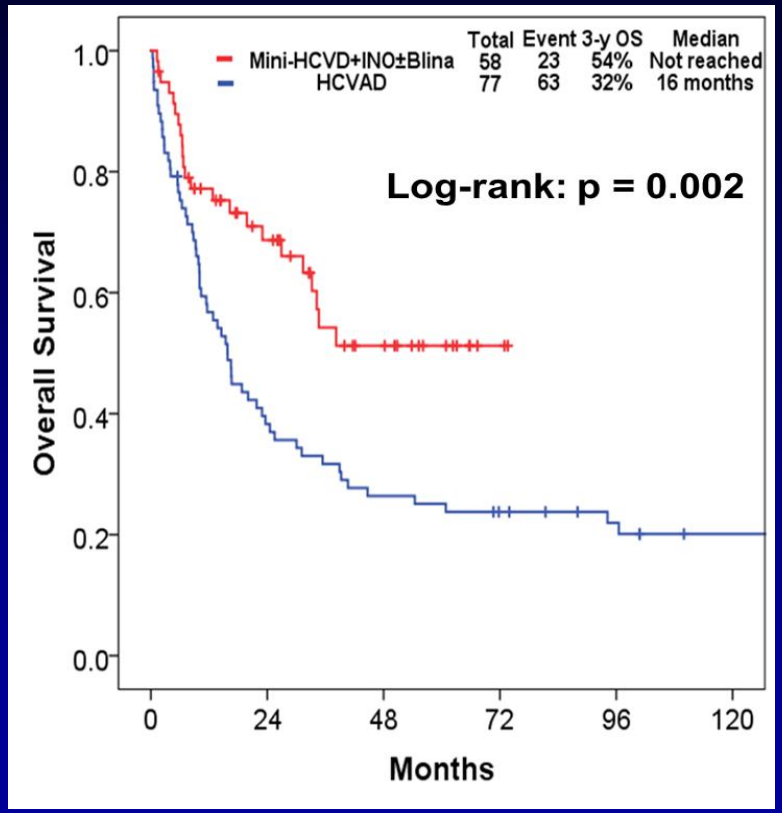
OS by age



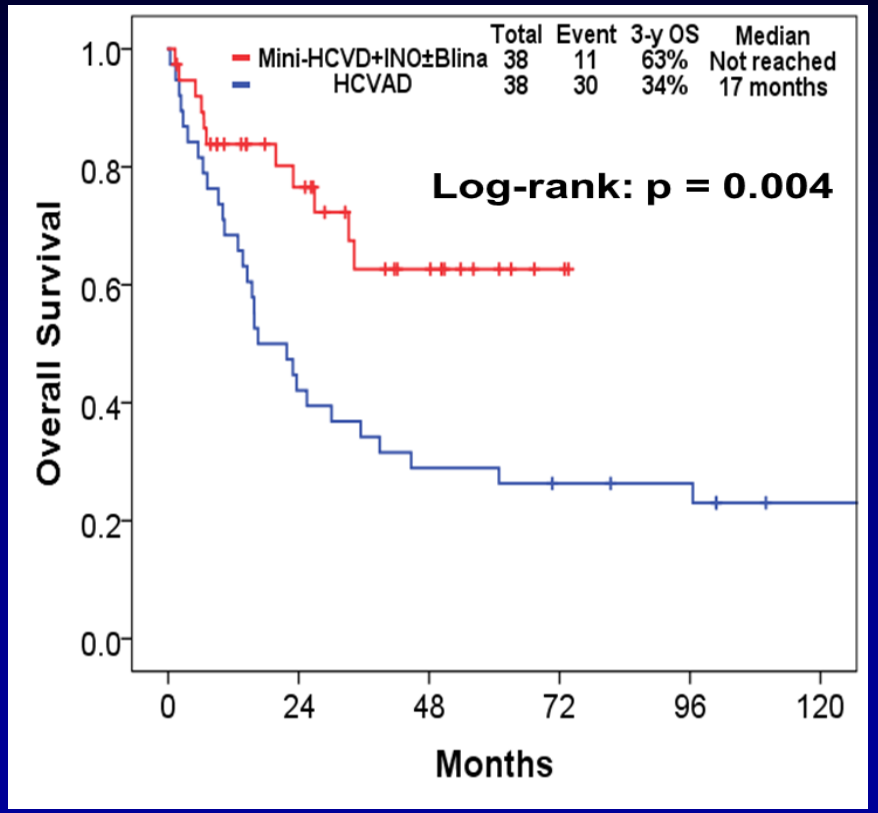
Short. *Blood.* 2019;134:abstract 823.

Mini-HCVD + Ino ± Blina vs HCVAD in Elderly ALL: Overall Survival

Prematched

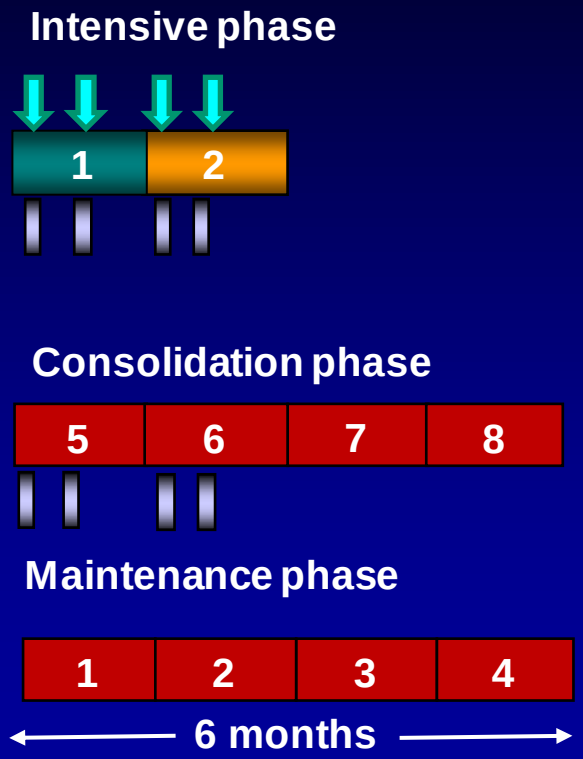


Matched



Sasaki. *Blood.* 2018;132:abstract 34.

Mini-HCVD + Ino ± Blina in Older ALL: Amended Design (pts ≥70 years)



Mini-HCVD

Mini-MTX–cytarabine

IT MTX, ara-C

Blinatumomab

POMP

Ino*	Total Dose (mg/m^2)	Dose per Day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2	0.6	0.3 D2 and D8

Total ino dose = 1.5 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Kantarjian H, et al. *Lancet Oncol.* 2018;19:240.

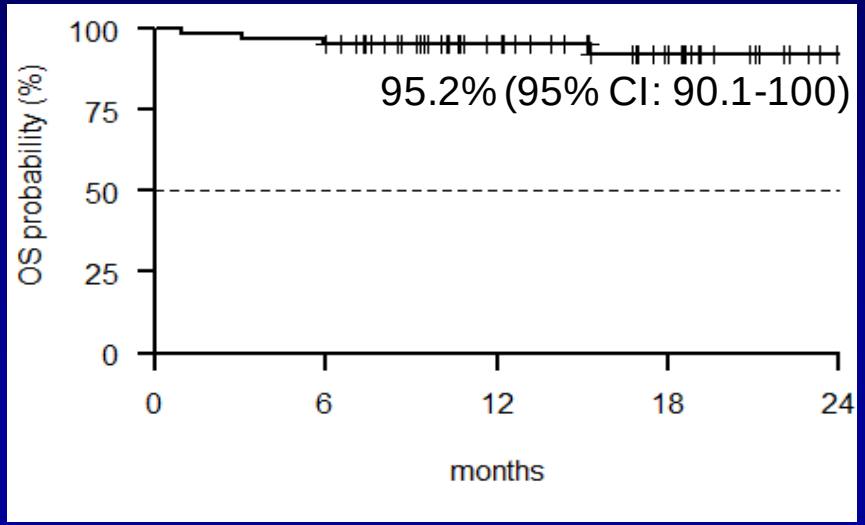
Treating ALL in the Time of COVID-19: Advantage of These Regimens

- Blina significantly less myelosuppressive. Although currently administered after 4 courses of HCVAD or mini-HCVD, pts switch to Blina earlier, after 2 courses, to avoid additional myelosuppression
- No or low tumor burden after intensive Rx, no CRS: need for hospitalization significantly reduced. Blina dose-escalation on day 5 instead of day 8
- 7-day bags: outpatient setting with reduced clinic visits
- Blina earlier deepens MRD response and safely shortens maintenance from 30 months to 18 months

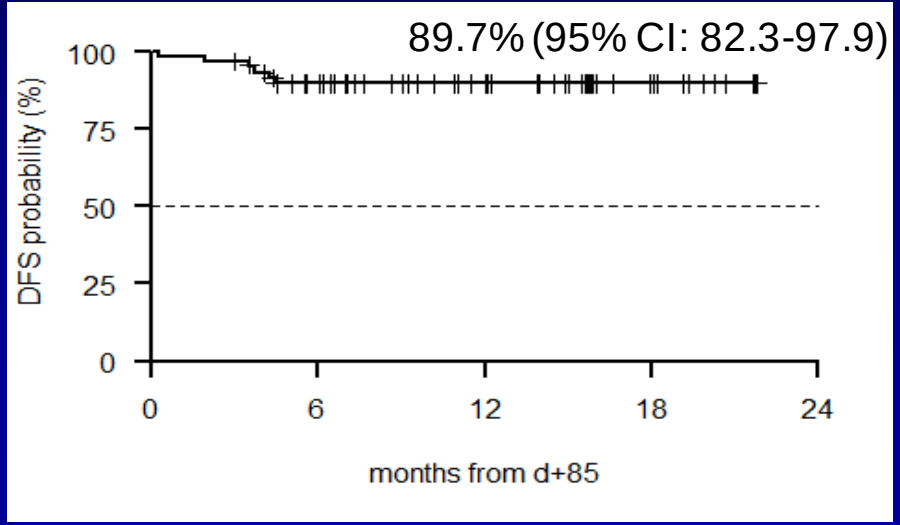
Dasatinib-Blinatumomab in Ph+ ALL

- 63 pts, median age 54 yr (24–82)
- Dasatinib 140 mg/D × 3 mo; add blinatumomab × 2–5
- 53 post–dasa-blina × 2 – molecular response 32/53 (60%), 22 CMR (41%); MRD ↑ in 15, 6 *T315I*; 12-mo OS 96%; DFS 92%

OS

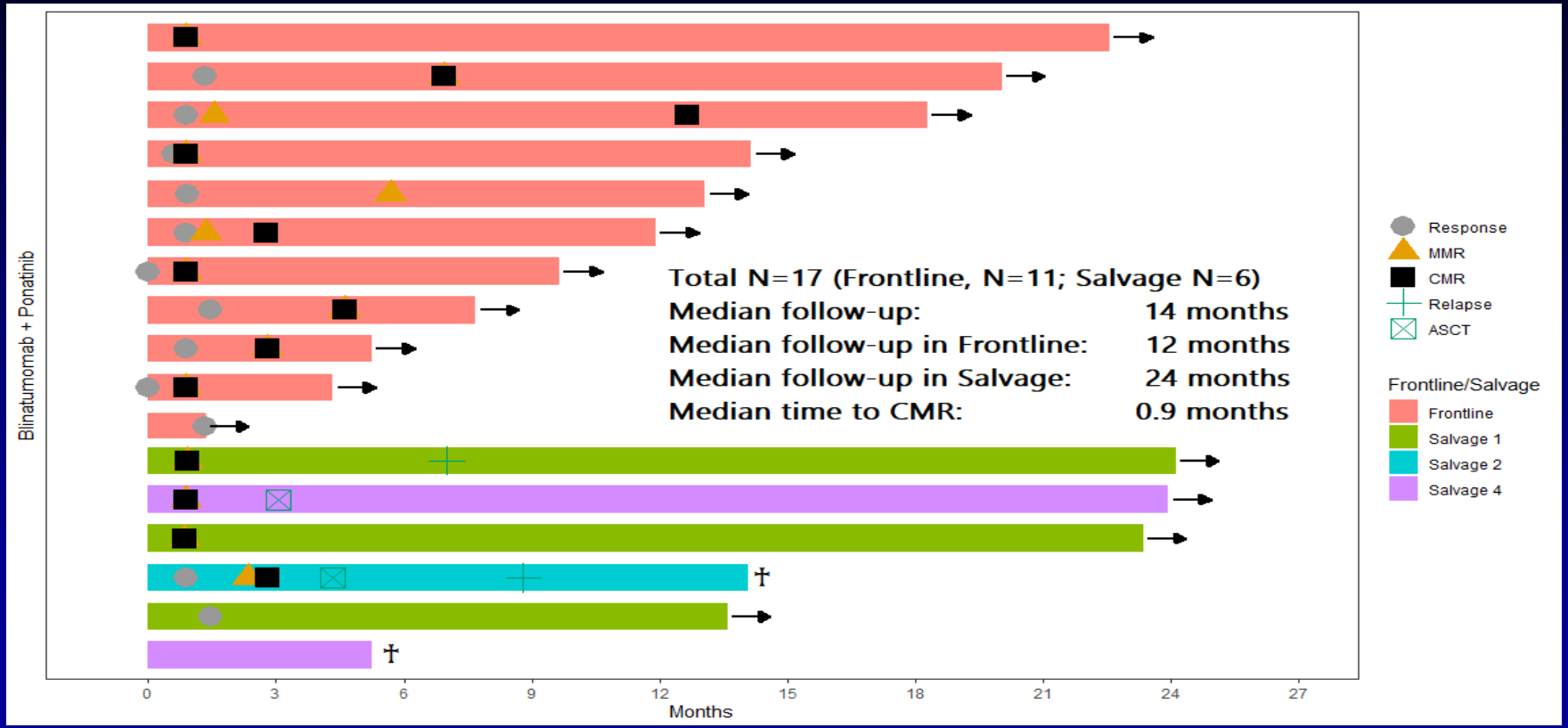


DFS



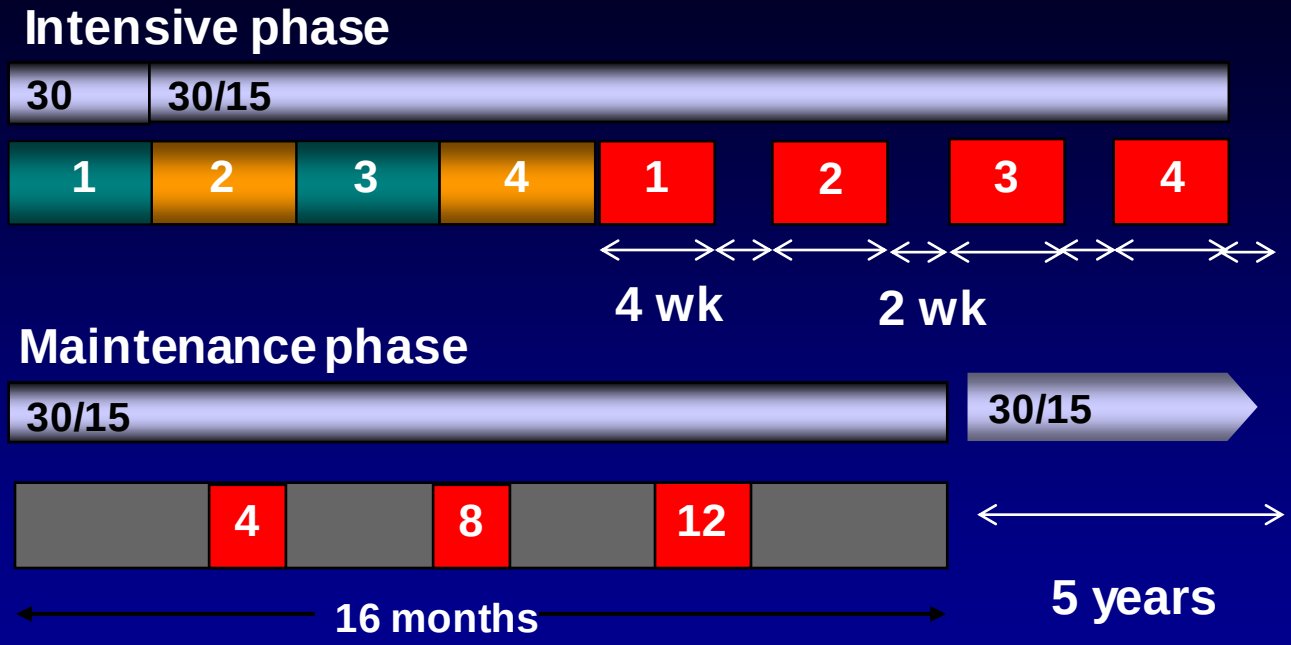
Chiaretti. *Blood.* 2019;134:abstract 615.

Blinatumomab + Ponatinib Swimmer Plot (N = 17)



Personal communication from Dr Jabbour.

Hyper-CVD + Ponatinib + Blinatumomab in Ph+ ALL



Risk-adapted intrathecal CNS prophylaxis (N = 12)

Mini-Hyper-CVD

Mini-MTX-cytarabine

Ponatinib 30 mg →15 mg

Vincristine + prednisone

Blinatumomab

https://clinicaltrials.gov/ct2/show/NCT03147612

Treating Leukemia in the Time of COVID-19

- Risk of COVID-19 complications weighed very carefully vs restricting access of patients to highly specialized centers and of advocating for regimens without known equivalent curative potential
- Efforts should be prioritized to reduce patient and staff exposure while maintaining optimal care
- Utilizing less-intensive Rx, reducing patient visits, and establishing collaborative care at local centers or through telemedicine
- Rx decisions individualized on the basis of patient-related factors, risk of added toxicity, and feasibility of treatment administration
- Standard hygiene and social distancing measures to be pursued

Global Leukemia Academy

Emerging Data and the Management of ALL Patients During COVID-19

Panel discussion

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Session Close

Elias Jabbour and Fatih Demirkan

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Virtual Breakout: Pediatric ALL Patients (Day 2)

Chair: Rob Pieters

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

Virtual Breakout: Adult ALL Patients (Day 2)

Chair: Elias Jabbour

TIME UTC+3	TITLE	SPEAKER
15.00 – 15.15	Session opening • Educational ARS questions for the audience	Elias Jabbour
15.15 – 15.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation • Q&A	Elias Jabbour
15.35 – 15.55	Current treatment options for relapsed ALL in adult and elderly patients • Presentation • Q&A	Fatih Demirkan
15.55 – 16.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, Fatih Demirkan, Andre Schuh, Josep-Maria Ribera	Fatih Demirkan Andre Schuh Discussion
16.45 – 17.00	Session close • Educational ARS questions for the audience	Elias Jabbour

Global Leukemia Academy

Closing Remarks

Elias Jabbour and Fatih Demirkan

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Thank You!

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

THANK YOU!