AMGEN

Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

23–24 July 2020

APTITUDE HEALTH®

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour and Eduardo Rego

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Meet the Faculty

Elias Jabbour, MD
Professor of Medicine
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University of Texas
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Houston, TX, USA

Patrick Brown, MD
Associate Professor of Oncology and Pediatrics, Director
Pediatric Leukemia Program
Johns Hopkins University
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Aaron Logan, MD, PhD
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Eduardo Rego, MD, PhD
Professor in the Faculty of Medicine
Medical School of Ribeirão Preto
São Paulo, Brazil

Roberta Demichelis, MD
Assistant Professor in the Department of Hematology/Oncology
INCMNSZ*
Mexico City, Mexico

*INCMNSZ, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

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
17.00 – 17.10	Welcome and meeting overview; introduction to the voting system	Elias Jabbour, Eduardo Rego
17.10 – 17.25	Review of prognostic value of MRD in ALL	Elias Jabbour
17.25 – 17.40	How and when to check for MRD in ALL	Eduardo Rego
17.40 – 17.55	MRD assessment and management in CR1 vs CR2 and beyond	Aaron Logan
17.55 – 18.10	Genetic variants in ALL – Ph+ and Ph-like	Elias Jabbour
18.10 – 18.25	AYA ALL patients – what is the current treatment approach for this diverse patient population?	Patrick Brown
18.25 – 18.45	Break	
18.45 – 19.00	Bispecific T-cell engagers as post-reinduction therapy improves survival in pediatric and AYA B-ALL	Patrick Brown
19.00 – 19.45	Panel discussion on the role of HSCT • Experience of HSCT in the region (ARS-guided assessment) • Pros and cons of HSCT, COVID-19 impact and measures • Discussion and voting	Moderator: Elias Jabbour Eduardo Rego Aaron Logan All faculty: A. Logan, P. Brown, E. Jabbour, E. Rego, R. Demichelis
19.45 – 20.25	Debate on CD19-targeted approaches • CAR T • Monoclonal antibodies and bispecifics • Discussion and voting	Moderator: Eduardo Rego Patrick Brown Elias Jabbour: All faculty: A. Logan, P. Brown, E. Jabbour, E. Rego, R. Demichelis
20.25 – 20.55	Emerging data and the management of ALL patients during COVID-19 • Presentation • Panel discussion	Moderator: Eduardo Rego Elias Jabbour All faculty
20.55 – 21.00	Session close	Elias Jabbour, Eduardo Rego

Virtual Breakout: Pediatric ALL Patients (Day 2)

Chair: Patrick Brown

TIME UTC-3	TITLE	SPEAKER
17.00 – 17.15	Session opening • Educational ARS questions for the audience	Patrick Brown
17.15 – 17.35	First-line treatment of pediatric ALL • Presentation • Q&A	Lia Gore
17.35 – 17.55	Current treatment options for relapsed ALL in children including HSCT and COVID-19 considerations • Presentation • Q&A	Franco Locatelli
17.55 – 18.15	Bispecific T-cell engagers for pediatric ALL • Presentation • Q&A	Patrick Brown
18.15 – 18.45	Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: María Sara Felice (Arg), Oscar González Ramella (Mex), Adriana Seber (Bra), Carlos Andres Portilla (Col)	Maria Sara Felice Carlos Andres Portilla Discussion
18.45 – 19.00	Session close • Educational ARS questions for the audience	Patrick Brown

Virtual Breakout: Adult ALL Patients (Day 2)

Chair: Elias Jabbour

TIME UTC-3	TITLE	SPEAKER
17.00 – 17.15	Session opening • Educational ARS questions for the audience	Elias Jabbour, Eduardo Rego
17.15 – 17.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation • Q&A	Elias Jabbour
17.35 – 17.55	Current treatment options for relapsed ALL in adult and elderly patients • Presentation • Q&A	Aaron Logan
17.55 – 18.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, Eduardo Rego, Aaron Logan, Roberta Demichelis	Roberta Demichelis Eduardo Rego Discussion
18.45 – 19.00	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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Q

Question 1

Where are you from?

a) Argentina
b) Brazil
c) Colombia
d) Mexico
e) Peru
f) Other

Q

Question 2

How many patients with ALL are you currently following?

a) 0
b) 1–5
c) 6–15
d) 16–20
e) ≥21

Q

Question 3

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

a) We do not check for MRD
b) Multicolor flow
c) Molecular PCR
d) 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

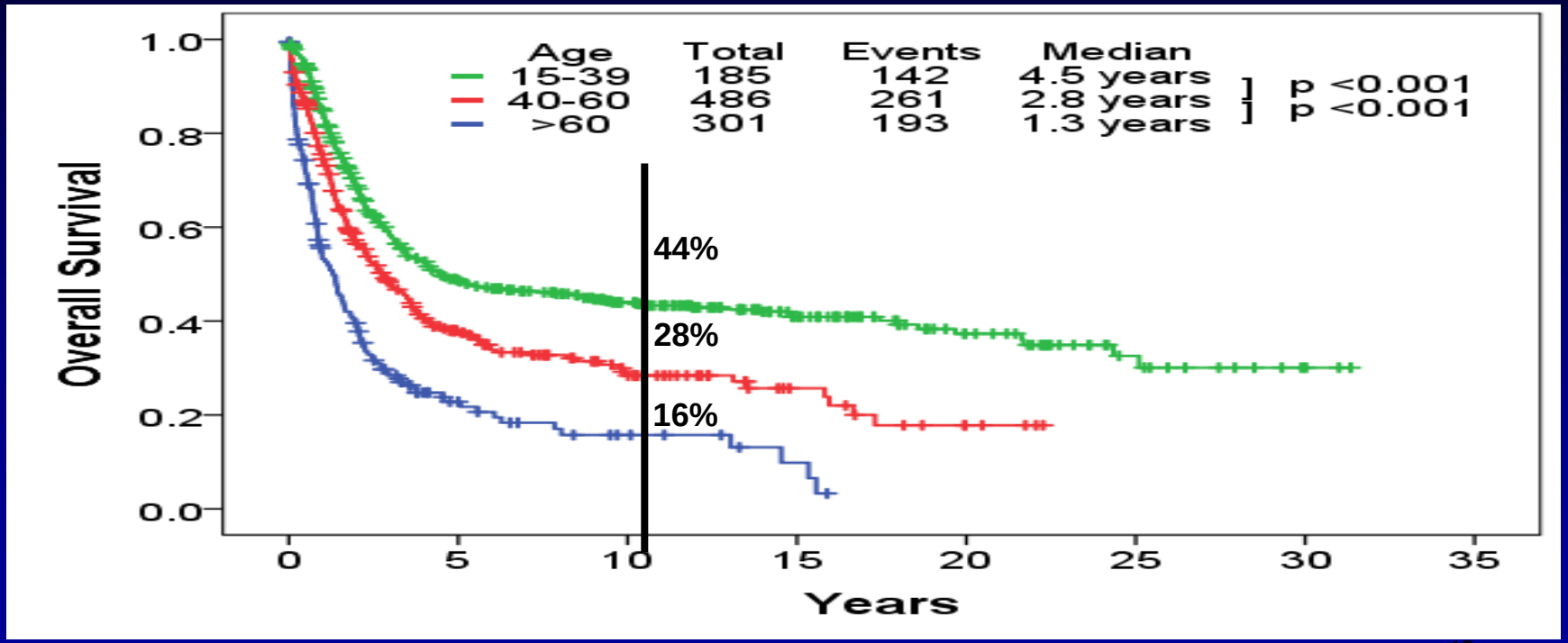
Conflict of Interest Disclosure

- **Research grants**
  - **Pfizer, Takeda, Amgen, AbbVie, Novartis**

- **Consultancy and advisory roles**
  - **Pfizer, Takeda, Amgen, AbbVie, BMS**

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} (1:10,000 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

Q

Question 1

When do you assess for MRD?

a) Monthly
b) At CR
c) At 3 months from induction
d) At CR and 3 months from induction, and every 3 months thereafter
e) 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

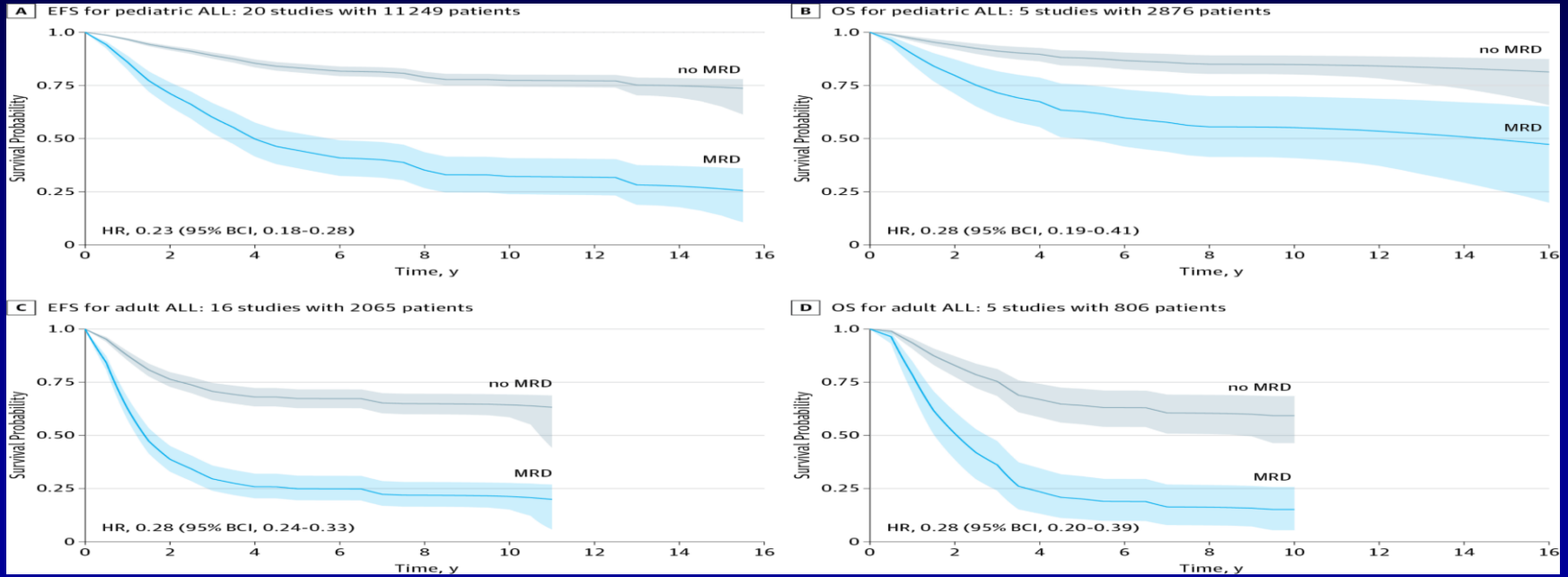
Treatment of ALL Before the MRD Era: High CR Rates but Relapse Is Common

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

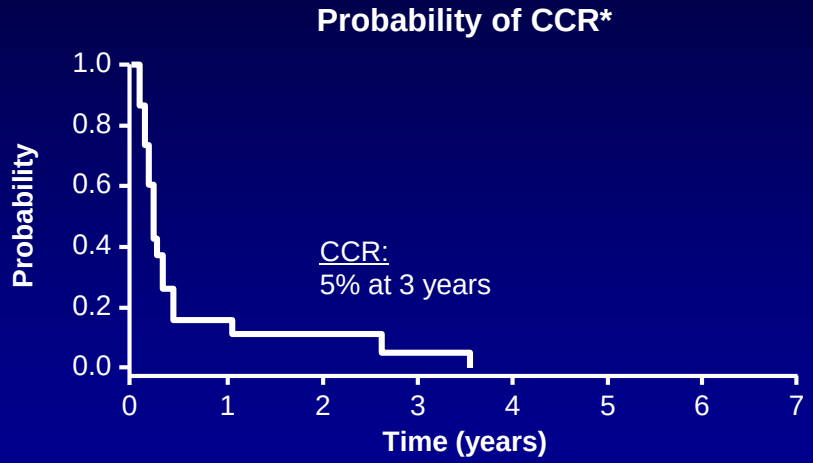
- Meta-analysis of 39 studies (pediatric and adult), including 13,637 patients with all subtypes
- Prognostic impact of MRD clearance consistent across therapies, MRD method, timing, level of cutoff, and subtypes

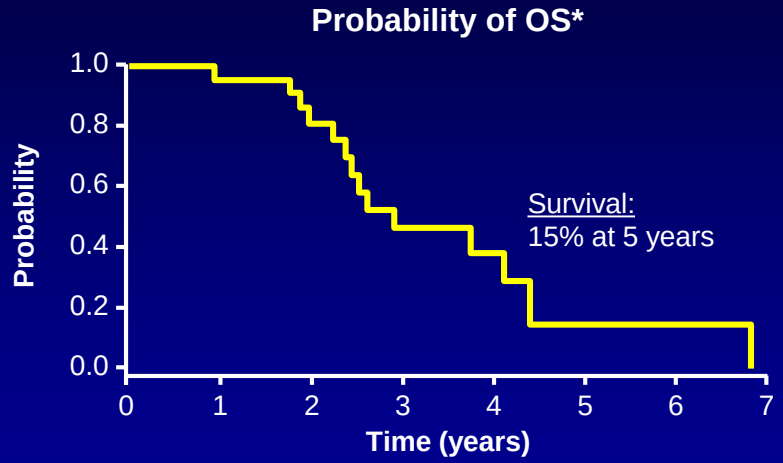


Berry DA. *JAMA Oncol.* 2017;3(7):e170580.

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.

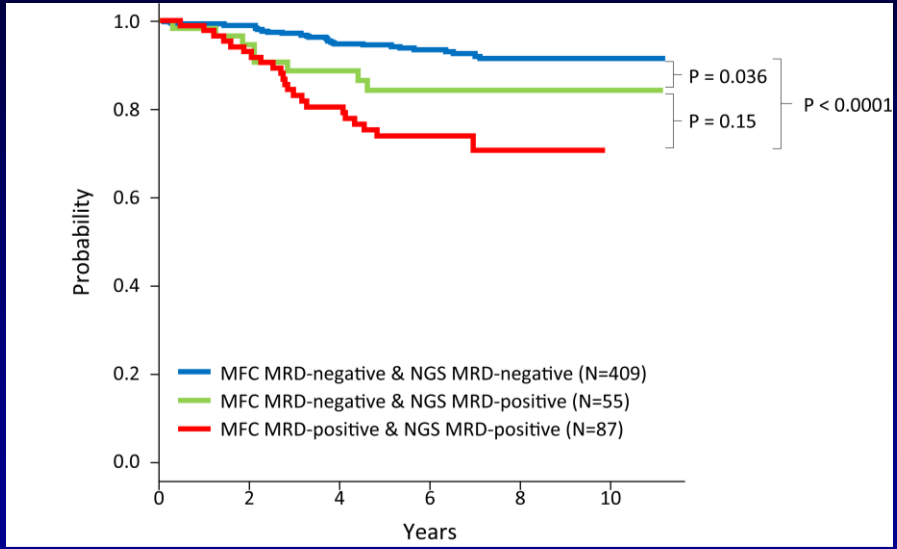
MRD Methods

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})



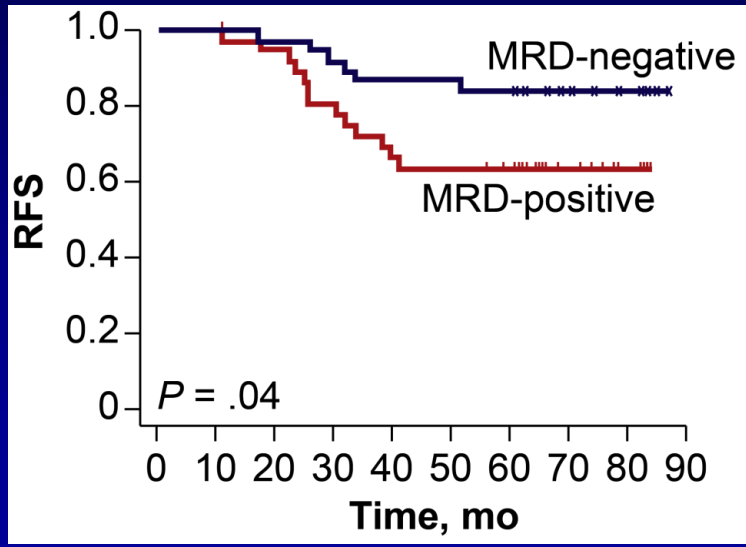
EFS was significantly worse in the NGS MRD+/flow cytometry MRD– group than patients who were MRD– by both methods (*P* = .036).
Six patients were identified as NGS MRD– and MFC MRD+.

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

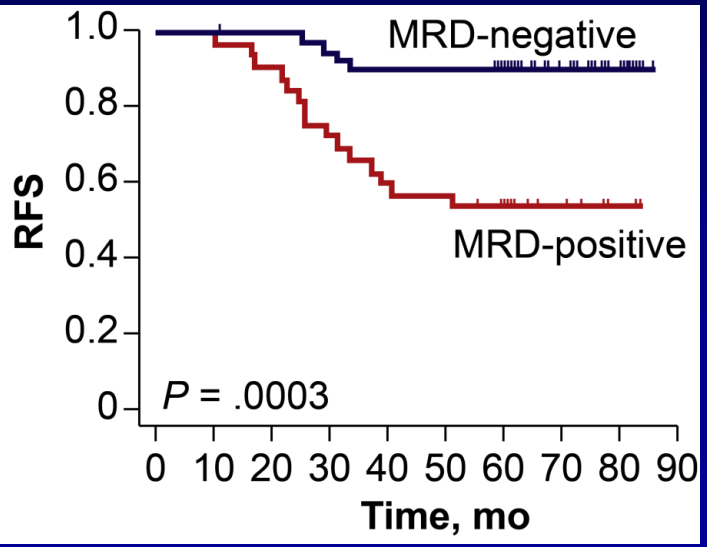
Comparison: NGS With RQ-PCR

- **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+ 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 $>10^{-4}$

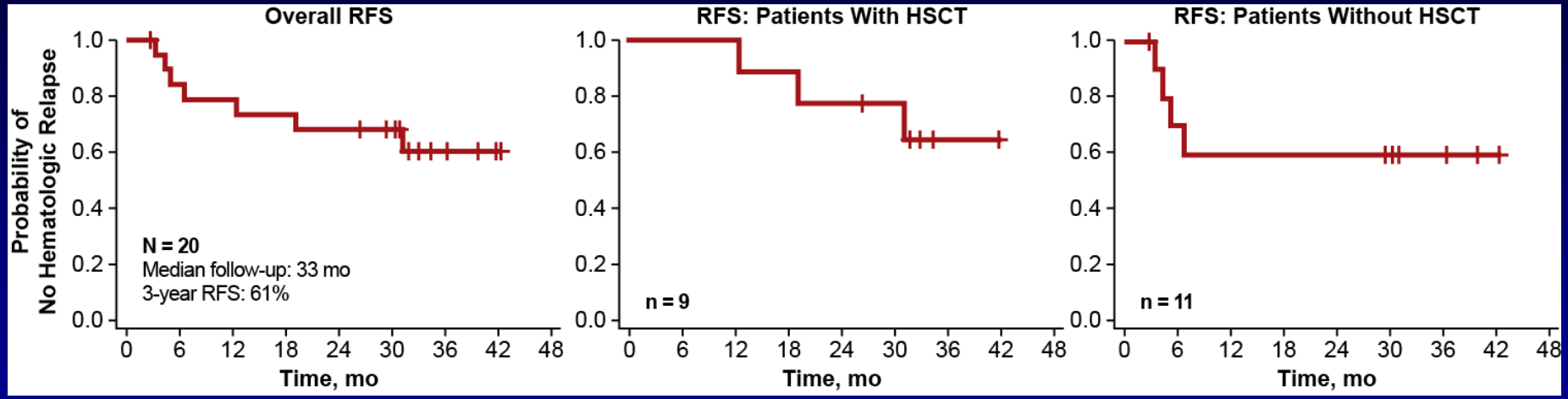
Postremission Rx of ALL According to FCM MRD

- 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 midconsolidation (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.

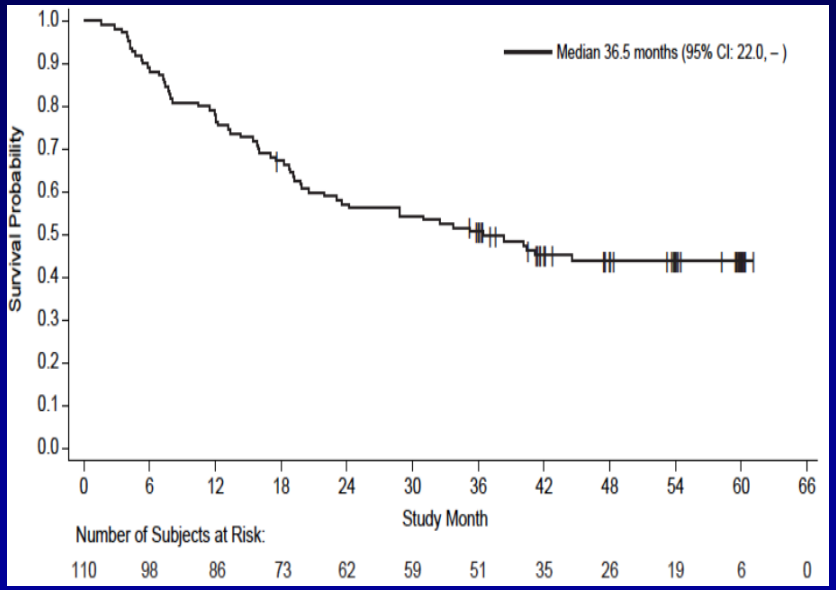
Blinatumomab in MRD+ BCP-ALL: MT103-202 Trial

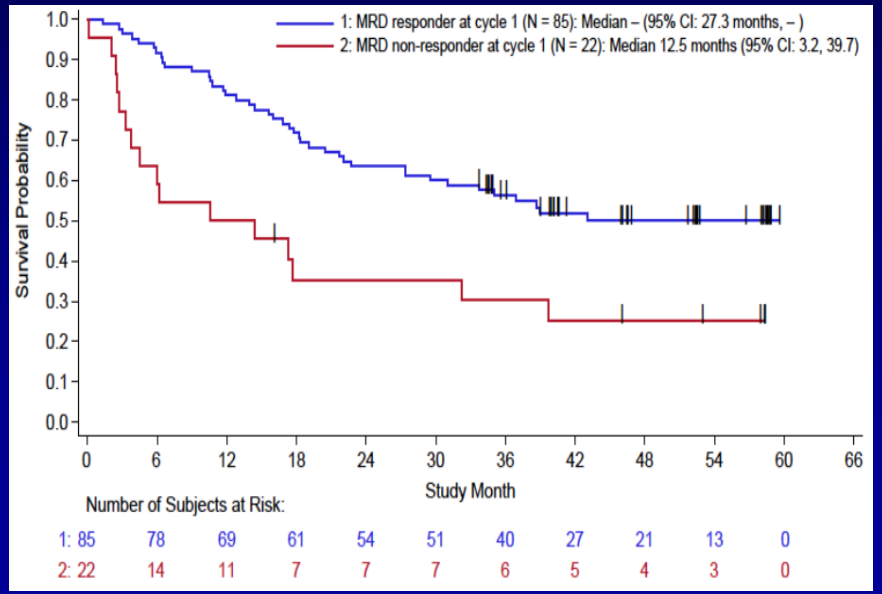


Topp MS, et al. *Blood*. 2012;120:5185-5187.

Blinatumomab for MRD+ ALL in CR1/CR2

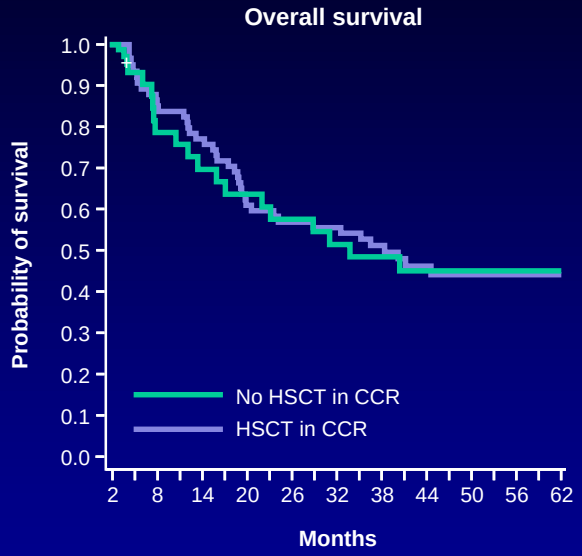
- 113 pts Rx. Post-blina **MRD– 88/113 = 78%**
- 110 evaluated (blasts <5%, MRD+); 74 received alloSCT. Median FU 53 mo
- Median OS 36.5 mo; **4-yr OS 45%; 4-yr OS if MRD– 52%**
- Continuous CR 30/74 post-alloSCT (40%); 12/36 without SCT (33%)

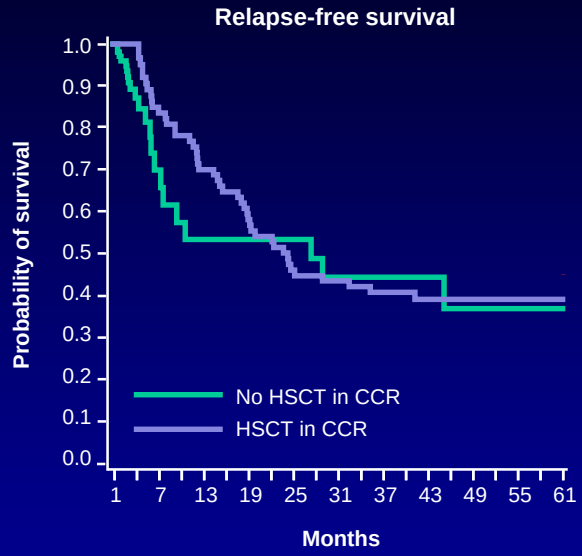


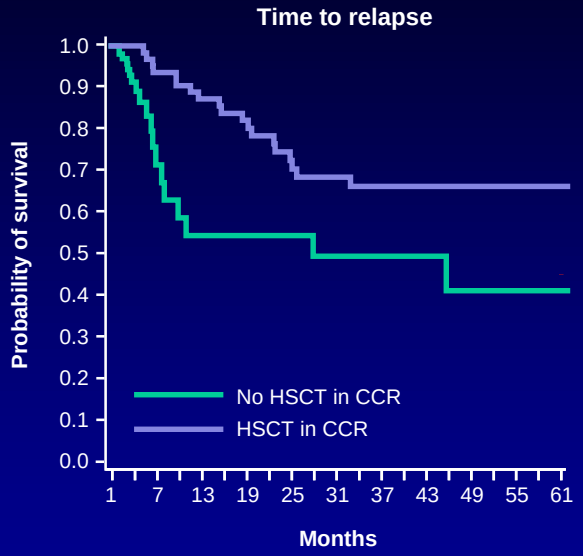


Goekbuget N, et al. *Blood.* 2018;132:abstract 554.

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

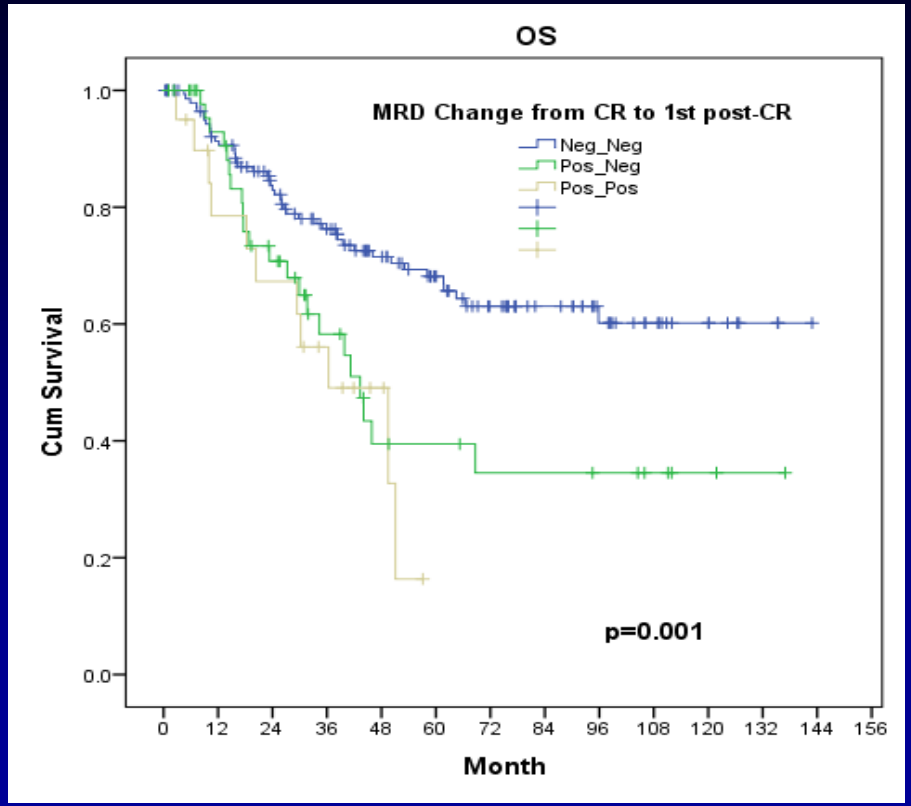
Non-HSCT	101	16	12	12	11	10	8	6	5	5	0
HSCT	2	61	53	42	34	33	25	19	14	7	0

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.

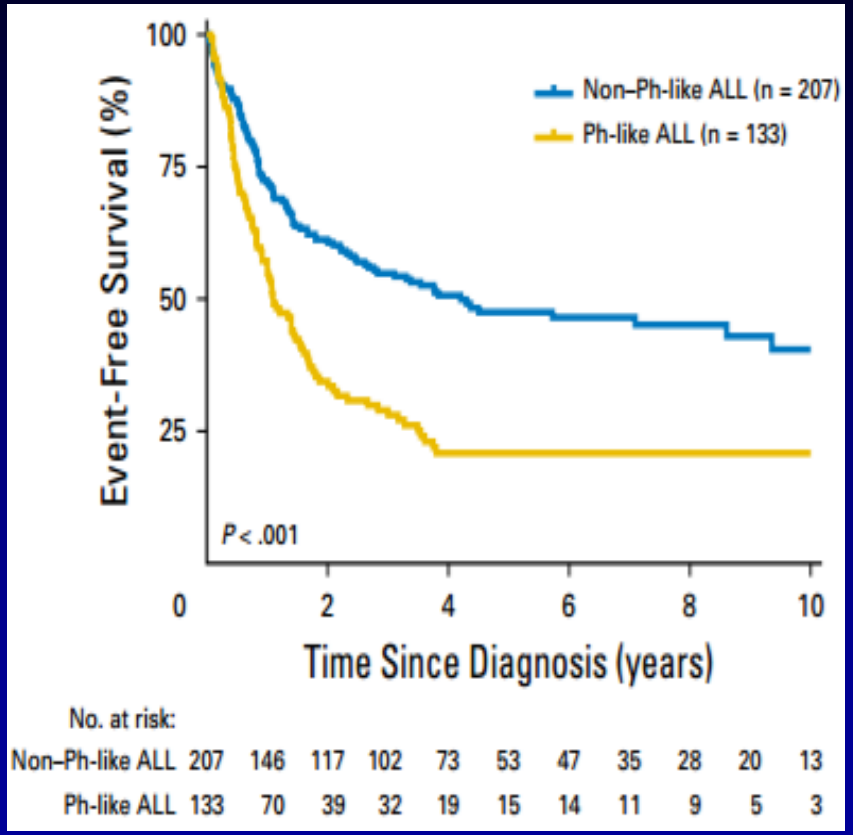
Dynamics of MRD: Outcome

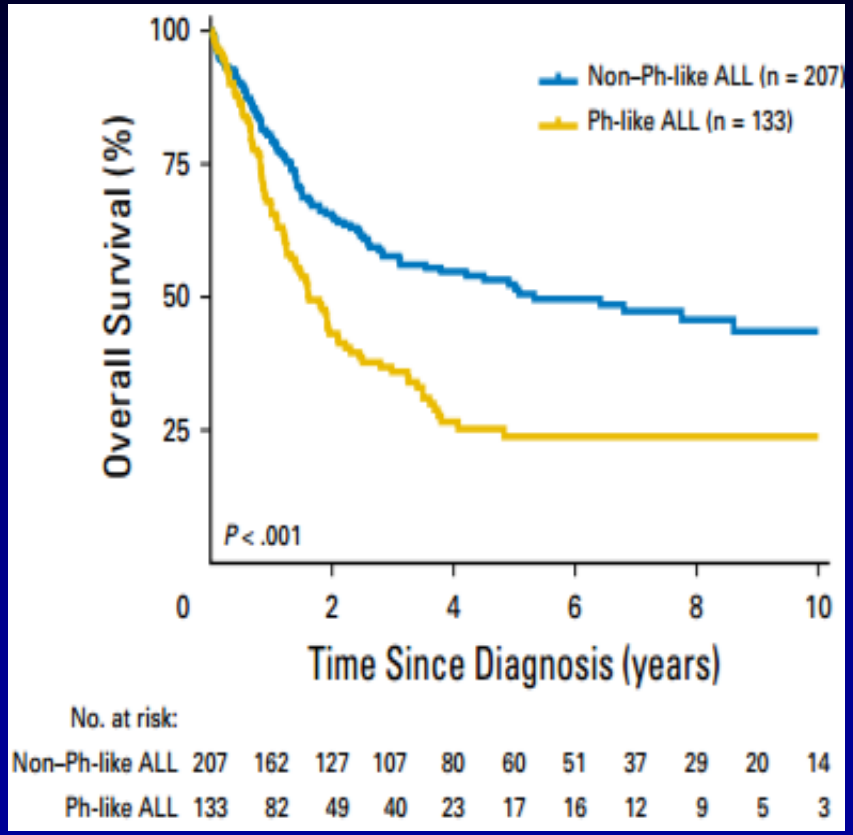
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA



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

Ph-Like ALL: Survival and EFS





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

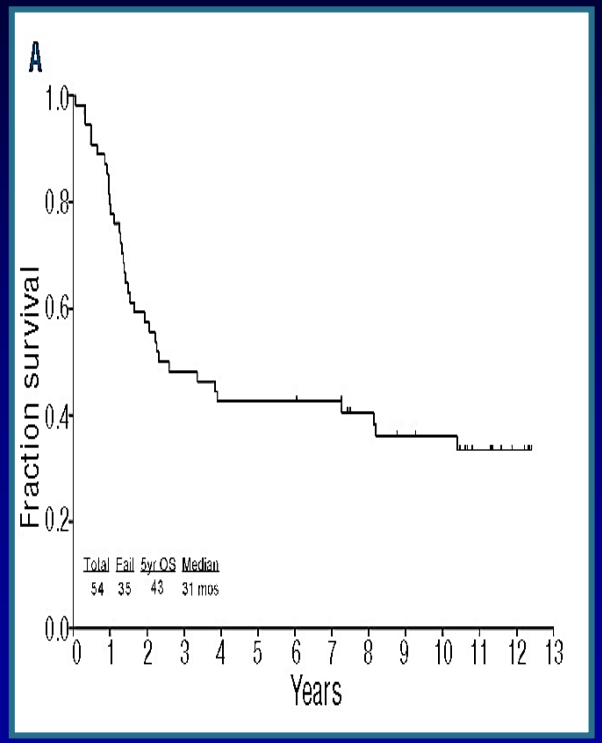
Ph-Like ALL: Higher MRD+ Rate

	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)	

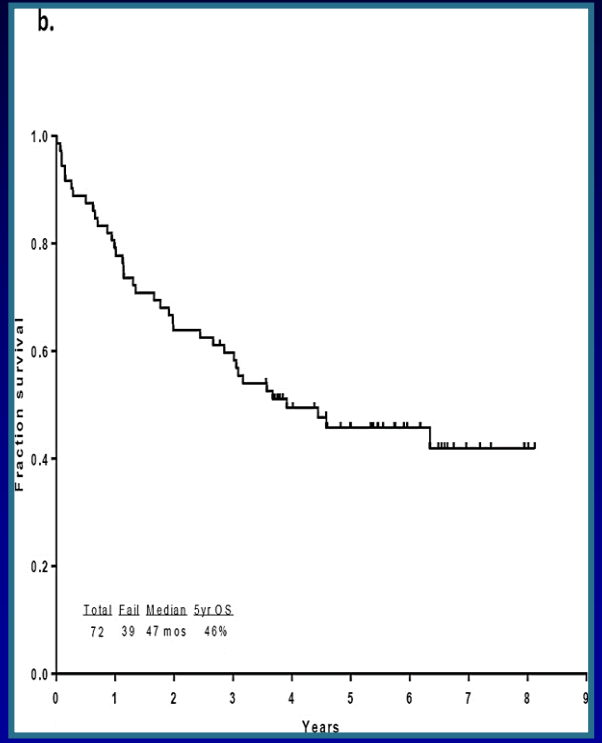
Jain. *Blood.* 2017;129:572-581.

TKI for Ph+ ALL

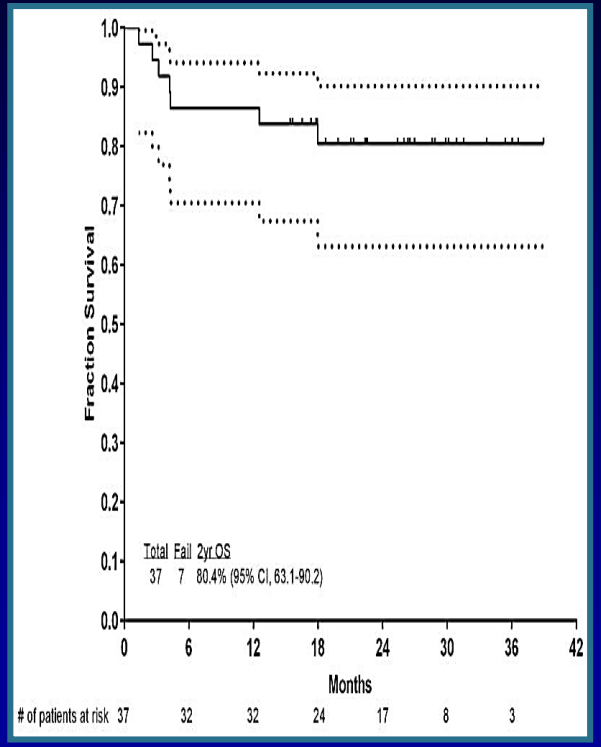
Imatinib: 5-yr OS = 43%



Dasatinib: 5-yr OS = 46%



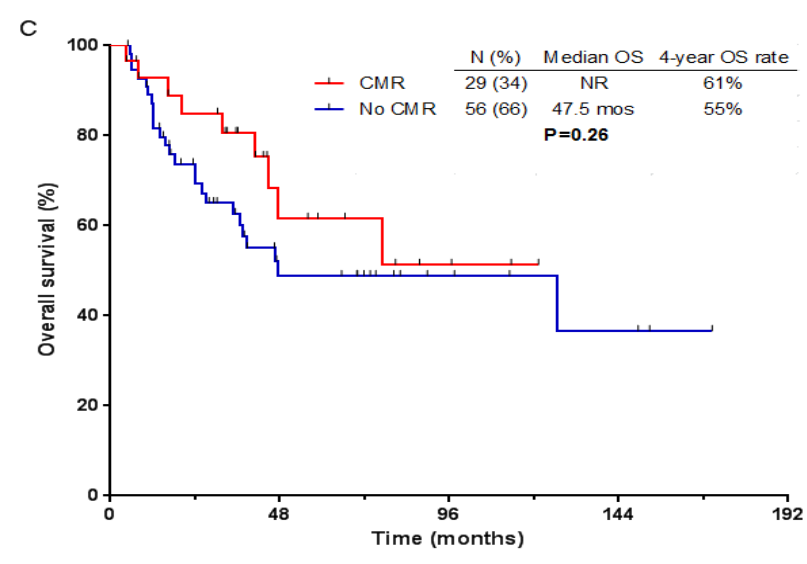
Ponatinib: 5-yr OS = 71%



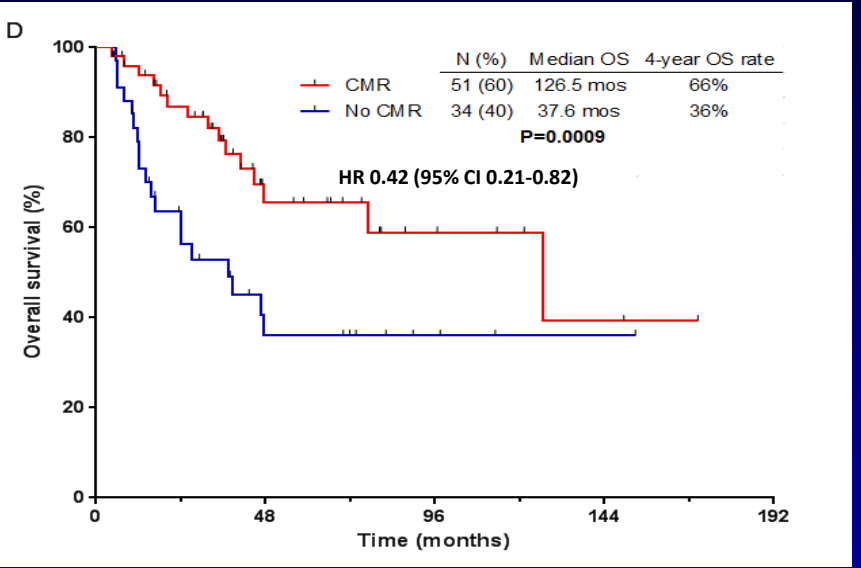
Daver. *Haematologica*. 2015; Ravandi. *Cancer*. 2015; Jabbour. *Lancet Oncol.* 2015; Jabbour. *Lancet Hematol.* 2018.

CMR in Ph+ ALL: OS for CMR vs Others

At CR



At 3 months

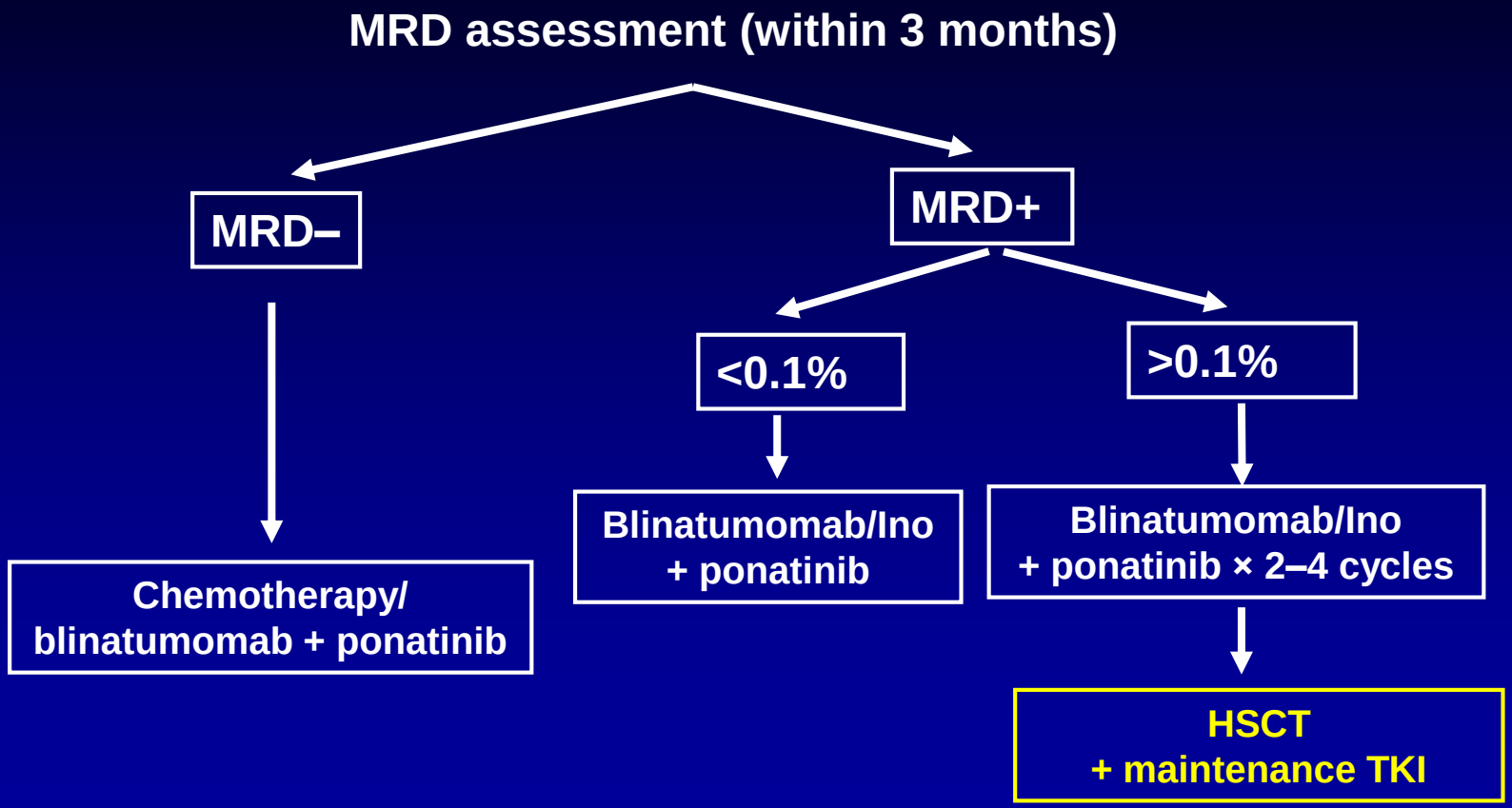


- **MVA for OS**

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

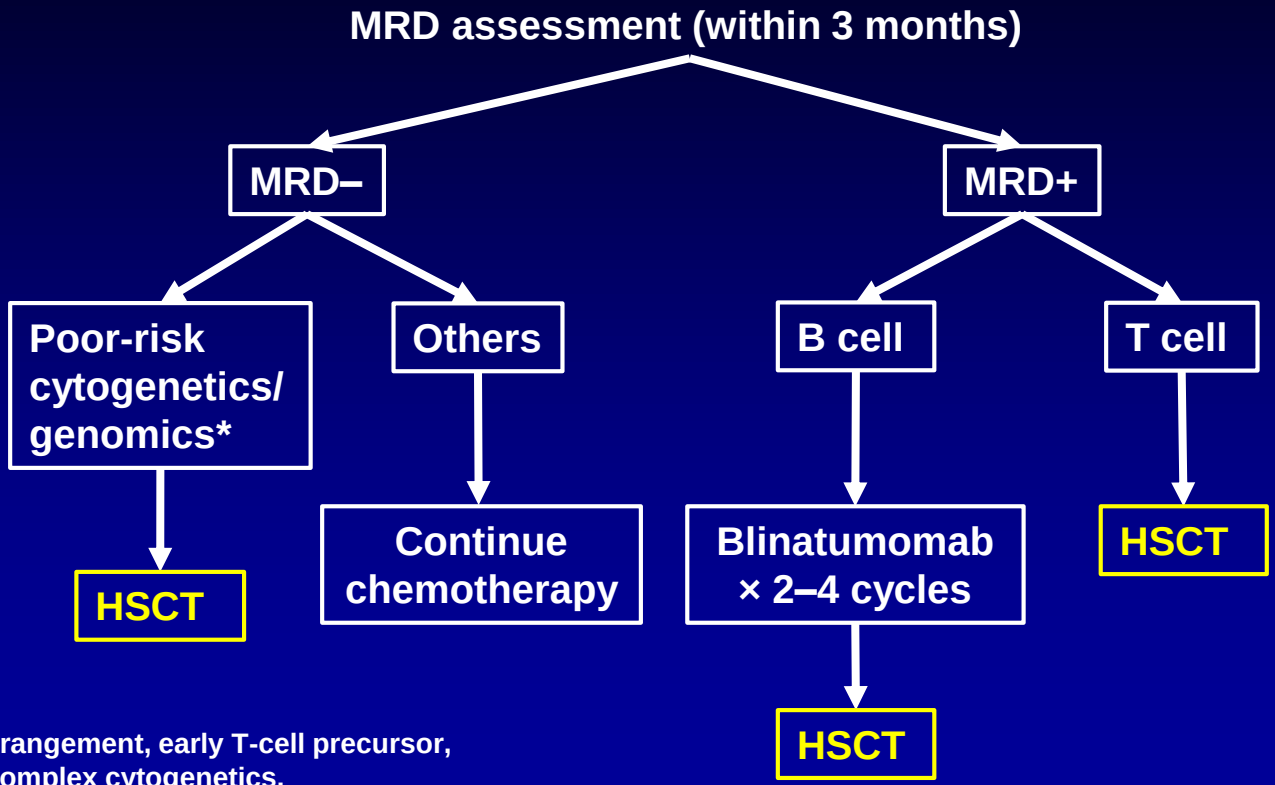
Short. *Blood.* 2016;128(4):504-507.

Indications for HSCT: Ph+ ALL



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

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



*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?

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How and When to Check for MRD in ALL

Eduardo Rego

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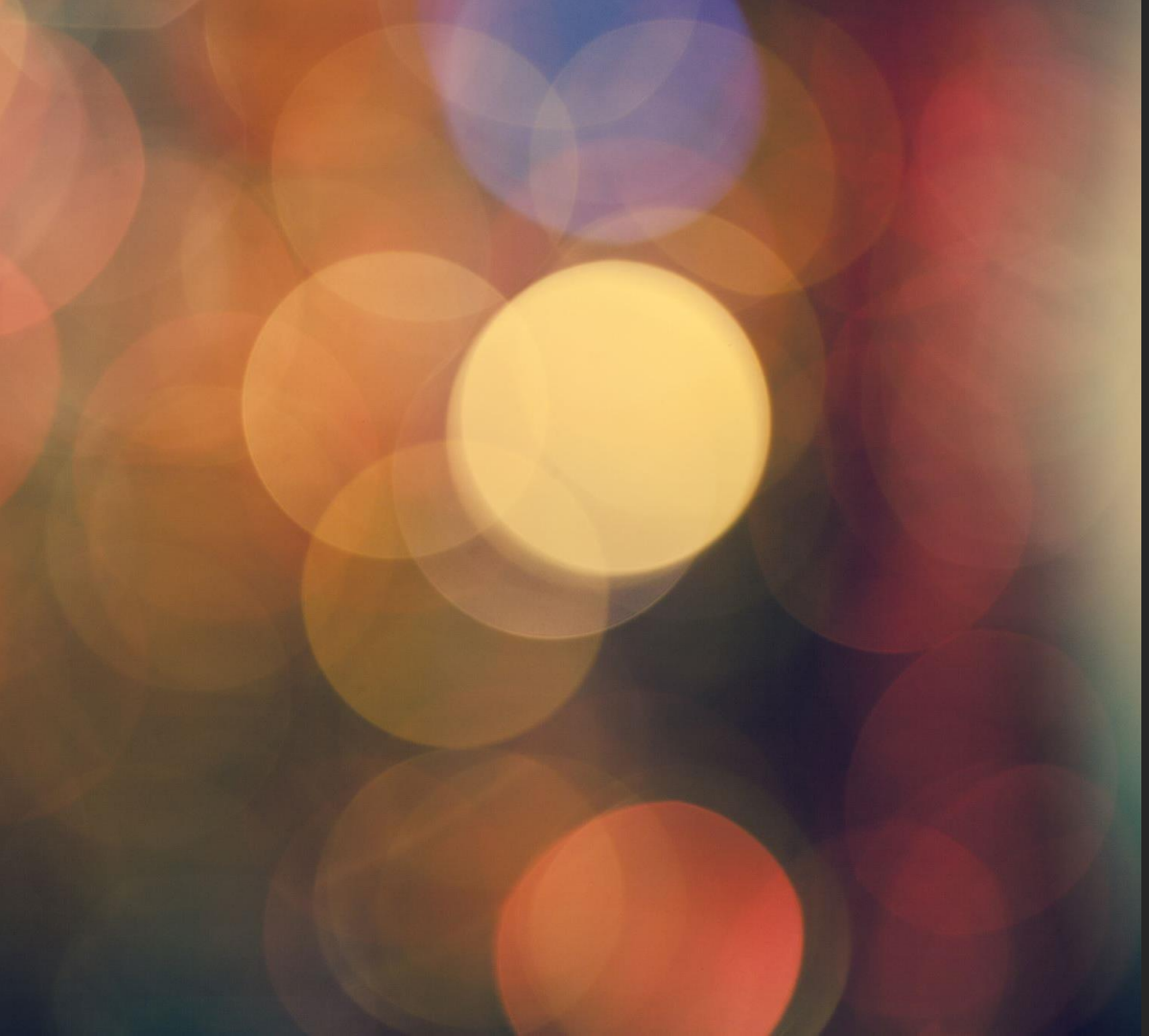


How and when to check for MRD in ALL

EDUARDO M. REGO

UNIVERSITY OF SÃO PAULO

ONCOLOGIA D'OR

BRAZIL

MRD and response duration

- 74%–91% of patients with ALL will achieve CR, but **one-third** will relapse because of submicroscopic levels of leukemic cells (measurable residual disease [MRD])

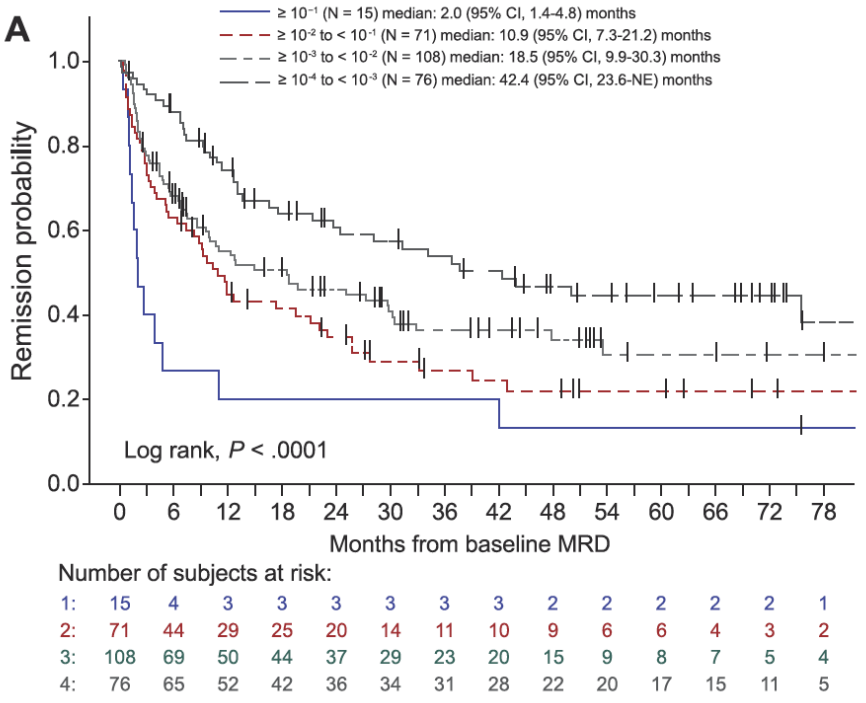
Of 272 patients in CR1, baseline MRD was:

$\geq 10^{-1}$ in 15 (6%)

10^{-2} to $<10^{-1}$ in 71 (26%)

10^{-3} to $<10^{-2}$ in 109 (40%)

10^{-4} to $<10^{-3}$ in 77 (28%)



How?

Ph-negative ALL

Author	Year	N	Ph	MRD method	MRD level	Test location	Phenotype	Disease stage	Pre-MRD tx
Gökbuget	2015	116 (112)	Neg	PCR	10^{-4}	Central	B-cell	CR1	Targeted
Jabbour	2017	78 (78)	NA	Flow (6color)	10^{-4}	Local	B-cell	CR2 or later	Targeted
Ravandi	2016	340 (260)	Mix	Flow (6color)	10^{-4}	Local	B-cell	CR1	Targeted
Bassan	2014	159 (106)	Neg	PCR	10^{-4}	NA	Mix (79% B-cell)	CR1	Chemo
Beldjord	2014	860 (423)	Neg	PCR	10^{-4}	Central	B-cell	CR1	Chemo
Gökbuget	2012	1648 (580)	Neg	PCR	10^{-4}	Central	Mix (66% B-cell)	CR1	Chemo
Holowiecki	2008	131 (116)	Neg	Flow (3color)	10^{-3}	Central	Mix (75% B-cell)	CR1	Chemo
Patel	2010	161 (161)	Neg	PCR	10^{-4}	NA	B-cell	CR1	Chemo
Bassan	2014	304 (141, [98 included in the analysis]	Neg	PCR	10^{-4}	NA	Mix (76% B-cell)	CR1	Chemo
Gökbuget	2014	189 (73)	Neg	PCR	10^{-4}	Central	B-cell	CR2 or later	Targeted
Giebel	2010	123 (123)	Neg	Mix	10^{-3}	Local	B-cell	CR1	Chemo
Weng	2013	125 (106)	Mix	Flow (6color)	10^{-4}	Local	B-cell	CR1	Chemo

Adapted from Bassan, et al. *Haematologica*. 2019;104(10):2028-2039.

MFC – Ph-negative/B and T-ALL

Author	MRD+ definition and sensitivity	Ph status
Holowiecki et al. 2008	MRD+ defined as expression of ≥2 aberrant phenotypes on >50% leukemic blasts; >0.1% used as cut-off point	Ph–
Ravandi et al. 2016	MFC (4-color); aberrant expression of ≥2 antigens required for assignment of MRD+; sensitivity 0.01%	Mixed
Weng et al. 2013	Flow cytometry (8-color) with validation by qRT PCR for BCR-ABL fusion gene MRD−: $<10^{-4}$	Mixed

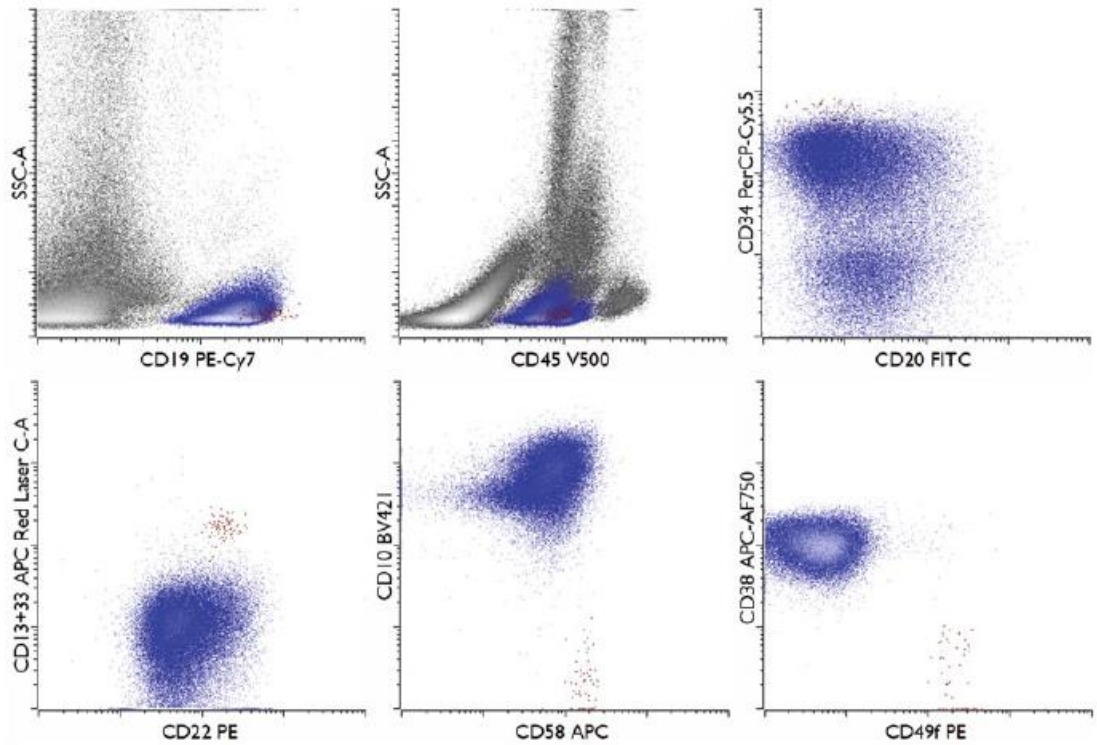
Adapted from Bassan, et al. *Haematologica*. 2019;104(10):2028-2039.

Antibody combinations suitable for diagnosis and detection of minimal residual disease in acute lymphoblastic leukemia

Tube	FITC	PE	PerCP-Cy5.5	PE-Cy7	APC	APC-AF750	PB, V450, or BV421	V500
1	Kappa	Lambda	CD20	CD19	CD10	CD38	CD5	CD45
2	CD20	CD22	CD34	CD19	CD13 + CD33	CD38	CD10	CD45
3	CD20	CD49f	CD34	CD19	CD58	CD38	CD10	CD45
4	CD24	CD304	CD34	CD19	CD86	CD38	CD10	CD45
5	CD16	CD56	CD5	CD3	CD7	CD8	CD4	CD45
6	CD7	CD1a	CD3	CD2	CD5	CD8	CD4	CD45
7	cyMPO	cyCD3	CD34	–	CD7	–	HLA-DR	CD45
8	cyMPO	cyCD22	cyCD79a	CD19	CD34	–	HLA-DR	CD45
9	nTdt	cyCD3	cyCD79a	CD19	CD34	–	HLA-DR	CD45

FITC fluorescein isothiocyanate, *PE* phycoerythrin, *PerCP-Cy5.5* peridinin-chlorophyll-Cy5.5, *APC* allophycocyanin, *APC-AF750* APC-Alexa Fluor 750, *PB* Pacific Blue, *V450* BD Horizon™ V450, *BV421* Brilliant Violet™ 421, *V500* BD Horizon™ V500

DiGiuseppe, Cardinali. *Methods Mol Biol.* 2019;2032:297-310.



Example of MRD+ ALL Ph-negative

DiGiuseppe, Cardinali. *Methods Mol Biol.* 2019;2032:297-310.

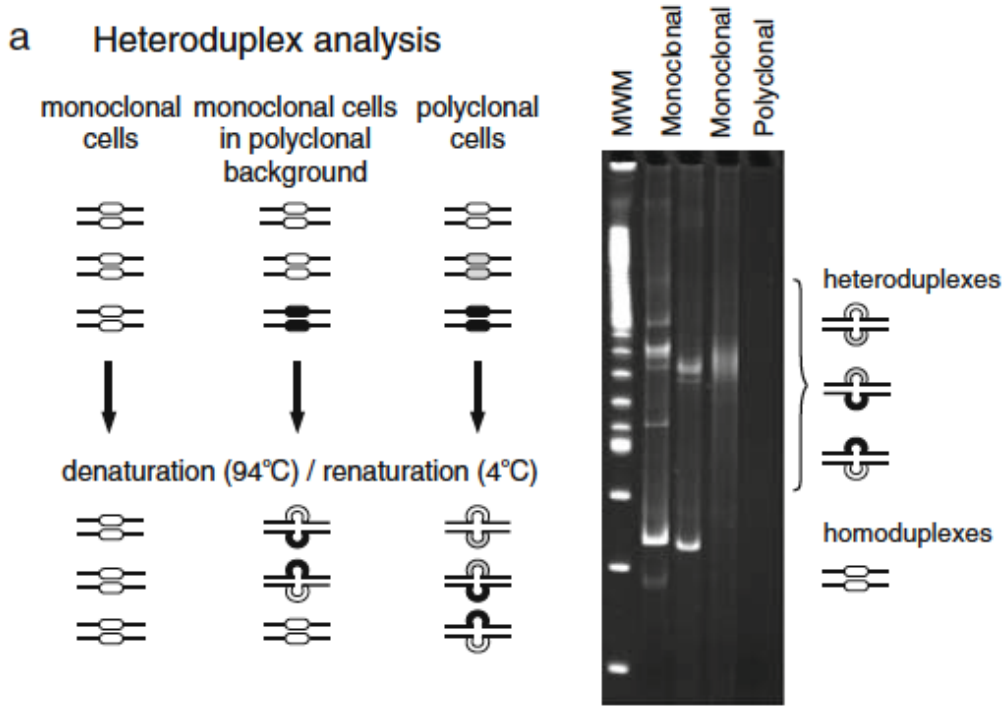
qRT PCR – Ph-negative

	Type of study	Treatment	HSCT	Method/Definition of MRDneg
GRAALL 2003 and 2005 trials, Dhèdin et al. (2015)	Phase 2 (GRAALL 2003) and Phase 3 (GRAALL 2005)	Chemotherapy	Allogeneic (planned after 3 or 6 blocks of consolidation); some patients received UBCT	**qRT PCR for ≥2 Ig/T-cell receptor gene rearrangements**; bone marrow samples assessed in a central reference laboratory; sensitivity $\geq 10^{-4}$
GMALL 06/99 and 07/03 trials, Gökbuget et al. (2012)	Retrospective, German centers	Chemotherapy	Allogeneic (high-risk patients)	**qRT PCR for leukemia-specific Ig/T-cell receptor gene rearrangements**; assessed in a central laboratory Molecular CR: MRD− with assay sensitivity of $\geq 10^{-4}$
NILG 09-2000 trial, Mannelli et al. (2012)	Prospective; Italy	Chemotherapy	Allogeneic (high-risk patients)	qRT PCR for BCR-ABL or Ig MRD−: $<10^{-4}$ at Week 16 and negative at Week 22
UKALL XII trial, Mortuza et al. (2002)	Prospective; UK	Chemotherapy	Allogeneic (for patients with available donor) or autologous PCR	α-32P dCTP PCR and ASO PCR MRD+: 1–5 leukemic cells in 10^2–10^3 normal cells
UKALL XII/ ECOG2993 trial, Patel et al. (2010)	Prospective; multicenter; UK	Chemotherapy	Allogeneic or autologous	**qRT PCR for rearrangements in Ig/T-cell receptor** genes among others, ASO PCR MRD−: qRT PCR $<10^{-4}$
BLAST, Gökbuget et al. (2015)	Phase 2; prospective; Europe	Blinatumomab	HSCT	PCR (per EuroMRD guidelines) MRD response defined as no PCR amplification at a sensitivity of 10^{-4} or $<10^{-4}$ leukemic cells; MRD assessed at central reference laboratory

Adapted from Bassan, et al. *Haematologica*. 2019;104(10):2028-2039.

RT-qPCR detection of Ig/TCR arrangements

1. Bone marrow sample processing at diagnosis
2. Detection and selection of clonal Ig/TCR gene rearrangement at diagnosis
   a) PCR heteroduplex analysis
   b) Sequencing of clonal rearrangements
3. RQ-PCR sensitivity testing
   a) Selection of MRD-PCR targets
   b) Design of allele-specific oligonucleotide primers
4. MRD analysis of follow-up samples
   a) Control gene RQ-PCR analysis
   b) MRD-PCR target RQ-PCR analysis
   c) RQ-PCR MRD data interpretation



van der Velden, et al. *Methods Mol Biol.* 2009;538:115-150.

Selection of targets, quantitative range, and sensitivity

1. Preferably 2 MRD-PCR targets should be used for each ALL patient
2. MRD-PCR targets should be selected based on: (1) expected stability and (2) expected sensitivity
   a. Monoclonal Ig/TCR gene rearrangements have a much higher stability (80%–90%) than oligoclonal rearrangements (40%–50%)
3. To limit the risk of losing MRD-PCR targets by such processes – select "end-stage" Ig/TCR rearrangements (eg, IGK -Kde or V γ -J γ 2.3 rearrangements)
4. Concerns about the variation between replicates evaluated through mean CT values of the replicates
5. The "**quantitative range**" reflects the part of the standard curve in which the MRD levels can be quantified reproducibly and accurately, whereas the "**sensitivity**" reflects the lowest MRD level that still can be detected, although not reproducibly and accurately

van der Velden, et al. *Methods Mol Biol.* 2009;538:115-150.

Overall sensitivities of Ig/TCR gene rearrangements in RQ-PCR assays

Rearrangement		Quantitative range of at least 10^{-4} (%)[a]	Sensitivity of at least 10^{-4} (%)[a]
IGH	DJ	50	75
	VDJ	80	95
IGK-Kde		80	90
IGK Vκ-Jκ		45	80
Vλ-Jλ		50	80
TCRD	Incomplete	45	90
	Complete	80	95
Vδ2-Jα		75	90
TCRB	VDJ	70	90
	DJ	55	90
TCRG	precursor-B-ALL	25	45
	T-ALL	70	80

[a]Percentage of rearrangements with quantitative range/sensitivity of at least 10^{-4}

van der Velden, et al. *Methods Mol Biol.* 2009;538:115-150

How? Ph-positive ALL

Author	Year	N	Ph	MRD method	MRD level	Test location	Phenotype	Disease stage	Pre-MRD tx
Lussana	2016	106 (73)	Pos	PCR	10^{-5}	N/A	B-cell	CR1	Targeted
Chiaretti	2015	63 (60)	Pos	PCR	N/A	N/A	B-cell	CR1	Targeted
Nishiwaki	2016	432 (432)	Pos	PCR	10^{-5}	Local	B-cell	CR1/Pre-HSCT	Target
Yanada	2008	100 (85)	Pos	PCR	10^{-5}	Central	B-cell	CR1	Targeted
Wetzler	2014	34 (13)	Pos	PCR	N/A	Central	B-cell	CR1	Targeted
Tucunduva	2014	98 (98)	Pos	Mix	Mix	Local	B-cell	CR1	Targeted
Yoon	2016	173 (169)	Pos	PCR	10^{-4}	Central	B-cell	CR1	Targeted
Lim	2016	82 (78)	Pos	PCR	10^{-5}	Central	B-cell	CR1	Targeted
Short	2016	202 (122)	Pos	PCR	10^{-4}	Local	B-cell	CR1	Targeted

Adapted from Bassan, et al. *Haematologica*. 2019;104(10):2028-2039.

Ph-positive – Type of response

Author	Type of study	Treatment	HSCT	MRD detection methodology
Kim et al. (2015)	Prospective; single-center; Korea	Chemotherapy + imatinib	Allo	qRT PCR for BCR-ABL transcript; measured at a central reference laboratory MRD stratified by 3 groups after 2 courses of consolidation 1. EMRs (early and persistent MRD− [BCR-ABL:ABL ratio ≤0.1% or ≥3-log reduction in BCR-ABL transcript level from baseline]) 2. LMRs (conversion from MRD+ to MRD−) 3. PMRs (MRD+: MRD levels >1% or <3-log reduction in BCR-ABL transcript level from baseline)

Kim, et al. *Bone Marrow Transplant*. 2015;50(3):354–362.

When?

When?

Author	Year	N	Ph	MRD method	Disease stage	MRD timing	Pre-MRD tx	Post-MRD Tx
Gökbuget	2015	116 (112)	Neg	PCR	CR1	≤3 months from induction	Targeted	Mix
Jabbour	2017	78 (78)	NA	Flow (6color)	CR2 or later	≤3 months from induction	Targeted	Mix
Ravandi	2016	340 (260)	Mix	Flow (6color)	CR1	≤3 months from induction	Targeted	Mix
Bassan	2014	159 (106)	Neg	PCR	CR1	≥3 months from induction	Chemo	Mix
Beldjord	2014	860 (423)	Neg	PCR	CR1	≤3 months from induction	Chemo	Mix
Gökbuget	2012	1648 (580)	Neg	PCR	CR1	≤3 months from induction	Chemo	Mix
Bassan	2014	304 (141, [98 included in the analysis]	Neg	PCR	CR1	>3 months from induction	Chemo	Mix
Gökbuget	2014	189 (73)	Neg	PCR	CR2 or later	≤3 months from induction	Targeted	Mix
Weng	2013	125 (106)	Mix	Flow (6color)	CR1	≤3 months from induction	Chemo	Mix
Lussana	2016	106 (73)	Pos	PCR	CR1	Pre-HSCT	Targeted	HSCT
Tucunduva	2014	98 (98)	Pos	Mix	CR1	Pre-HSCT	Targeted	HSCT
Yoon	2016	173 (169)	Pos	PCR	CR1	Pre-HSCT	Targeted	HSCT
Lim	2016	82 (78)	Pos	PCR	CR1	≤3 months from induction	Targeted	Mix
Short	2016	202 (122)	Pos	PCR	CR1	≤3 months from induction	Targeted	Target

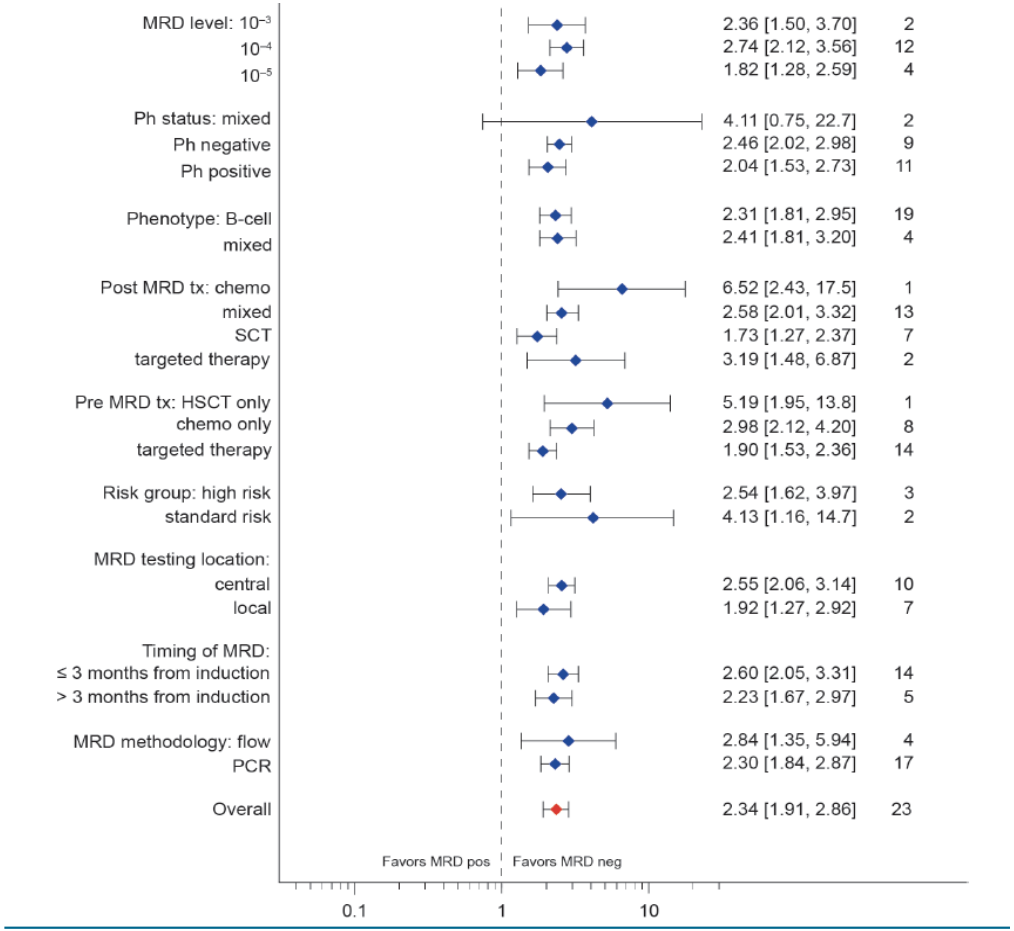
Regarding MRD analysis in acute lymphoblastic leukemia, which statement is true?

a. The prognostic relevance of residual measurable disease detection (MRD+) is higher in Ph-positive ALL than in Ph-negative ALL

b. Threshold levels for MRD detection at the level of 10^{-4} distinguish between patients that are more likely to relapse, but have no impact in the overall survival

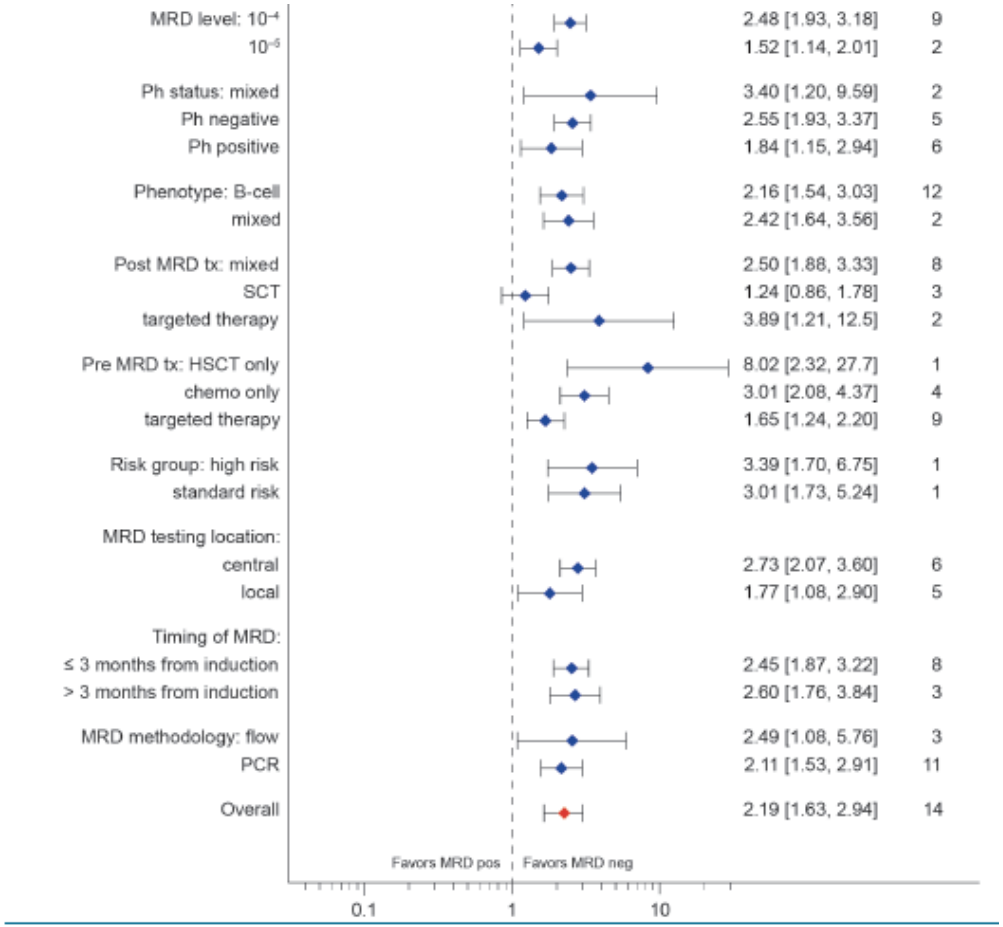
c. The detection of MRD in Ph-negative B-cell ALL is feasible both by PCR and flow cytometry methodologies

d. Regarding MRD detection by PCR methods, the terms “quantitative range” and “sensitivity” are synonyms



Meta-analysis relapse-free survival

Adapted from Bassan, et al. *Haematologica*. 2019;104(10):2028-2039.



Meta-analysis overall survival

Adapted from Bassan, et al. *Haematologica*. 2019;104(10):2028-2039.

The earlier, the better?

- Stock et al (2014) – Pts with Ph-negative B-ALL or T-ALL
  - MRD levels as early as 28 days following the initiation of induction therapy predicted outcomes
- Bruggemann et al (2006) – Patients with Ph-negative B-ALL or T-ALL
  - An early MRD response (day 11) was associated with the best prognosis
- Dhèdin et al (2015) – Patients with Ph-negative ALL
  - Lack of MRD response 6 weeks after induction initiation could identify patients who would benefit most from HSCT

Stock, et al. *Blood.* 2014;124 (21):796; Bruggemann, et al. *Blood*. 2006;107(3):1116–1123; Dehèdin, et al. *Blood.* 2015;125(16):2486–2496.

MRD detection could be used to spare pts from more-toxic treatments?

- PETHEMA ALL-AR03 – MRD to guide treatment decisions at the end of consolidation
  - HSCT could be avoided in patients who reached MRD-neg without adversely affecting their prognosis
- GRAALL-2003 or -2005 – MRD analysis
  - HSCT prolonged RFS compared with chemotherapy among those who did not achieve an early MRD response, but was no better than chemotherapy in patients who did achieve an early MRD response

Ribera, et al. *J Clin Oncol.* 2014;32(15):1595–1604; Bassant, et al. *Blood.* 2016;128(22):176.

Conclusions

- ✓ Achieving MRD negativity was consistently associated with better survival outcomes
- ✓ The prognostic ability of MRD negativity is the same in Ph-positive and Ph-negative cohorts
- ✓ Although the exact value for cut-off values between MRD+ and MRD– is controversial, the threshold of 10^{-4} was recommended by ESMO
- ✓ Timing of MRD assessment showed that there was no difference in RFS improvement for patients who achieved MRD negativity at early timepoints compared with those who achieved it at later timepoints. But controlled prospective trials suggest that MRD negativity could be used to spare patients from more-toxic regimens

Hoelzer, et al. *Ann Oncol*. 2016;27(suppl 5):v69–v82.

Global Leukemia Academy

MRD Assessment and Management in CR1 vs CR2 and Beyond

Aaron Logan

APTITUDE HEALTH®

UCSF Helen Diller Family Comprehensive Cancer Center

Measurable Residual Disease (MRD) Assessment and Management in CR1 vs CR2 and beyond

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MRD Case Study

Identification	
Age	42
Sex	Male
Diagnosis	Ph-negative B-cell ALL

Presentation at Time of Diagnosis	
CBC	WBC count: 46,000/mcL Hb: 6.5 g/dL Platelet count: 28,000/mcL
Blast count	60% peripheral & marrow blasts
Immunophenotype	CD10+, CD19+, CD20+, CD34+
Karyotype/Mutations	t(4;11)(q21;q23) (MLL/KMT2A+)

Treatment History
Achieved remission with hyper-CVAD, but relapsed during cycle 2B.
The patient then received blinatumomab and achieves a second remission and has a 10/10 HLA matched sibling donor identified for transplant.

For this patient, is MRD testing useful?

Is MRD testing useful for this patient in CR2 before he proceeds to allogeneic transplantation?

Q

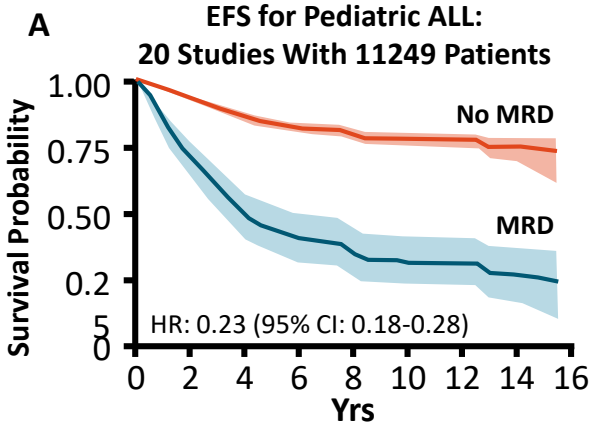
a. No, MRD is not prognostic at this time point.

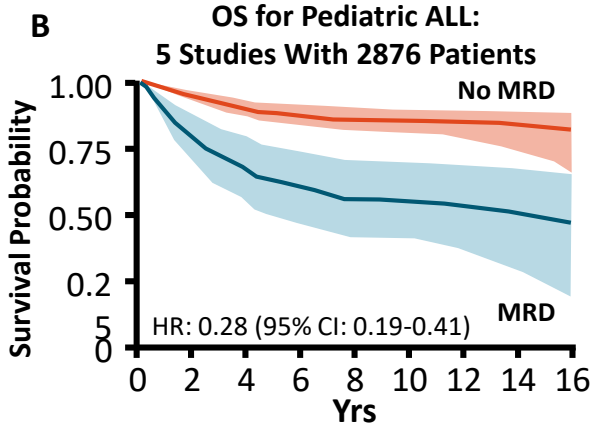
b. Yes, MRD is prognostic after first salvage therapy.

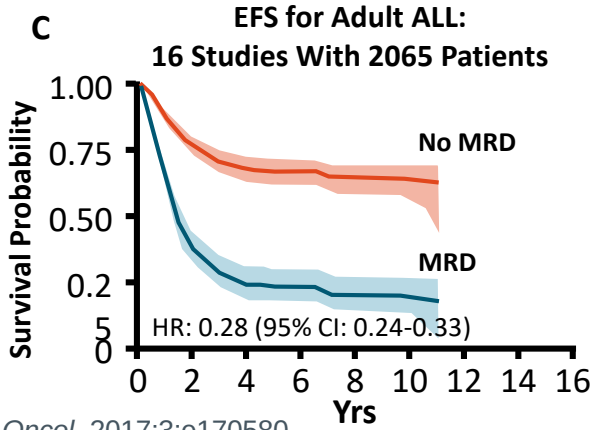
c. Yes, MRD is prognostic prior to allogeneic hematopoietic cell transplantation.

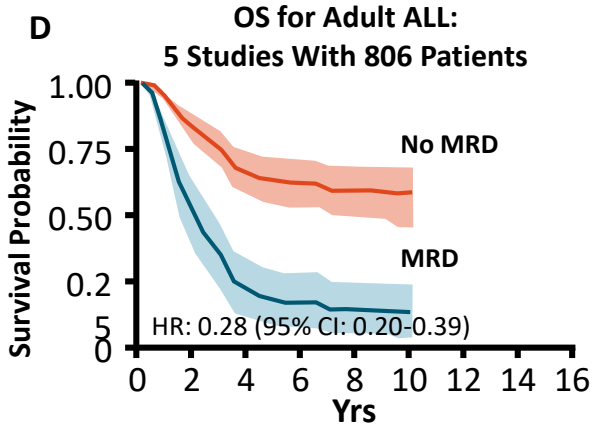
d. B and C

MRD Strongly Predicts Outcome in Pediatric and Adult ALL



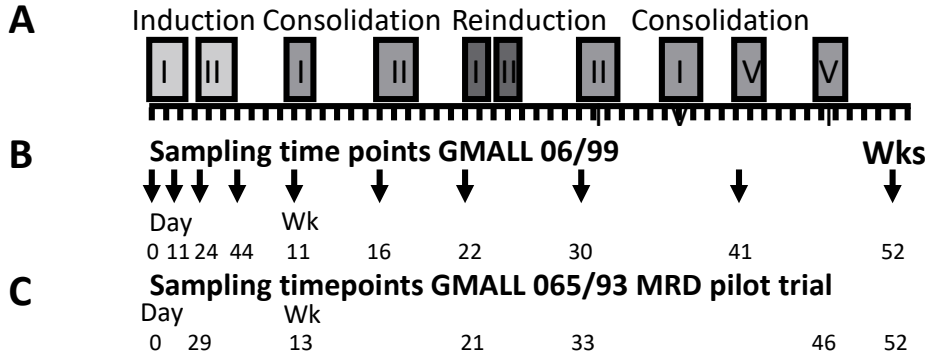






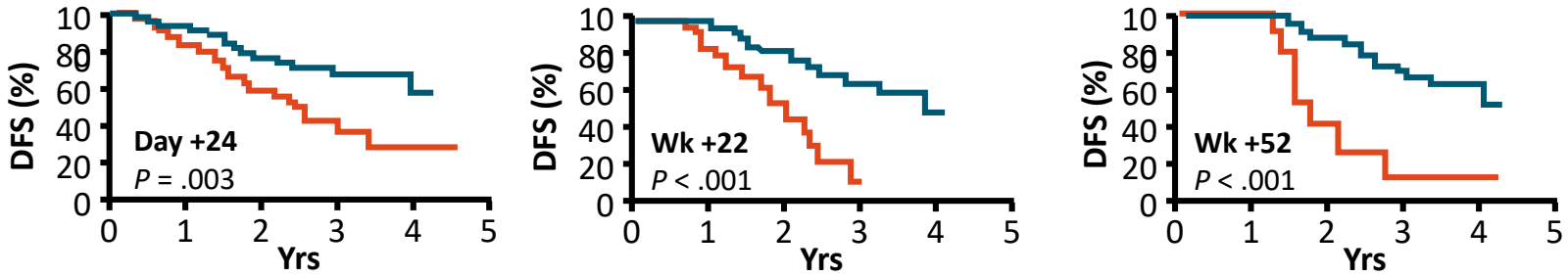
Berry, et al. *JAMA Oncol.* 2017;3:e170580.

MRD at Any Point in Therapy Predicts Outcome



MRD Quantified Using Quantitative PCR

Probability of DFS According to MRD



MRD	n	3-Yr DFS (95% CI)
Negative/<10^{-4}	75	68.6 (55.0-82.2)
>10^{-4}	82	37.8 (24.5-51.1)

MRD	n	3-Yr DFS (95% CI)
Negative/<10^{-4}	10	65.4 (54.1-76.7)
>10^{-4}	1	11.8 (0-31.6)
	25	

MRD	n	3-Yr DFS (95% CI)
Negative/<10^{-4}	11	67.9 (56.9-80.6)
>10^{-4}	3	14.6 (0.0-40.0)
	11	

Brüggemann, et al. *Blood*. 2006;107:1116-1123.

MRD Predicts RFS at Achievement of CR2 (1/3)

Table 2. Response and minimal residual disease status after first relapse therapy.

	Type of complete response, *n* (%)				MRD status, *n* (%)[a]		
Relapse therapy	CR	CRp	CRi	*p*	Positive	Negative	*p*
Hyper-CVAD ($n = 32$)	25 (78)	5 (16)	2 (6)	.15	5 (21)	19 (79)	.57
BFM-based ($n = 19$)	14 (74)	5 (26)	0		2 (20)	8 (80)	
HDAC ± Mitoxantrone ($n = 15$)	10 (67)	3 (20)	2 (13)		2 (40)	3 (60)	
Inotuzumab[b] ($n = 11$)	8 (73)	3 (27)	0		1 (17)	5 (83)	
Nelarabine[c] ($n = 7$)	7 (100)	0	0		2 (33)	4 (66)	
Blinatumomab[b] ($n = 5$)	3 (60)	0	2 (40)		0	2 (100)	
Other chemotherapy ($n = 17$)	11 (65)	4 (23)	2 (12)		4 (50)	4 (50)	

Table 3. Correlation of MRD with response to first relapse therapy.

MRD status	All patients, *n* (%)	CR, *n* (%)	CRp, *n* (%)	CRi, *n* (%)	*p*
Total	61	47	11	3	
Positive	16 (26)	11 (23)	2 (18)	3 (100)	.01
Negative	45 (74)	36 (77)	9 (82)	0	

CR: complete response; CRi: complete response with incomplete count recovery; CRp: complete response with incomplete platelet recovery; MRD: minimal residual disease.

Saygin, et al. *Leuk Lymphoma*. 2018;59(2):363-371.

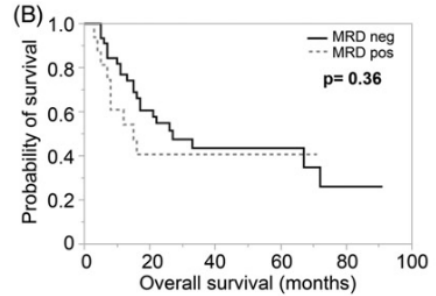
MRD Predicts RFS at Achievement of CR2 (2/3)

Table 5. Multivariable Cox regression analysis of prognostic factors for overall and relapse-free survival after first relapse.

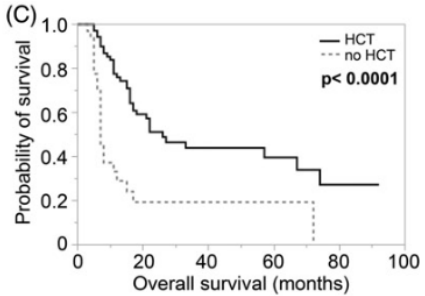
	Overall survival, months		Relapse-free survival, months	
Prognostic factors	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (continuous)[a]	1.01 (1–1.03)	.28		
WBC count at diagnosis ($\times 10^9$/L)[a] (continuous)	1.01 (1–1.02)	.02		
Time to relapse (<18 versus ≥18 months)	1.19 (0.62–2.34)	.6	0.76 (0.3–1.78)	.53
Response to first relapse therapy CRh versus CR	1.77 (0.91–3.3)	.09	1.16 (0.51–2.44)	.71
MRD status at relapse response (positive versus negative)			3.36 (1.36–8.64)	.009
HCT after relapse (yes versus no)[b]	0.32 (0.17–0.6)	.0005	0.47 (0.22–0.99)	.03

Saygin, et al. *Leuk Lymphoma*. 2018;59(2):363-371.

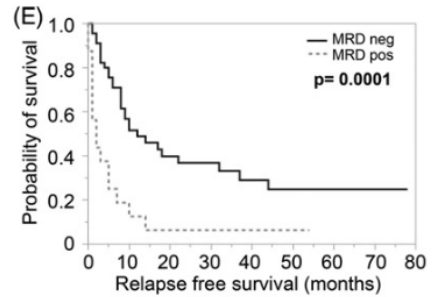
MRD Predicts RFS at Achievement of CR2 (3/3)



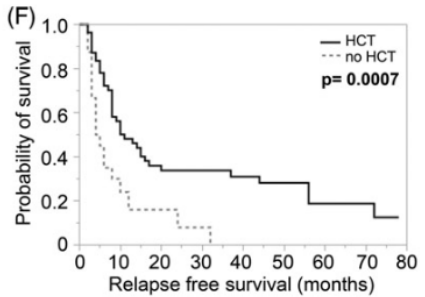
Number of subjects at risk						
Neg:	45	22	11	7	2	0
Pos:	16	6	4	3	0	0



Number of subjects at risk						
HCT:	72	33	16	10	3	0
No HCT:	32	5	2	2	0	0



Number of subjects at risk									
Neg:	45	22	14	11	8	5	4	3	0
Pos:	16	3	2	2	2	2	0	0	0



Number of subjects at risk									
HCT:	55	28	16	14	12	9	6	4	0
No HCT:	24	5	3	2	0	0	0	0	0

Saygin, et al. *Leuk Lymphoma*. 2018;59(2):363-371.

Blinatumomab – Results Best in 1st Salvage

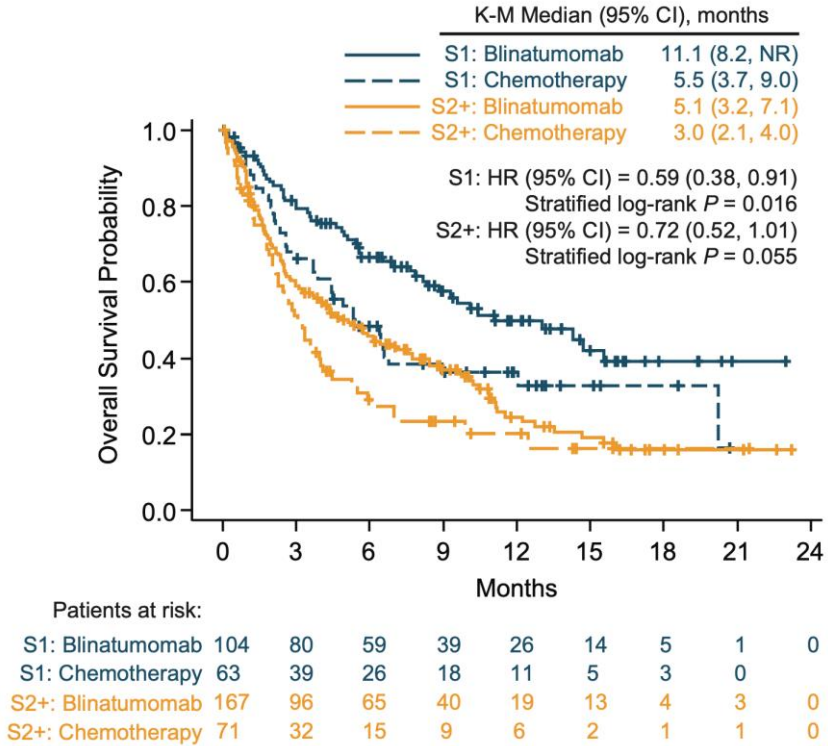


Table 3. Best hematologic response and minimal residual disease response within 12 weeks of treatment initiation.

	First salvage							Second or later salvage						
	Blinatumomab (N = 104)			Chemotherapy (N = 63)				Blinatumomab (N = 167)			Chemotherapy (N = 71)			
Response category	No.	%	95% CI	No.	%	95% CI	p[a]	No.	%	95% CI	No.	%	95% CI	p[a]
Best hematologic response														
CR	46	44.2	34.5, 54.3	18	28.6	17.9, 41.3	.050	45	26.9	20.4, 34.3	3	4.2	0.9, 11.9	<.001
CRh	6	5.8	2.1, 12.1	2	3.2	0.4, 11.0		18	10.8	6.5, 16.5	4	5.6	1.6, 13.8	
CRi	1	1.0	0.0, 5.2	3	4.8	1.0, 13.3		3	1.8	0.4, 5.2	3	4.2	0.9, 11.9	
CR/CRh/CRi	53	51.0	41.0, 60.9	23	36.5	24.7, 49.6	.069	66	39.5	32.1, 47.4	10	14.1	7.0, 24.4	<.001
MRD responses among patients with CR/CRh/CRi														
Any MRD response	33	62.3	47.9, 75.2	13	56.5	34.5, 76.8	.70	41	62.1	49.3, 73.8	3	30.0	6.7, 65.2	.031
Complete MRD response	26	49.1	35.1, 63.2	9	39.1	19.7, 61.5	.53	32	48.5	36.0, 61.1	1	10.0	0.3, 44.5	.008

allo-HSCT: allogeneic hematopoietic stem-cell transplantation; CR: complete remission with full hematologic recovery; CRh: complete remission with partial hematologic recovery; CRi: complete remission with incomplete hematologic recovery; MRD: minimal residual disease.
[a]Cochran–Mantel–Haenszel's test adjusting for the stratification factors (age (<35 versus ≥35 years) and prior allo-HSCT (yes/no)).

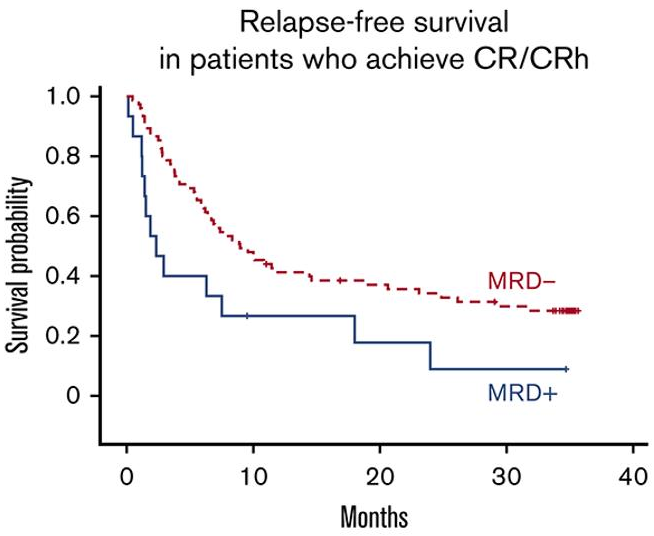
Complete MRD response (blina vs chemo)

49 vs 39% in 1st salvage

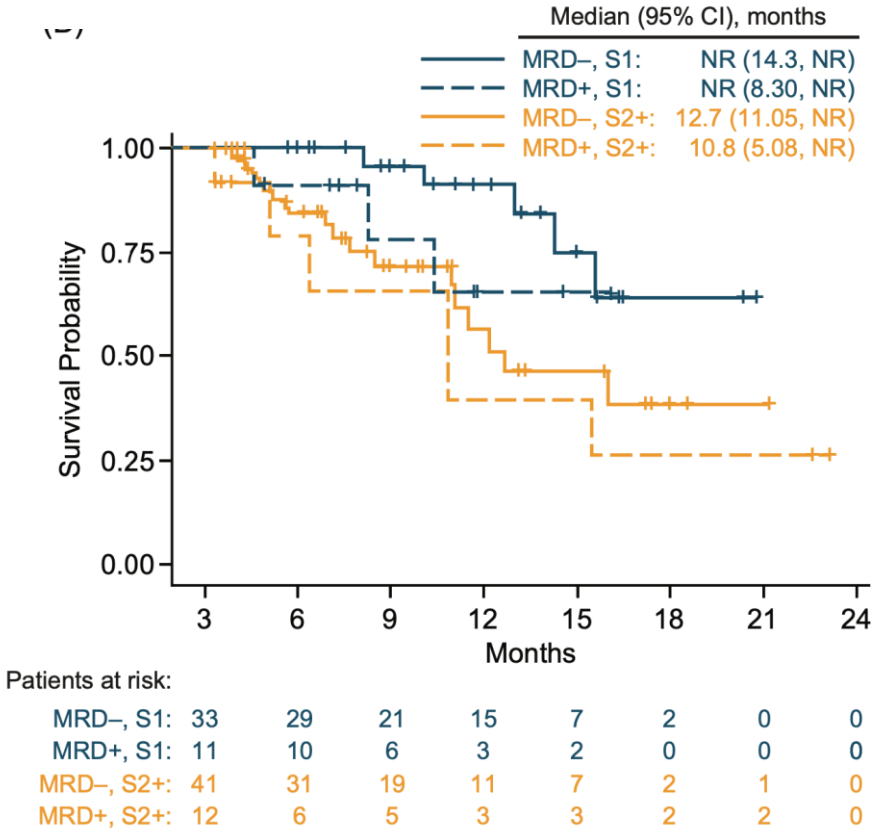
48.5 vs 10% in 2nd or later salvage

Dombret, et al. *Leuk Lymphoma.* 2019;60:2214-2222.

Blinatumomab – MRD Response Predicts Outcome in 1st Salvage



RFS	n	Median (months)	95% CI
MRD–	75	9.0	(6.2–14.6)
MRD+	15	2.3	(1.2–7.5)

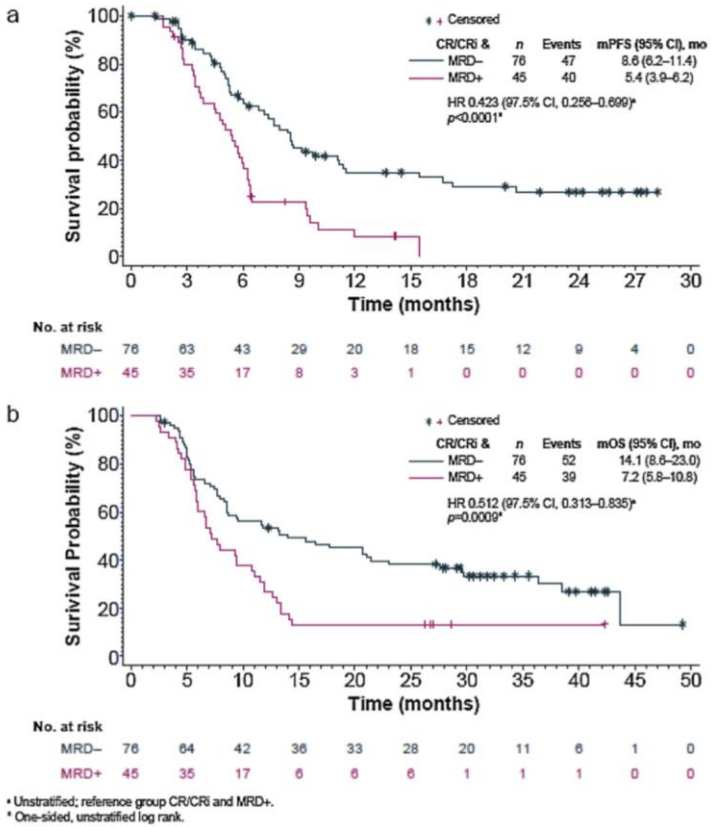


Gokbuget N, et al. *Blood Adv.* 2019;3:3033-3037.

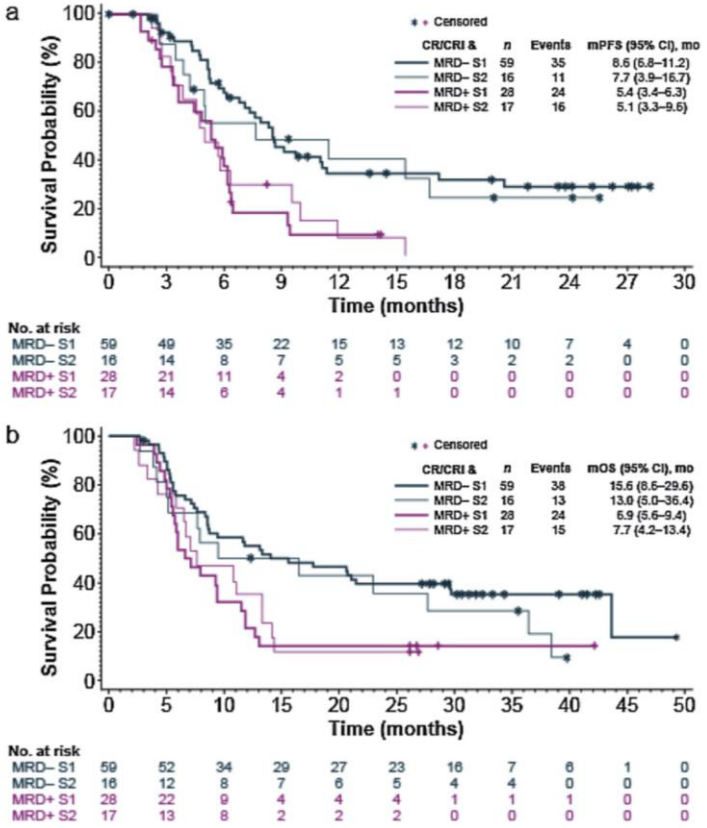
Dombret, et al. *Leuk Lymphoma.* 2019;60:2214-2222.

Inotuzumab – MRD Response Predicts Outcome in 1st/2nd Salvage

PFS



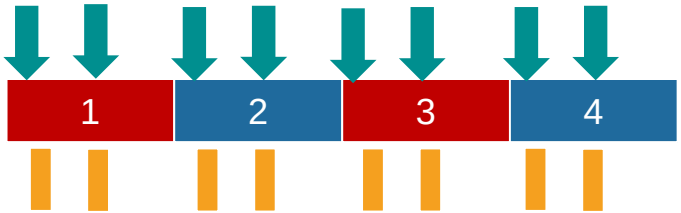
OS



Jabbour E, et al. *Leuk Res.* 2020;88:106283.

Mini-HyperCVD + Inotuzumab – R/R ALL (1/2)

Intensive phase



Mini-hCVD

Mini-MTX-cytarabine

Blinatumomab

POMP

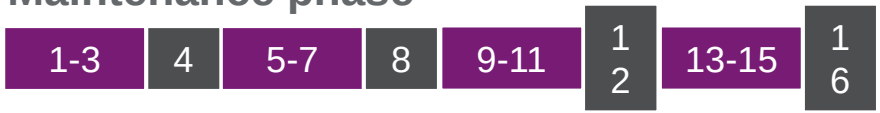
IT MTX/AraC

Consolidation phase

Inotuzumab	Dose per day (mg/m²)
C1	0.6 D1, 0.3 D8
C2-4	0.3 D1 and D8

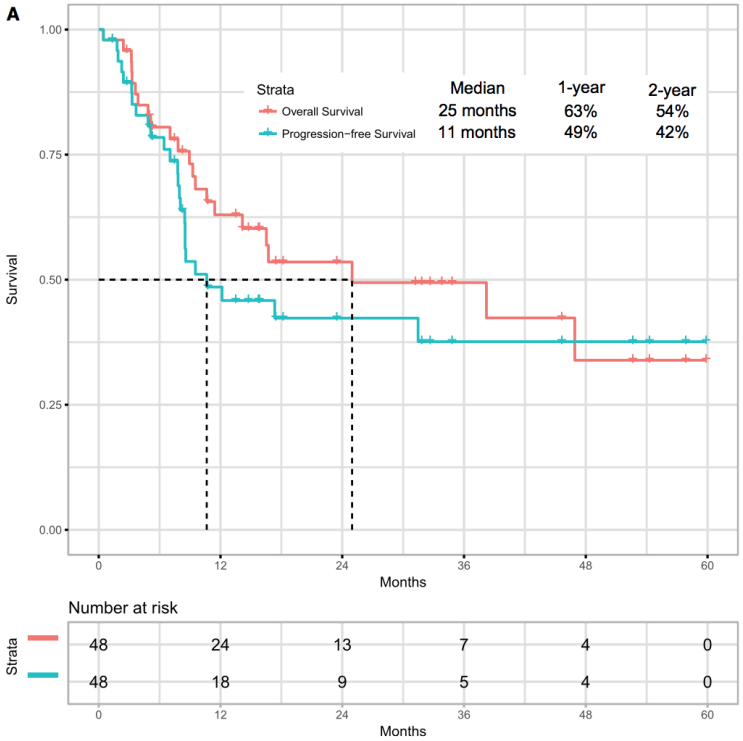
Total Ino dose = 2.7 mg/m²

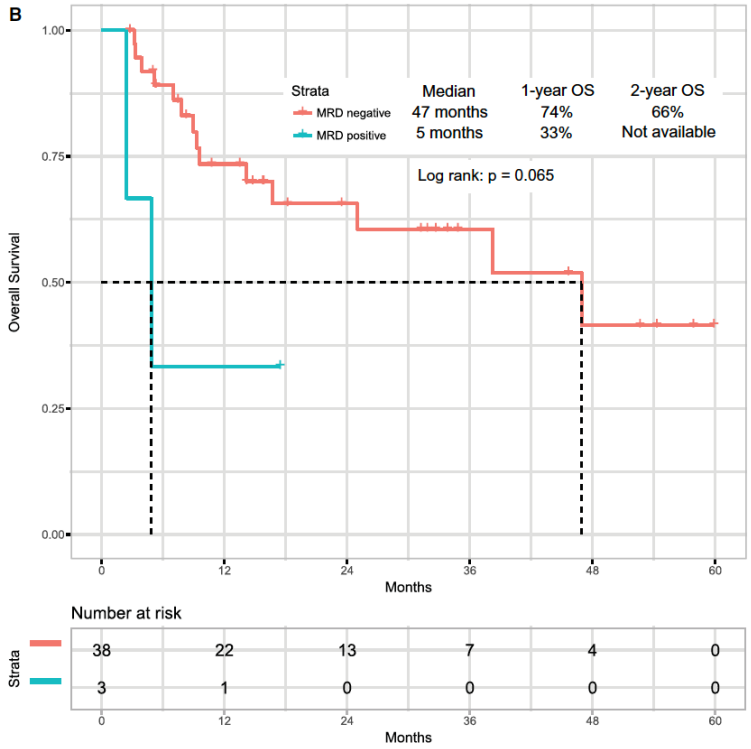
Maintenance phase



Jabbour E, et al. *JAMA Oncol.* 2018;4(2):230-234; Jabbour E, et al. *Cancer.* 2018;124:4044-4055.

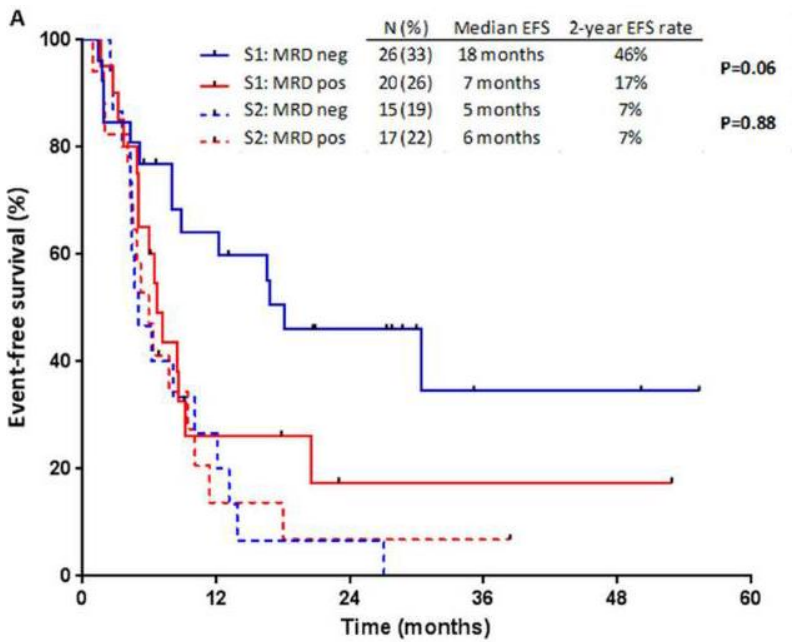
Mini-HyperCVD + Inotuzumab – R/R ALL (2/2)

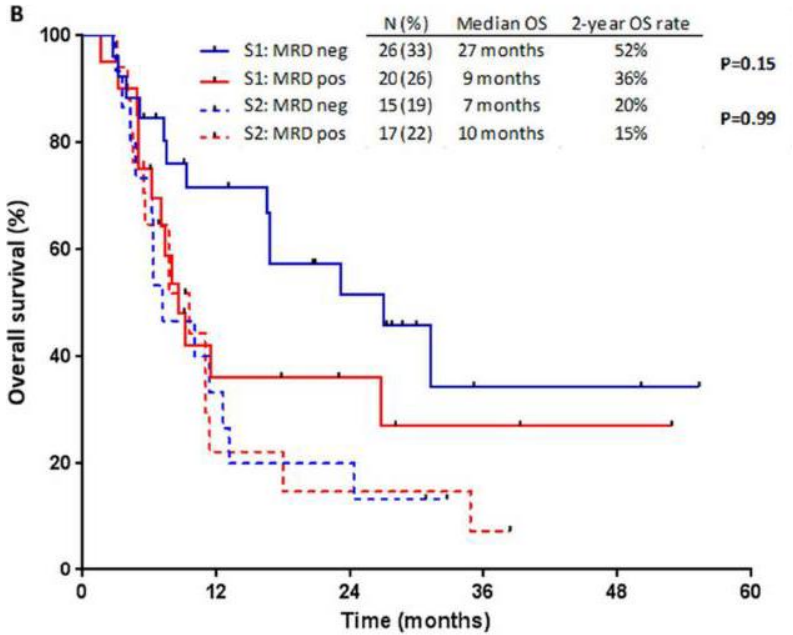




Jabbour E, et al. *Cancer.* 2018;124:4044-4055.

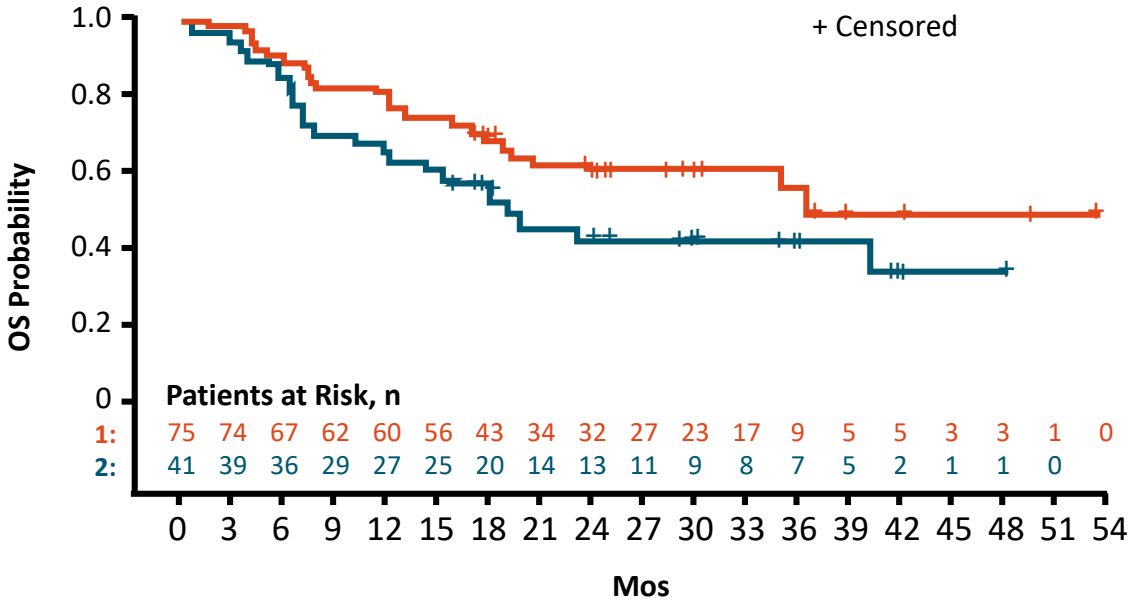
Mini-HyperCVD + Inotuzumab – Predictive Value of MRD Negativity Decreases After 1st Salvage





Jabbour E, et al. *Cancer.* 2017;123(2):294-302.

Blinatumomab BLAST Trial – Preemption of B-ALL Relapse Using MRD-Directed Treatment

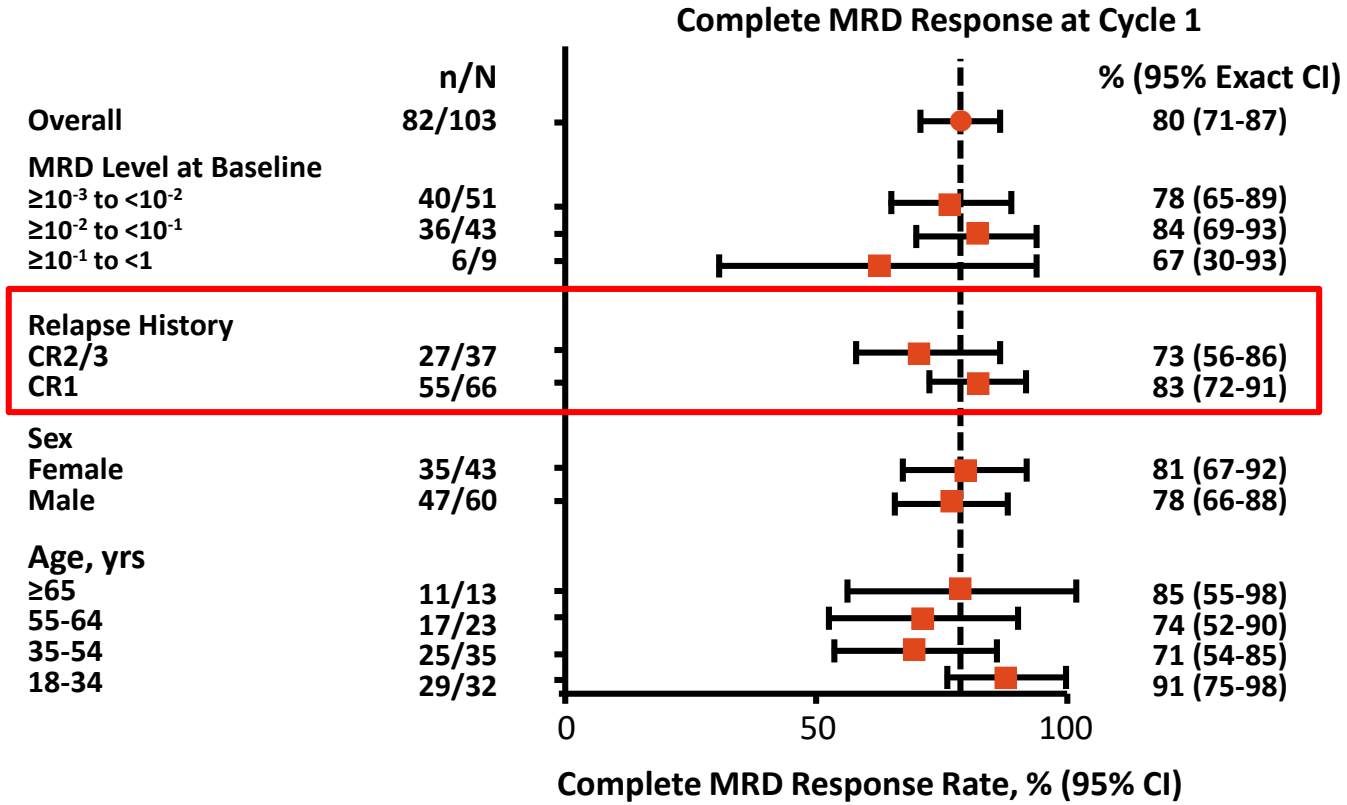


1: Patients in 1st CR (n = 75); median: 36.5 (95% CI: 20.6-NR)

2: Patients in 2nd or 3rd CR (n = 41); median: 19.1 (95% CI: 11.9-NR)

Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

Blinatumomab BLAST Trial – Preemption of ALL Relapse Using MRD-Directed Treatment



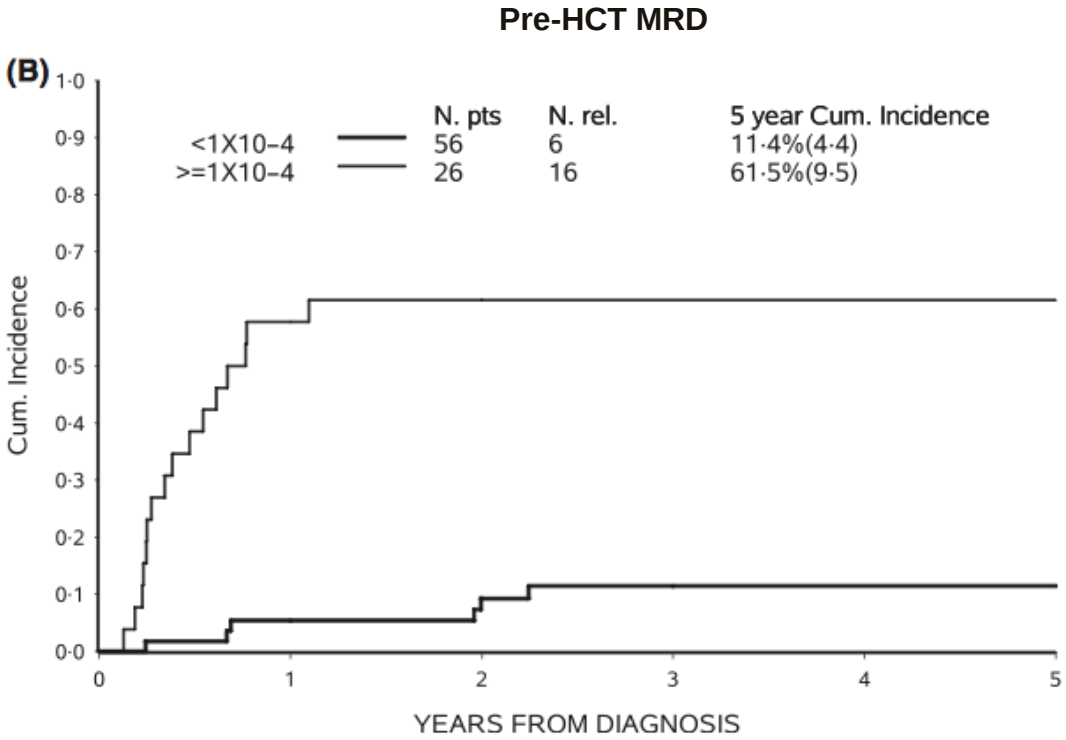
Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

MRD Status Pre-Transplant Predicts RFS and OS (1/2)

N = 82, age <1-20
MRD by ASO-PCR
Median f/u 4.9 yrs

HCT in CR1 if
- Day +78: >5 × 10^{-4} MRD
- Induction failure
- Ph+, MLL+
- T-lin w/ WBC >100K

HCT for all CR2+



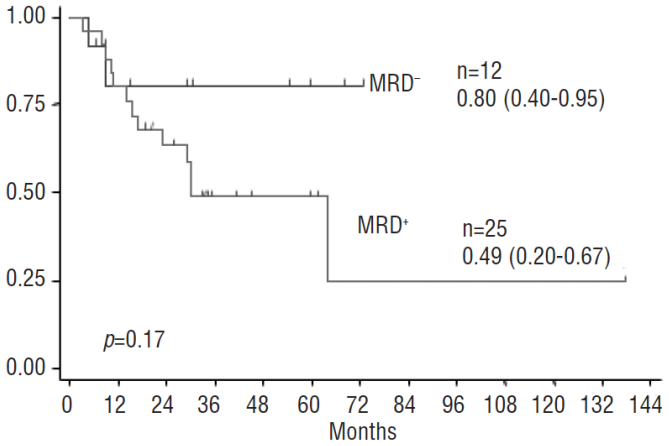
Balduzzi, et al. *Br J Haematol.* 2014;164:396-408.

MRD Status Pre-Transplant Predicts RFS and OS (2/2)

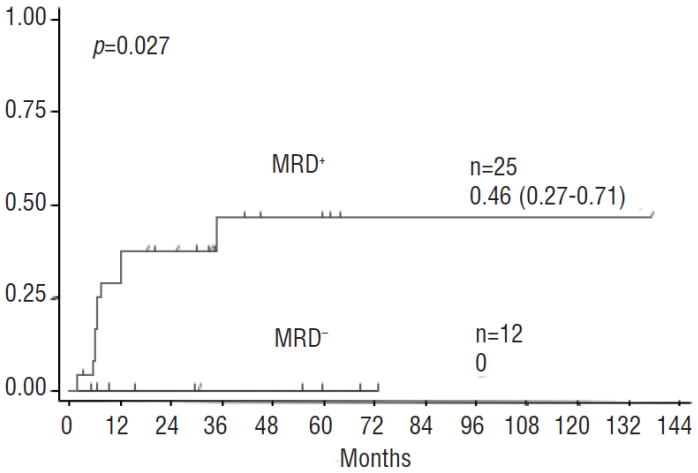
N = 43, age 18-63
MAC alloHCT in CR1

MRD quant:
TCR/Ig ASO-PCR
or
BCR/ABL Q-PCR
or
MLL/AF4 Q-PCR

MRD status pre-HCT: OS



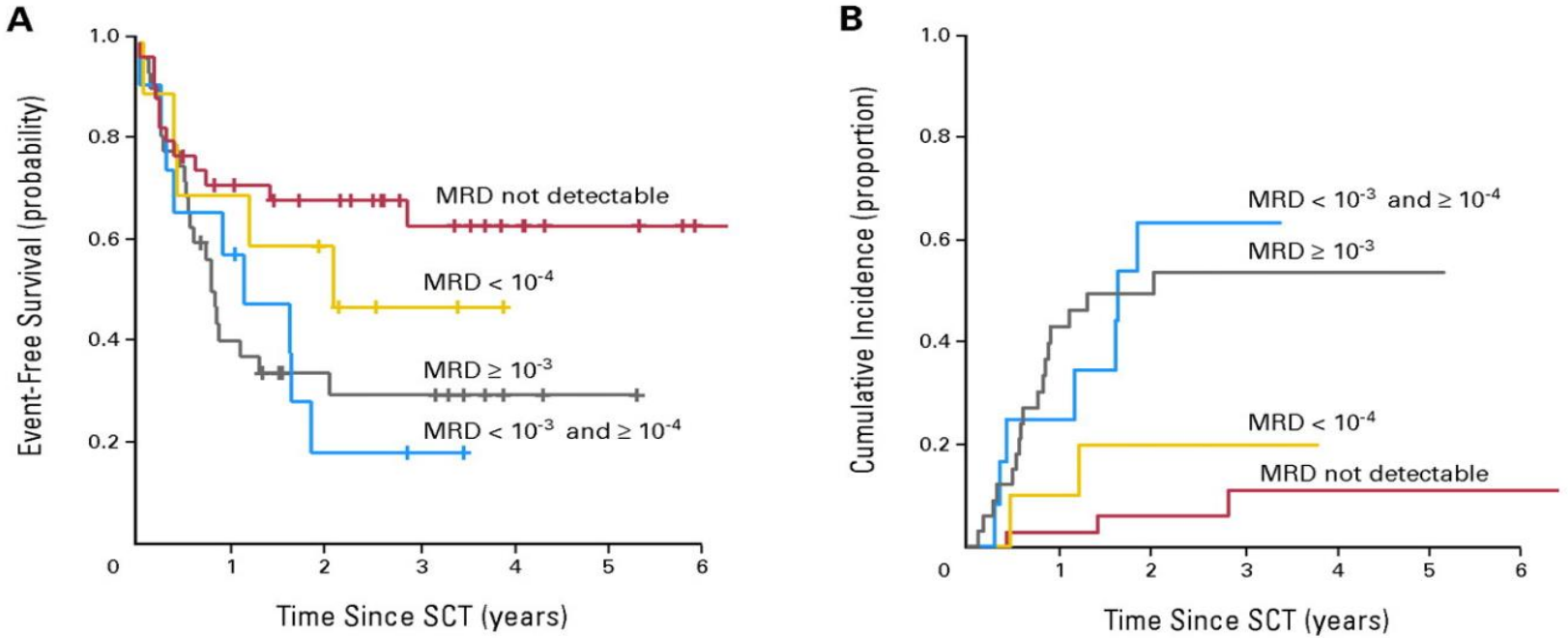
MRD status pre-HCT: CIR



Spinelli, et al. *Haematologica*. 2007;92:612-618.

MRD in CR2 Pre-Transplant Predicts Outcome

- N = 91 in CR2 (77) or CR3 (14)
- Pediatric ALL-REZ BFM study



Bader P, et al. *J Clin Oncol.* 2009;27(3):377-384.

MRD Assessment in CR2 and Beyond Summary

- MRD in CR2 remains a useful predictor of relapse-free survival in studies with chemotherapy and novel agents
- MRD in CR2 also a predictor of overall survival with use of novel agents (inotuzumab, blinatumomab)
- MRD may have limited predictive value for RFS/OS in CR3+
- MRD pre-transplant is highly predictive of outcome in CR1 and CR2+
- Patients treated with blinatumomab for MRD positivity in CR2/3 have similar likelihood for conversion to MRD negativity (78%) as patients treated for MRD positivity in CR1 (83%), but shorter median OS (19.1 vs 36.5 mos)


Thank you!

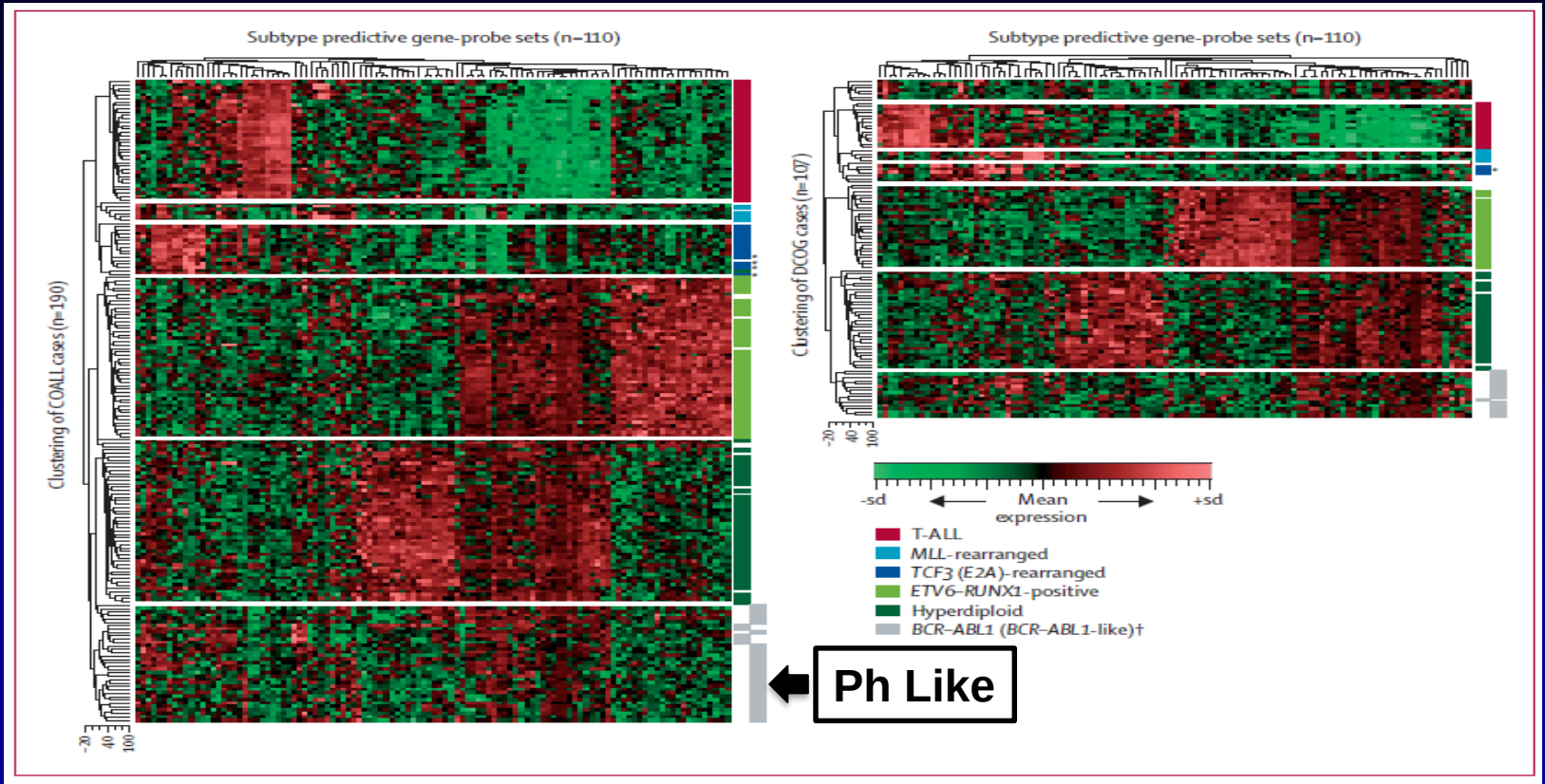
Global Leukemia Academy

Genetic Variants in ALL – Ph+ and Ph-Like

Elias Jabbour

APTITUDE HEALTH®

Ph-Like ALL



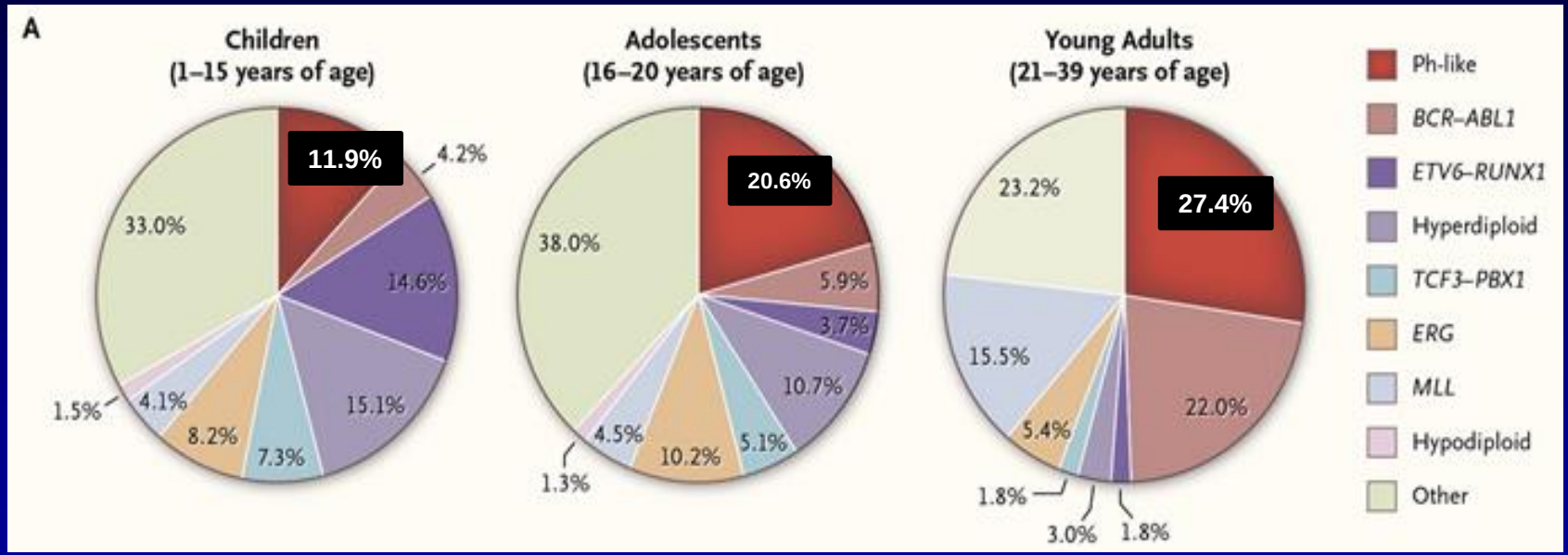
Den Boer. *Lancet Oncol*. 2009.

2016 WHO Classification

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

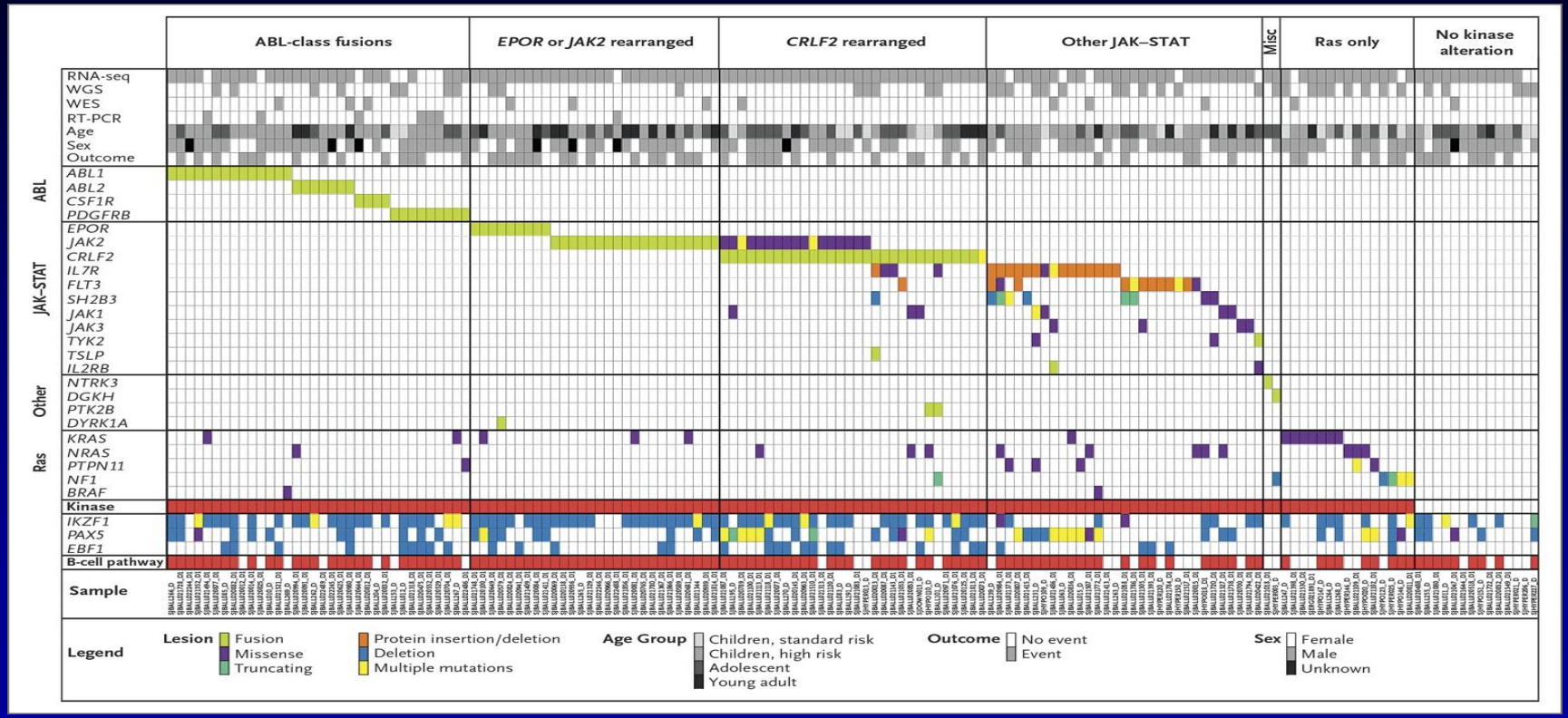
Arber. *Blood.* 2016;127(20):2391-2405.

Ph-Like ALL Occurs in 25%–30% of Young Adults With B-cell ALL



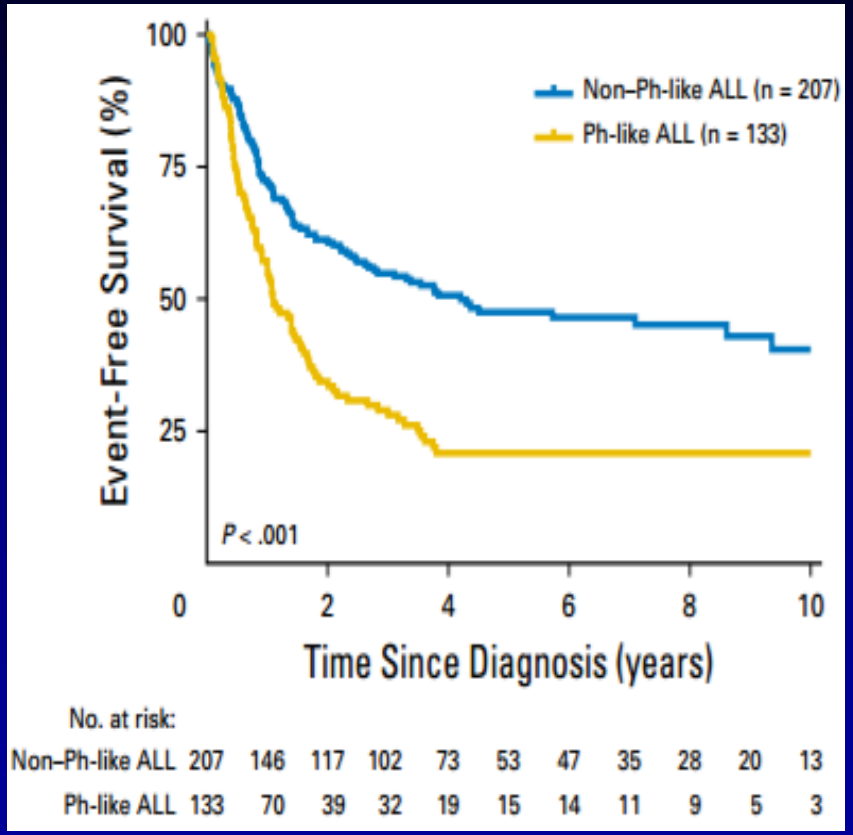
Roberts. *N Engl J Med*. 2014; 371:1005-1015.

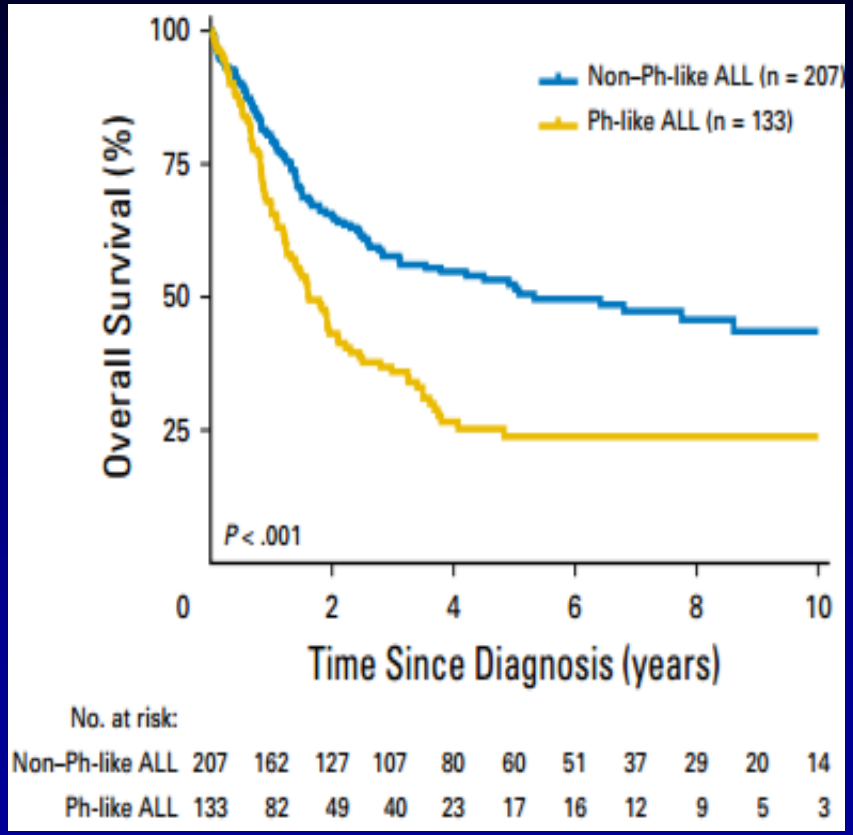
Recurring Kinase Alterations in Ph-Like ALL



Roberts. *N Engl J Med*. 2014; 371:1005-1015.

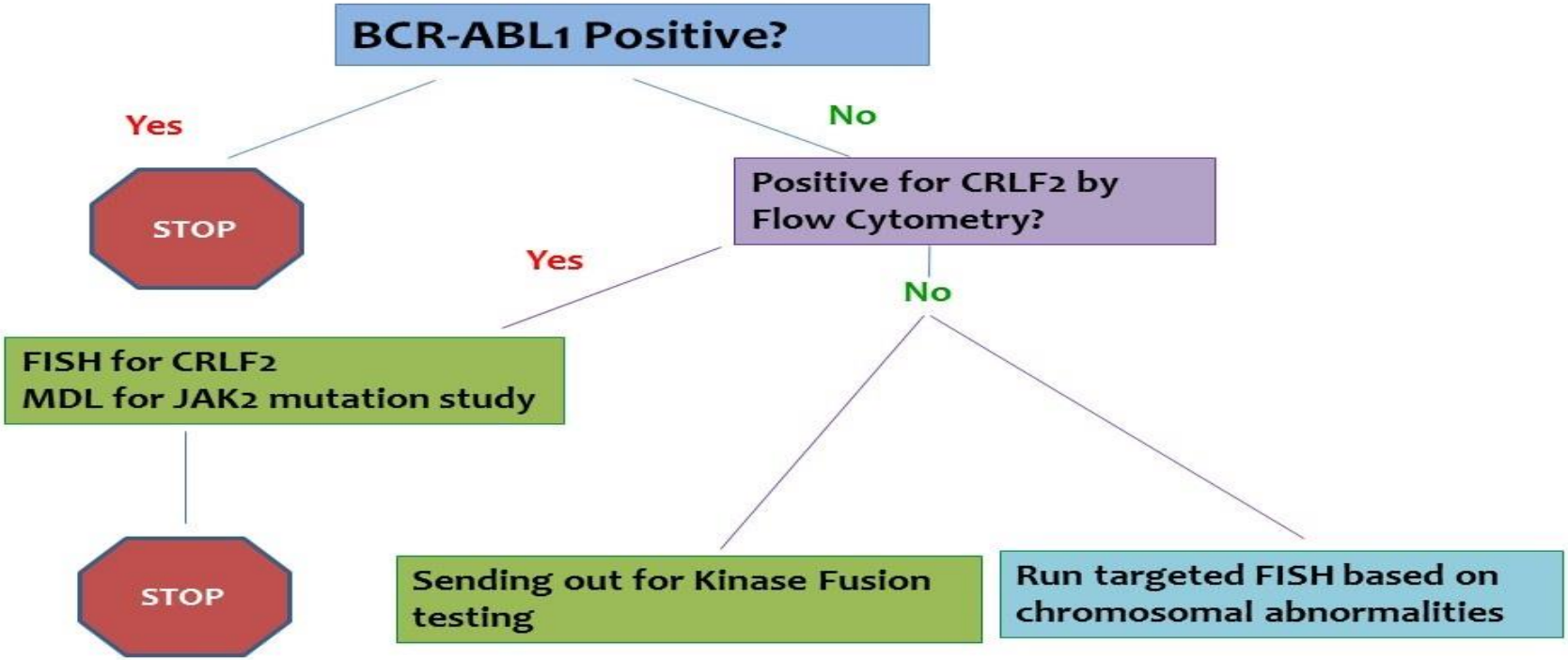
Ph-Like ALL: Survival and EFS





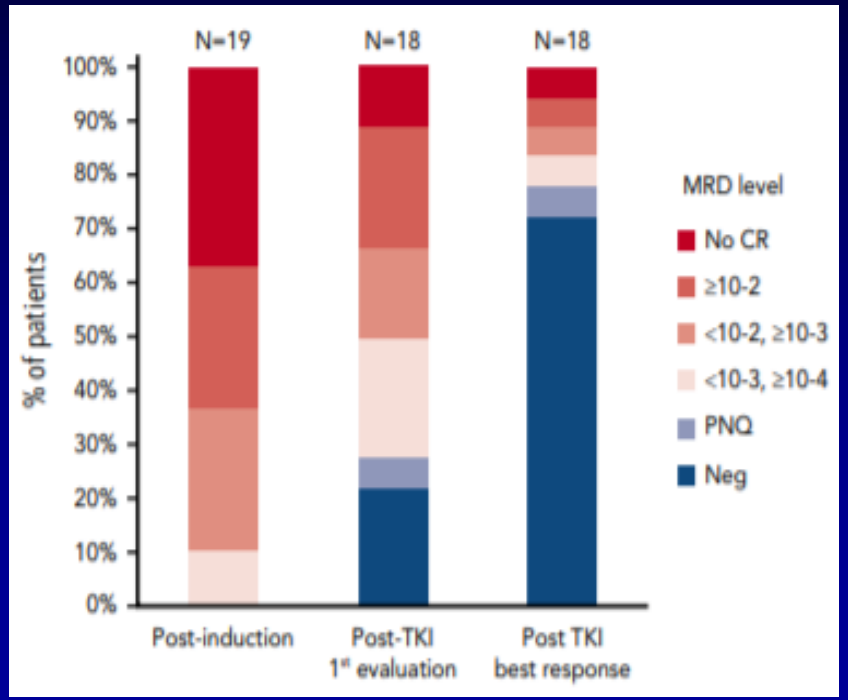
Roberts. *J Clin Oncol.* 2017;35:394.

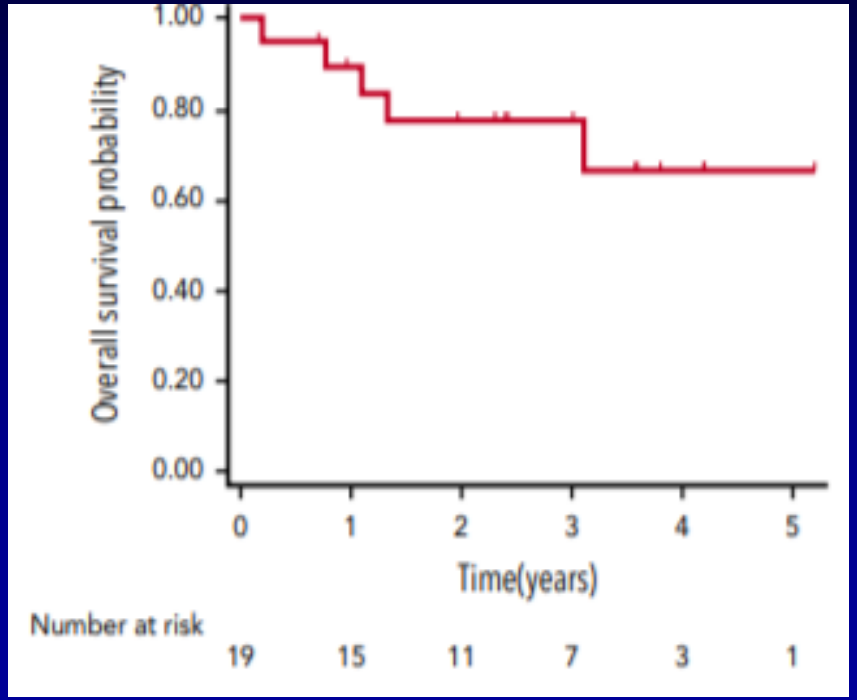
Ph-Like FISH Testing Algorithm



BCR-ABL TKIs + Chemo Rx in Ph-Like ALL

- **24 pts with Ph-like ALL: *NUP214-ABL1* – 6, *ETV6-ABL1* – 3, others –9; 19 frontline, 5 relapse. All Rx with chemo Rx + TKI**





Tanasi. *Blood.* 2019;134:1351.

Ph-Like ALL: Higher MRD+ Rate

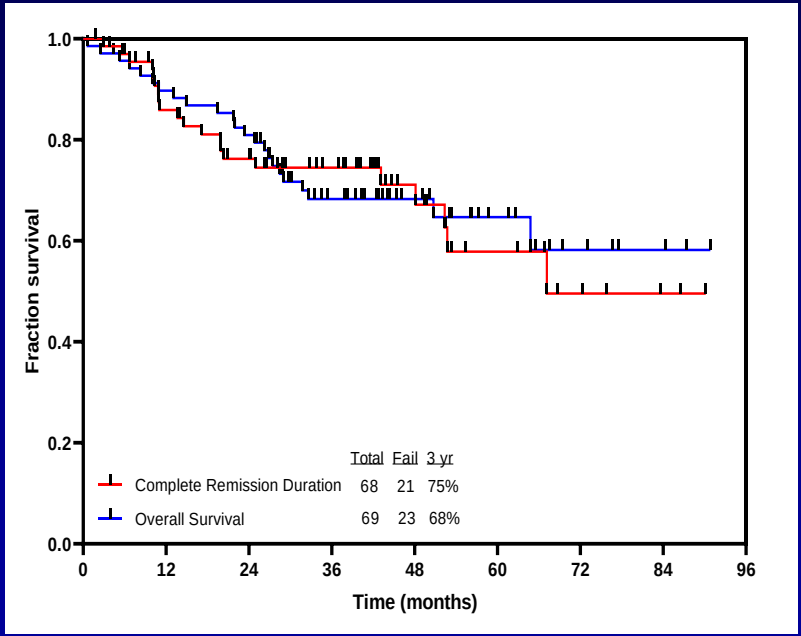
	B-ALL Categories (N = 155)			
	Ph-like	Ph+	B – other	*P* value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	.57
MRD at CR				
Positive	23 (70)	15 (44)	4 (13)	<.001
Negative	10 (30)	19 (56)	27(87)	

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

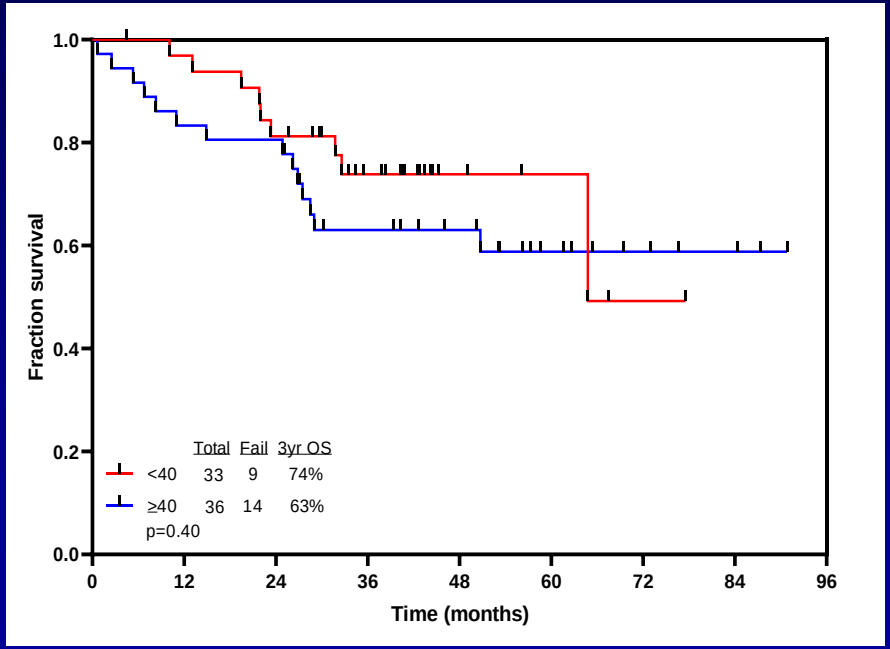
HCVAD + Ofatumumab: Outcome (N = 69)

- Median follow up of 44 months (4–91)
- CR 98%, MRD negativity 93% (at CR 63%), early death 2%

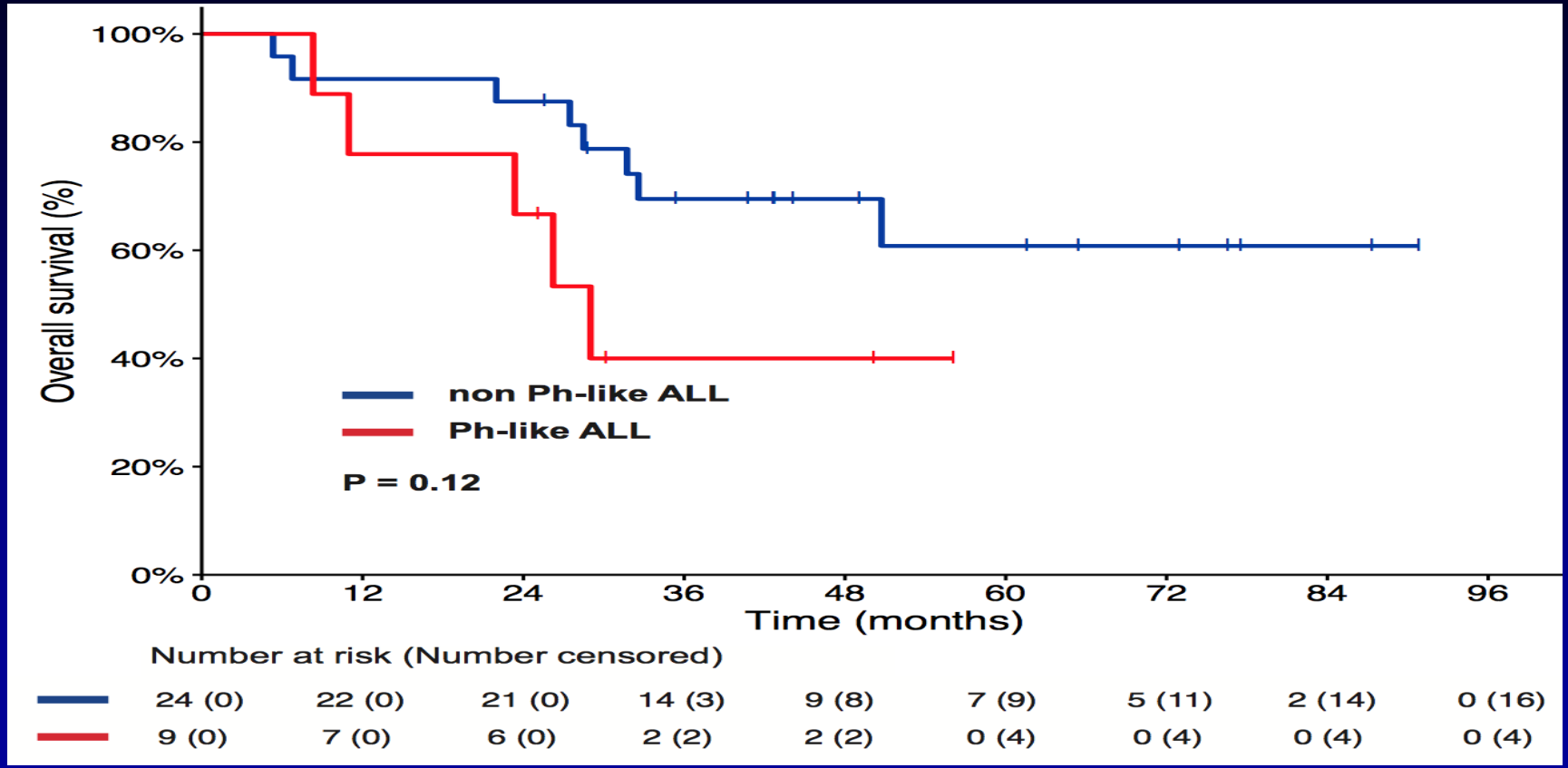
CRD and OS overall



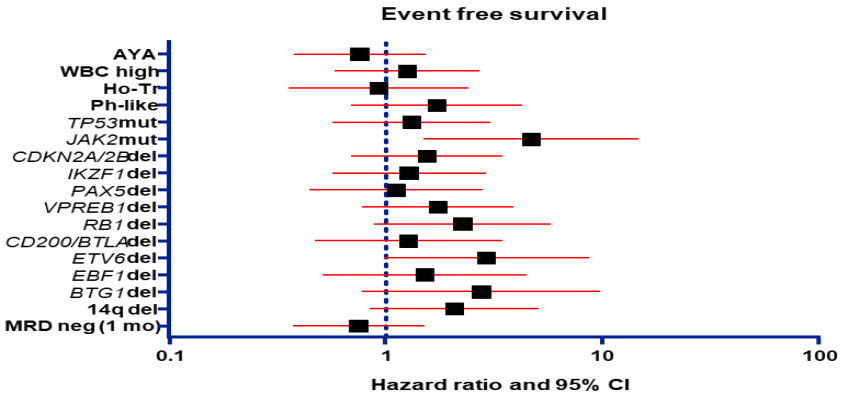
OS by age



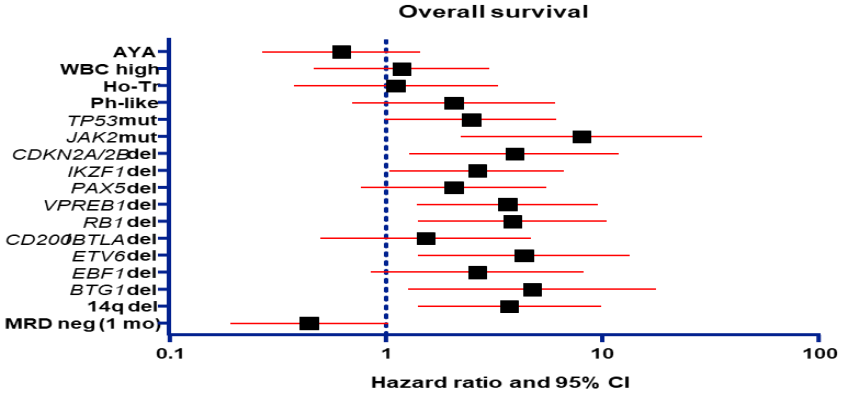
HCVAD + Ofatumumab: Outcome by Ph-Like (RNA-seq)



Hyper-CVAD + Ofatumumab: Molecular Alterations and Outcome



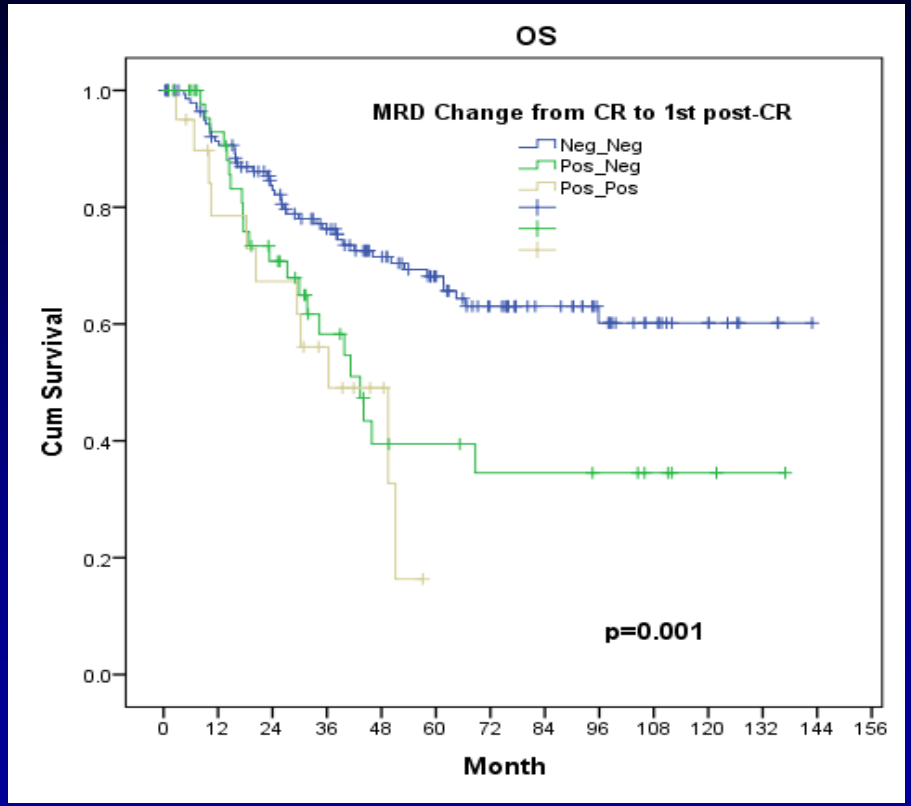
Univariate analysis	p. value	Multivariate analysis	p. value
0.7578 (0.3754-1.53)	0.4389		
1.254 (0.582-2.700)	0.5638		
0.9261 (0.3548-2.418)	0.8754		
1.727 (0.6928-4.305)	0.2410		
1.316 (0.5649-3.066)	0.5245		
4.707 (1.495-14.82)	0.008104	4.118 (1.125-15.07)	0.03252
1.549 (0.6931-3.461)	0.2862	1.479 (0.6235-3.508)	0.3746
1.282 (0.5661-2.905)	0.5511	1.269 (0.5136-3.134)	0.6059
1.122 (0.4470-2.817)	0.8062		
1.738 (0.7746-3.898)	0.1802		
2.262 (0.8834-5.794)	0.08883		
1.274 (0.4700-3.455)	0.6338		
2.922 (0.9825-8.693)	0.05383		
1.518 (0.5144-4.477)	0.4498		
2.763 (0.7830-9.752)	0.1142		
2.079 (0.8468-5.107)	0.1102		
0.7484 (0.3714-1.508)	0.4176	0.6752 (0.296-1.54)	0.3505



Univariate analysis	p. value	Multivariate analysis	p. value
0.6243 (0.2682-1.453)	0.2744		
1.185 (0.4665-3.010)	0.7212		
1.114 (0.3754-3.304)	0.8462		
2.065 (0.7015-6.079)	0.1880		
2.489 (1.002-6.185)	0.04951		
8.062 (2.229-29.16)	0.001461	5.136 (1.251-21.09)	0.02319
3.936 (1.291-12.00)	0.01598	2.828 (1.069-7.482)	0.0362
2.656 (1.049-6.723)	0.03932	2.986 (0.9092-9.805)	0.07138
2.067 (0.7728-5.527)	0.1480		
3.659 (1.391-9.628)	0.008578		
3.855 (1.415-10.50)	0.008316		
1.532 (0.5006-4.688)	0.4548		
4.347 (1.408-13.42)	0.01063		
2.660 (0.8597-8.230)	0.08958		
4.766 (1.277-17.79)	0.02014		
3.729 (1.407-9.883)	0.00812		
0.4432 (0.1912-1.028)	0.05792	0.3955 (0.1391-1.124)	0.08181

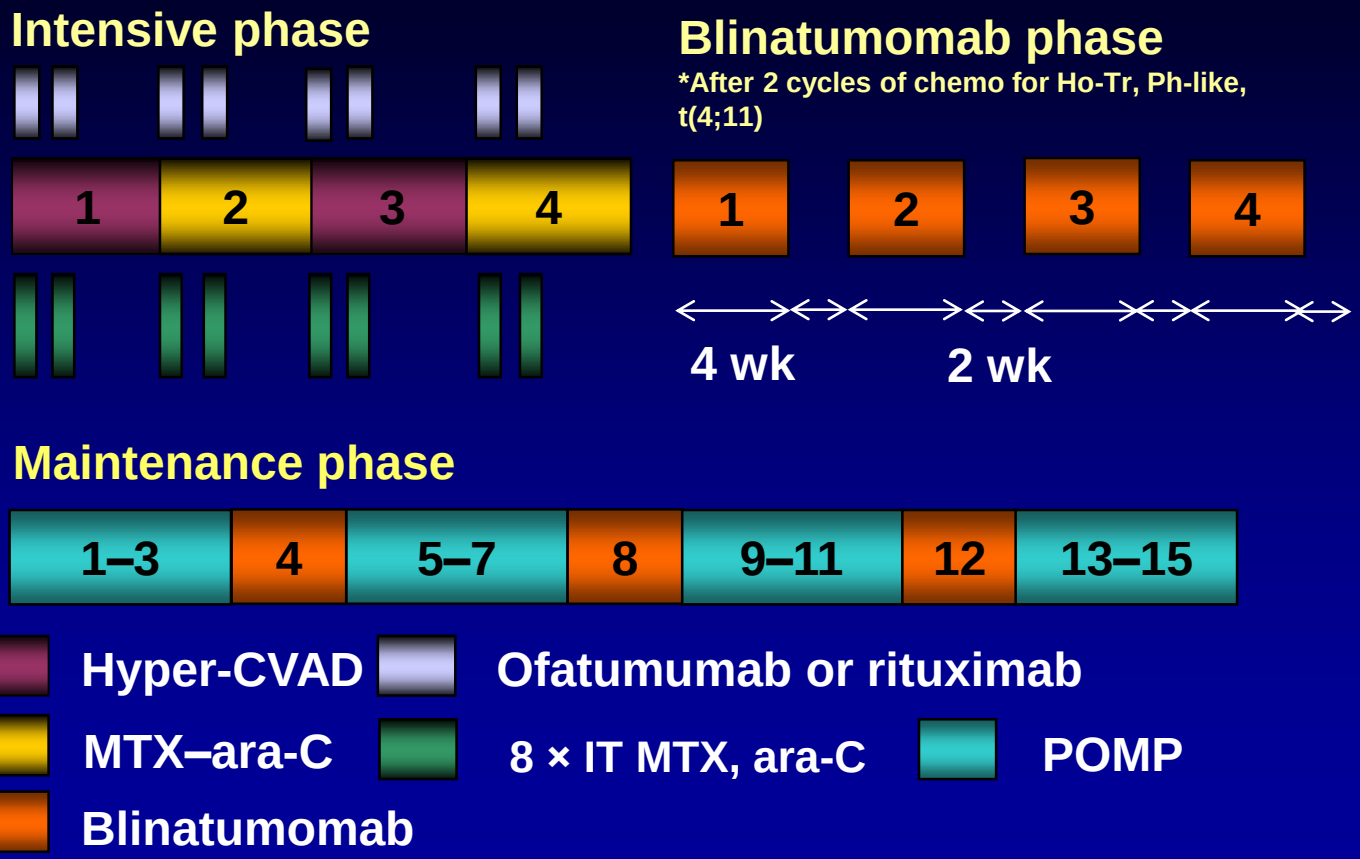
Dynamics of MRD: Outcome

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.

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

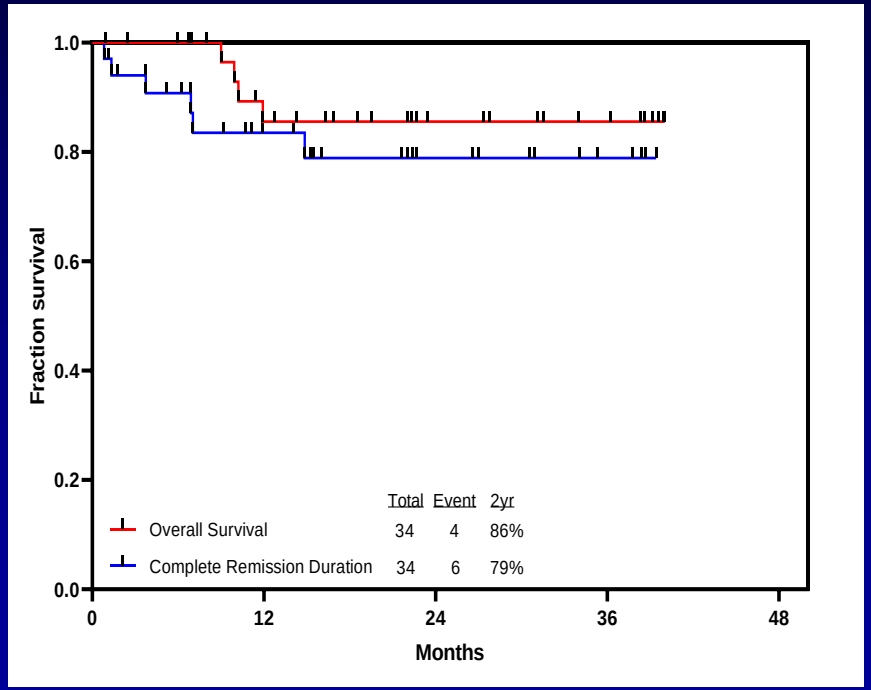


Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

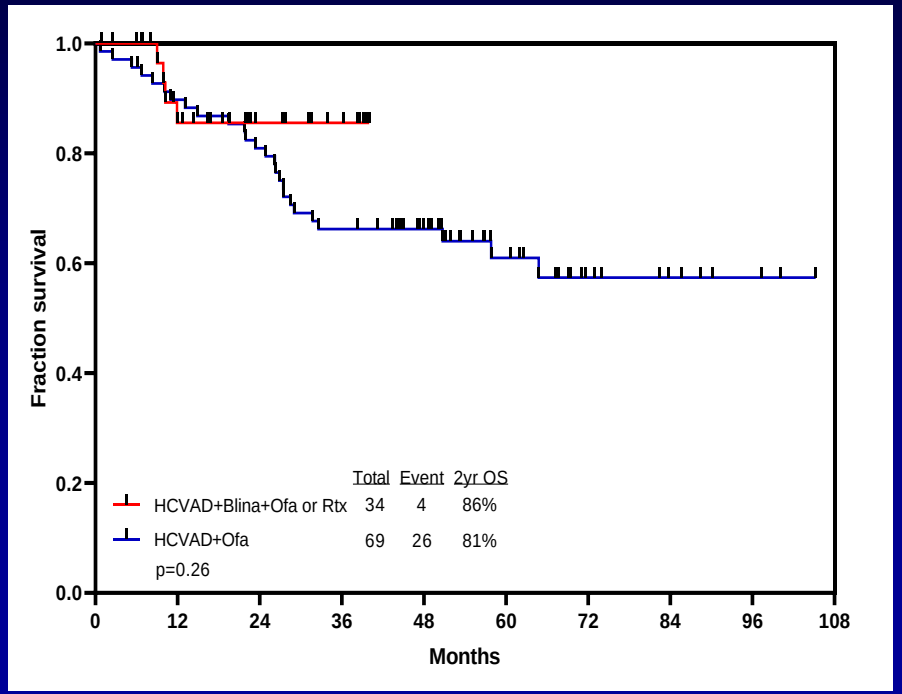
Hyper-CVAD + Blinatumomab in FL B-ALL (N = 34)

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

CRD and OS Overall



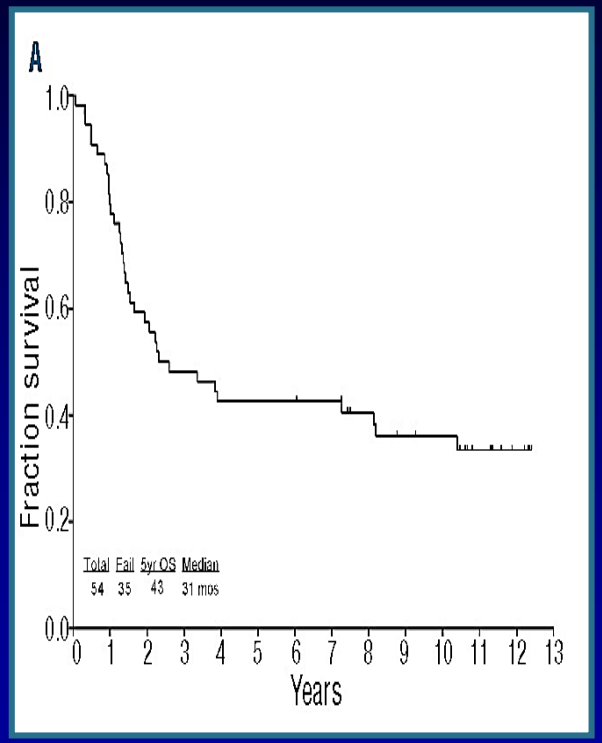
OS: HCVAD-Blina vs O-HCVAD



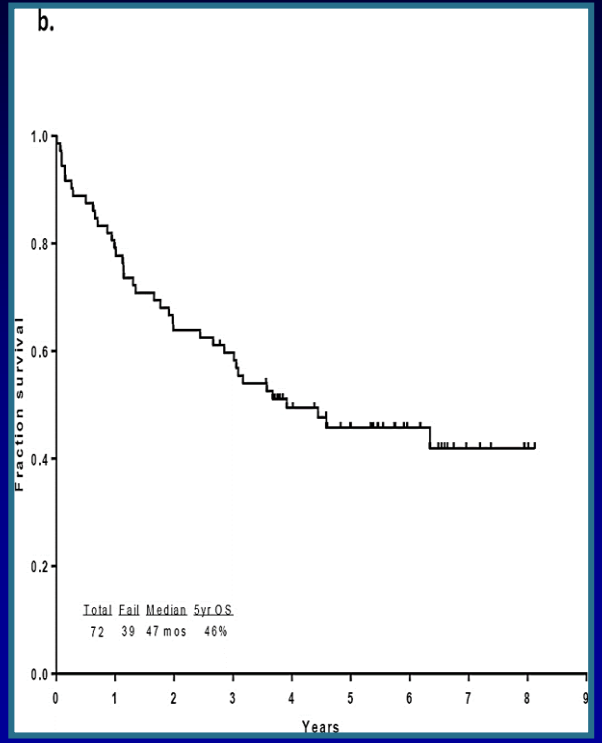
Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

TKI for Ph+ ALL

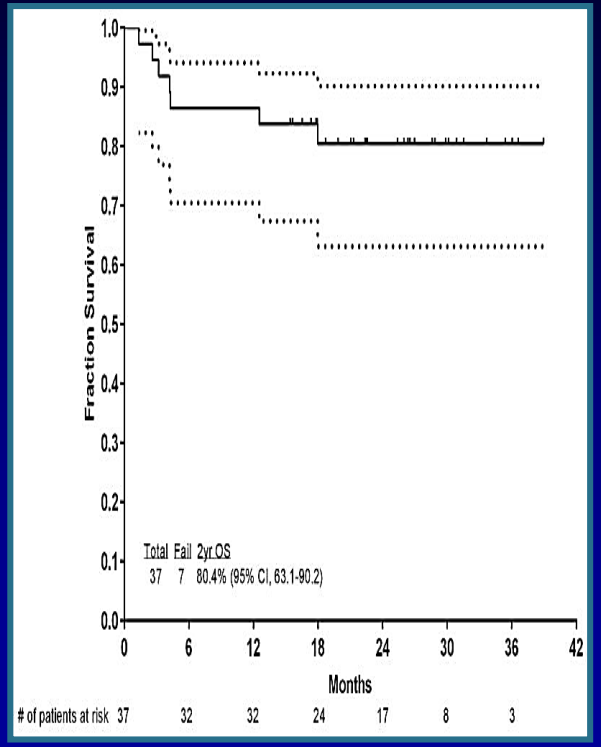
Imatinib: 5-yr OS = 43%



Dasatinib: 5-yr OS = 46%



Ponatinib: 5-yr OS = 71%



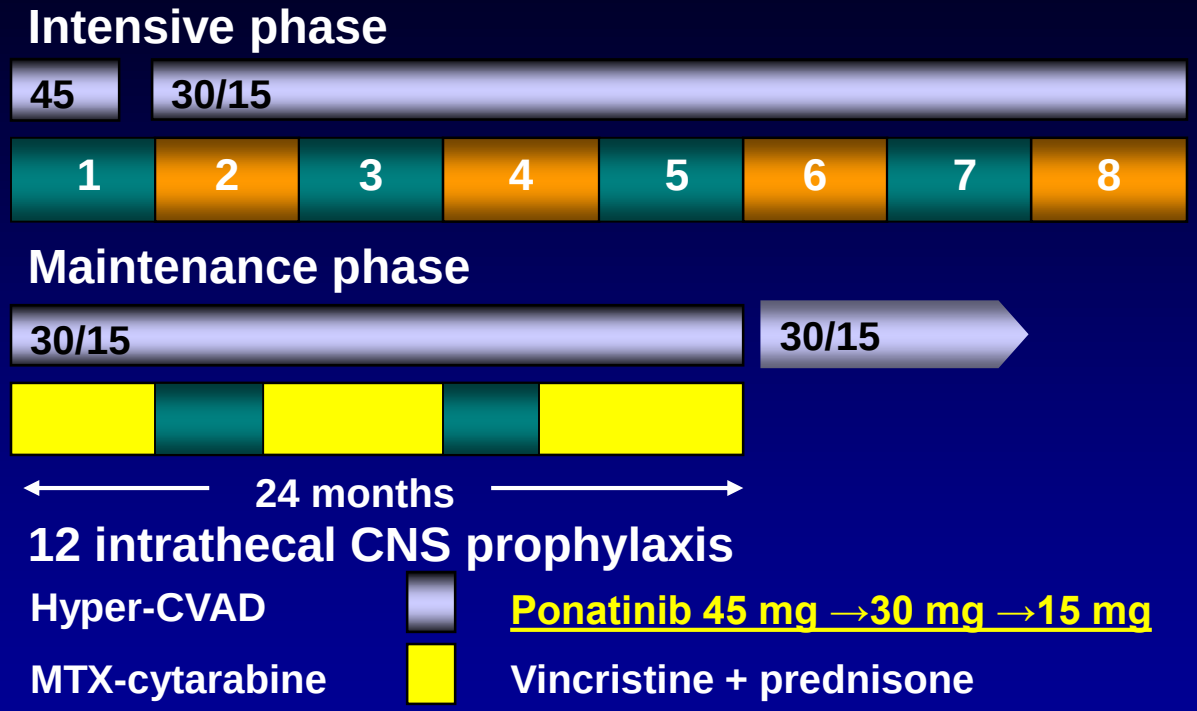
Daver. *Haematologica*. 2015; Ravandi. *Cancer*. 2015; Jabbour. *Lancet Oncol.* 2015; Jabbour. *Lancet Hematol.* 2018.

Low-Intensity Chemo Rx + Dasatinib in Ph+ ALL ≥55 Years

- 71 pts (2007–2010); median age 69 yr (58–83)
- Dasatinib 100–140 mg/D, VCR 1 mg Q wk, dex 20–40 mg/D × 2, Qwk
- Consolidations: dasatinib 100 mg/D; MTX-asp C1, 3, 5; ara-C C2, 4, 6. Maintenance: dasatinib + POMP
- CR 96%; MMR 65%; CMR 24%
- 5-yr survival 36%; EFS 25%
- *T315I* at dx 23% by NGS
- 36 relapses; *T315I* in 75%

Rousselot. *Blood.* 2016;128(6):774-782.

Hyper-CVAD + Ponatinib: Design



- After the emergence of vascular toxicity, protocol was amended: beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Jabbour. *Lancet Oncol.* 2015;16:1547; Jabbour. *Lancet Hematol*. 2018

Hyper-CVAD + Ponatinib in Ph+ ALL: Response Rates

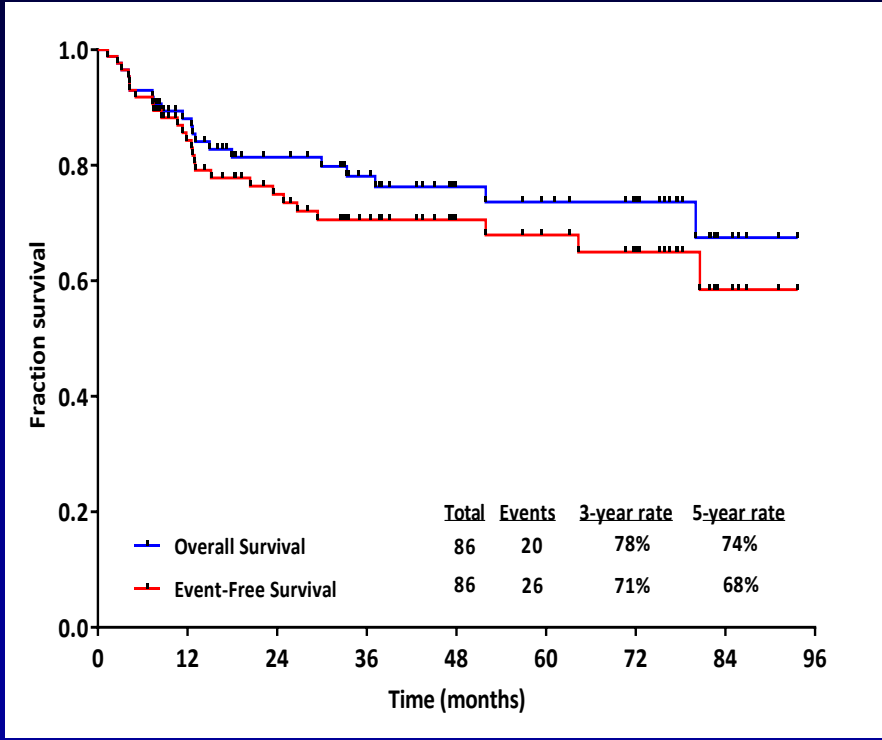
Median follow-up: 44 months (4–94 months)

Response	n/N (%)
CR	68/68 (100)
CCyR	58/58 (100)
MMR	80/85 (94)
CMR	**73/85 (86)**
3-month CMR	63/85 (74)
Flow negativity	83/85 (95)
Early death	0

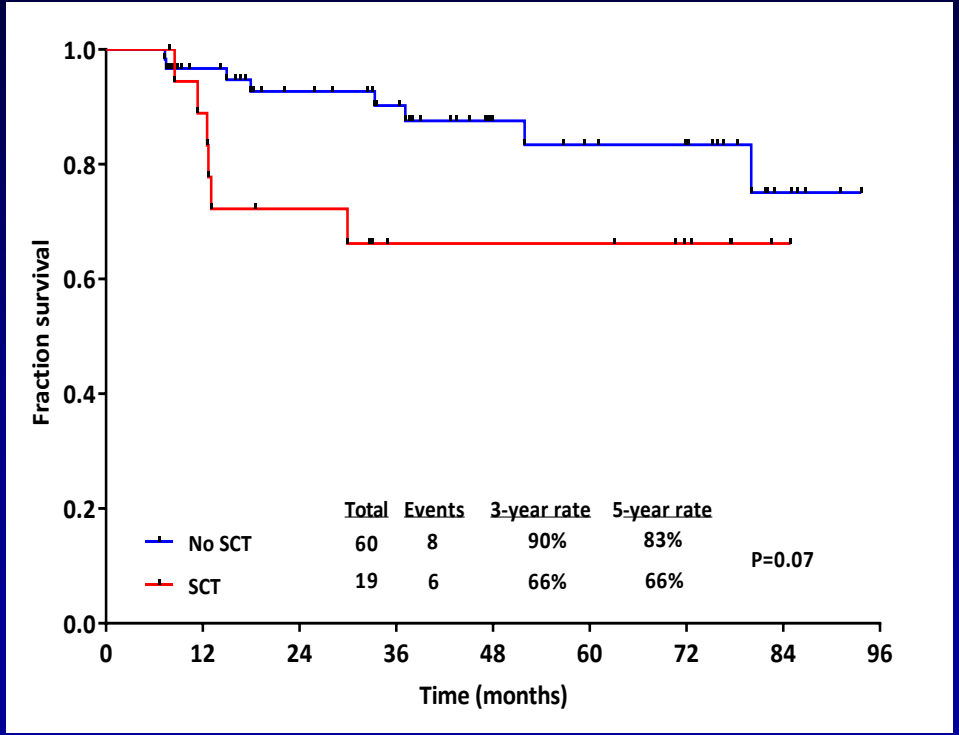
Short. *Blood*. 2019;134:abstract 283.

Hyper-CVAD + Ponatinib in Ph+ ALL: Outcome

EFS and OS

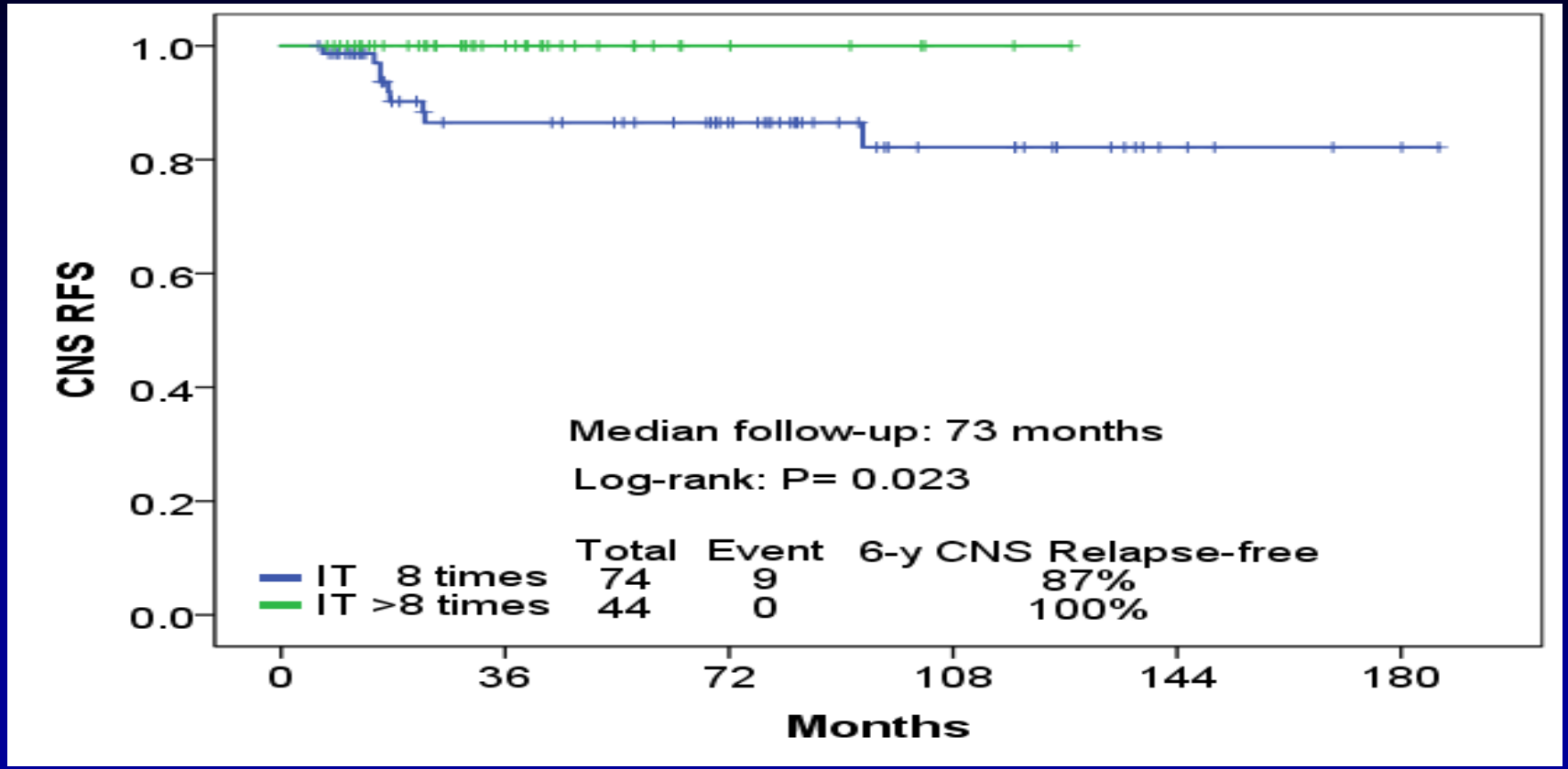


Impact of allo-SCT: 6-mo landmark



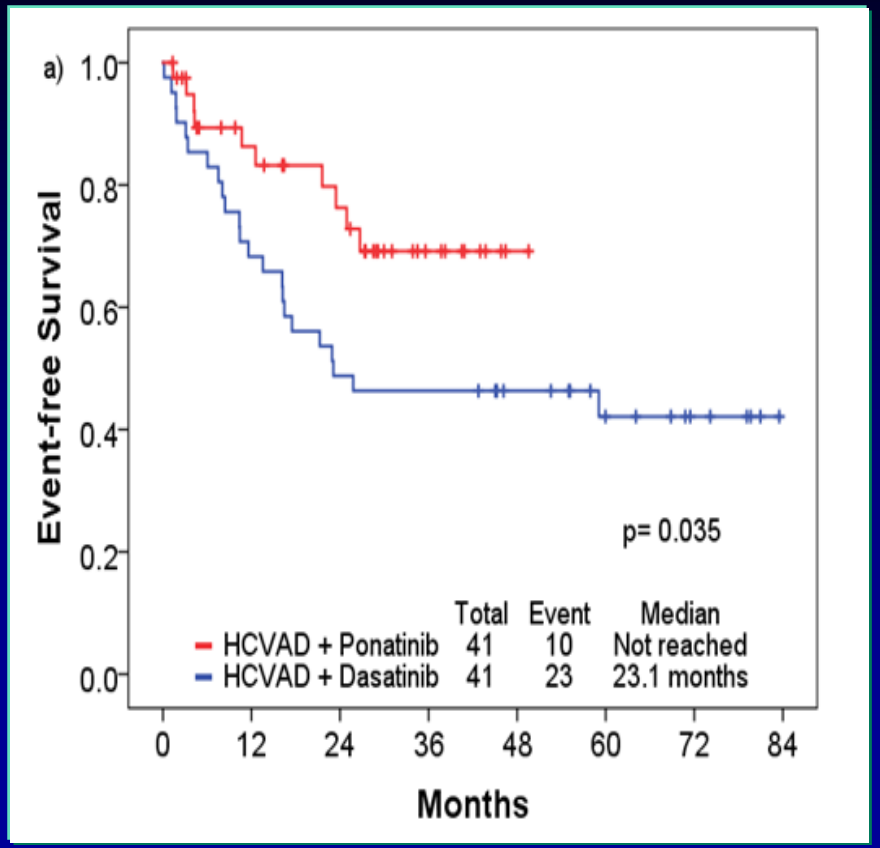
Short. *Blood*. 2019;134:abstract 283.

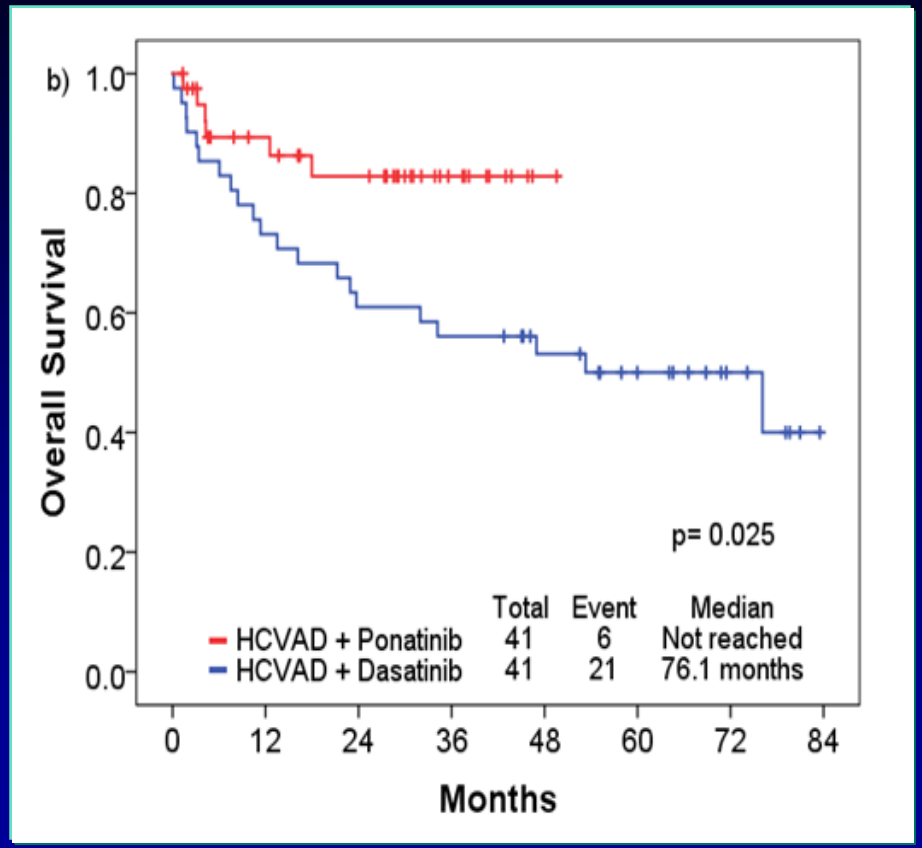
IT × 8 vs IT × 12 in Ph+ ALL: 6-Month Landmark – CNS Relapse-Free Survival



Paul. *Blood*. 2019;134:abstract 3810.

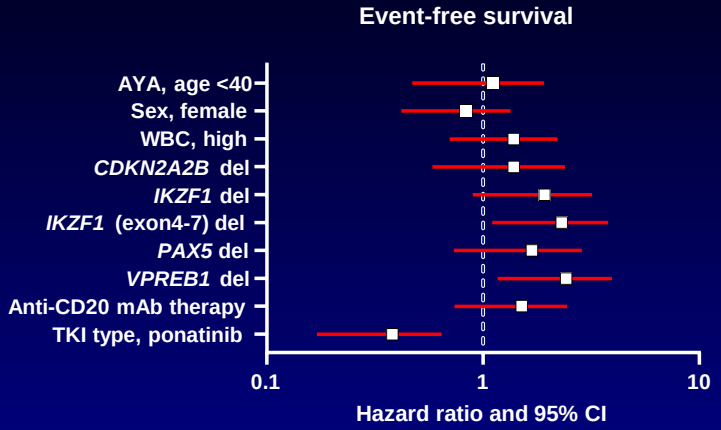
Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph+ ALL



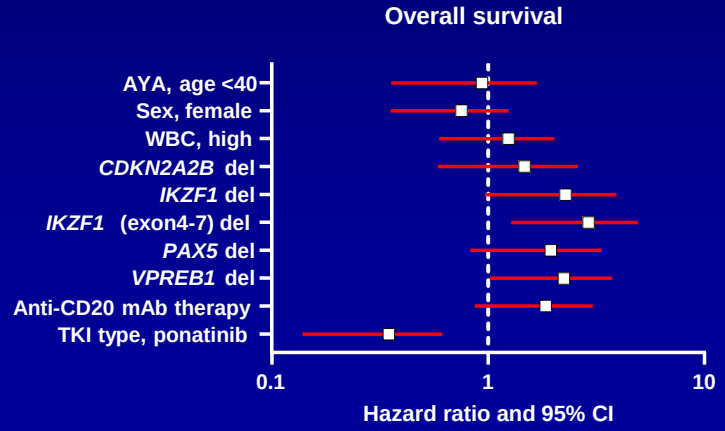


Sasaki. *Cancer*. 2016;122(23):3650-3656.

Event-Free Survival/Overall Survival (entire cohort, N = 107)



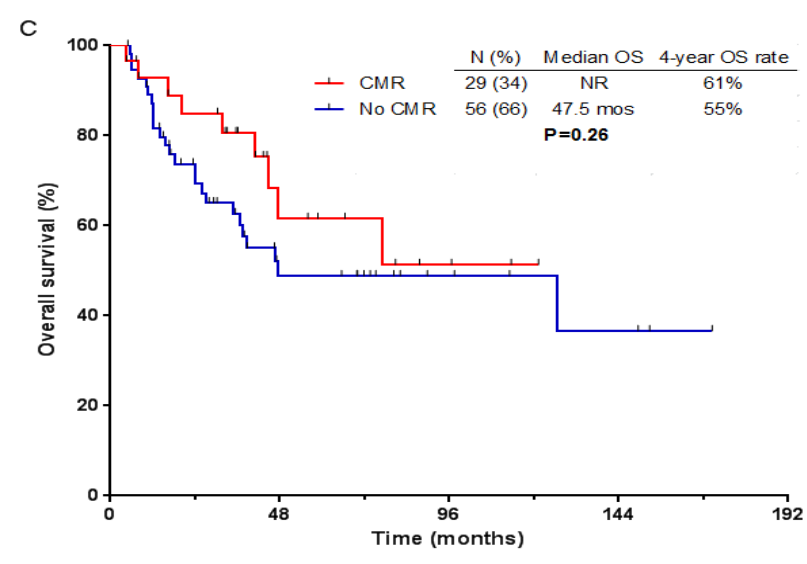
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
AYA, age <40	0.9522 (0.4723-1.92)	.8911	0.8493 (0.3956-1.823)	.6753
Sex, female	0.7494 (0.4194-1.339)	.3299	0.7017 (0.3761-1.309)	.2657
WBC, high	1.246 (0.7027-2.211)	.4513		
CDKN2A2B del	1.181 (0.5842-2.389)	.6427		
IKZF1 del	1.694 (0.8978-3.197)	.1037		
IKZF1 (exon4-7) del	2.049 (1.107-3.792)	.02239	1.67 (0.8854-3.149)	.1132
PAX5 del	1.45 (0.7328-2.869)	.2859		
VPREB1 del	2.145 (1.166-3.945)	.01408		
Anti-CD20 mAb therapy	1.345 (0.7382-2.45)	.333		
TKI type, ponatinib	0.3309 (0.1703-0.6427)	.001095	0.3959 (0.1894-0.8274)	.01375



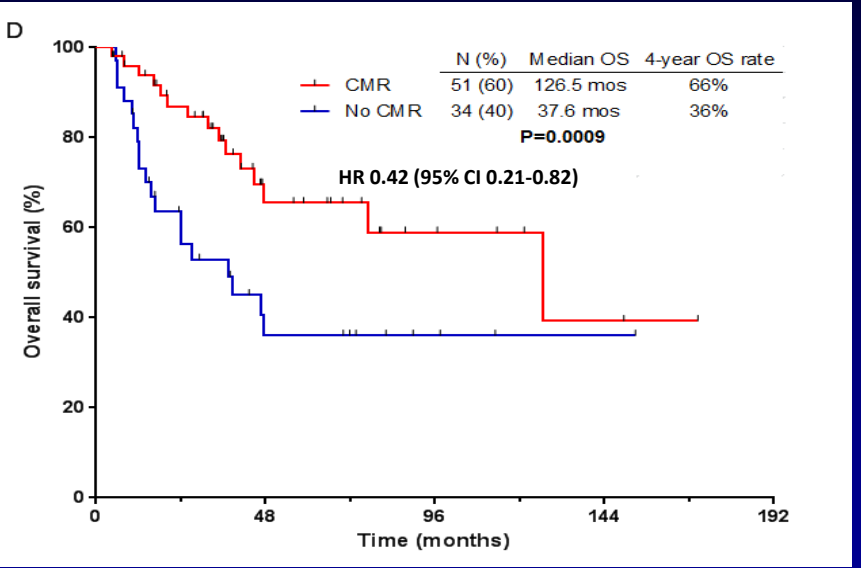
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
AYA, age <40	0.7735 (0.3562-1.679)	.5161	0.5868 (0.2487-1.384)	.2234
Sex, female	0.6641 (0.3539-1.246)	.2025	0.6136 (0.3106-1.212)	.1596
WBC, high	1.098 (0.5942-2.028)	.7655		
CDKN2A2B del	1.236 (0.5864-2.606)	.5775		
IKZF1 del	1.948 (0.9659-3.927)	.06245		
IKZF1 (exon4-7) del	2.517 (1.281-4.945)	.007392	1.875 (0.923-3.81)	.08213
PAX5 del	1.664 (0.8268-3.35)	.1536		
VPREB1 del	1.954 (1.019-3.749)	.04389	1.597 (0.8075-3.157)	.1785
Anti-CD20 mAb therapy	1.625 (0.8674-3.045)	.1296		
TKI type, ponatinib	0.2918 (0.1385-0.6149)	.0012	0.3491 (0.1482-0.8223)	.01606

CMR in Ph+ ALL: OS for CMR vs Others

At CR



At 3 months



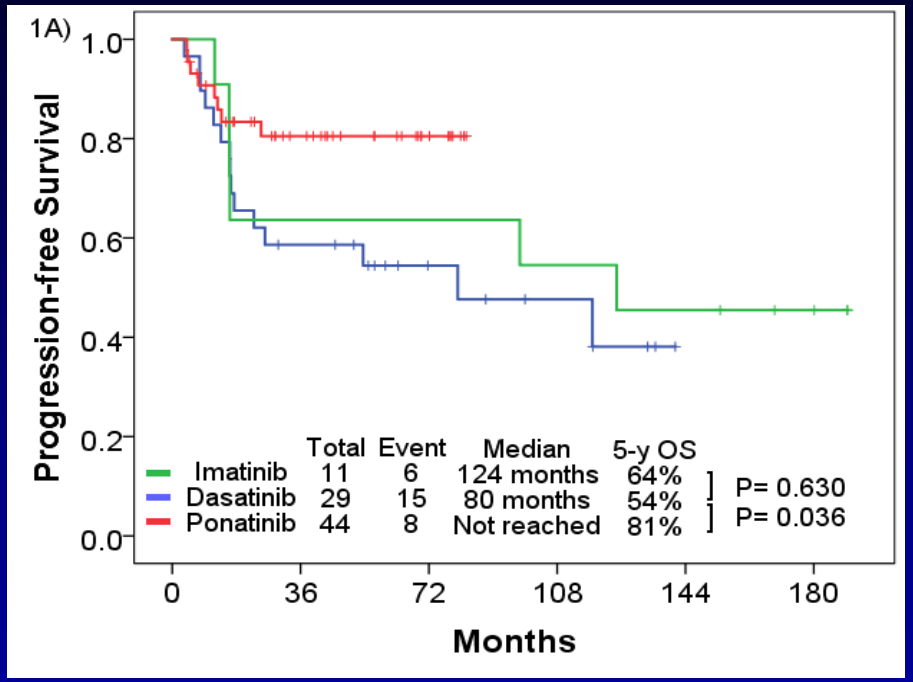
- **MVA for OS**

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

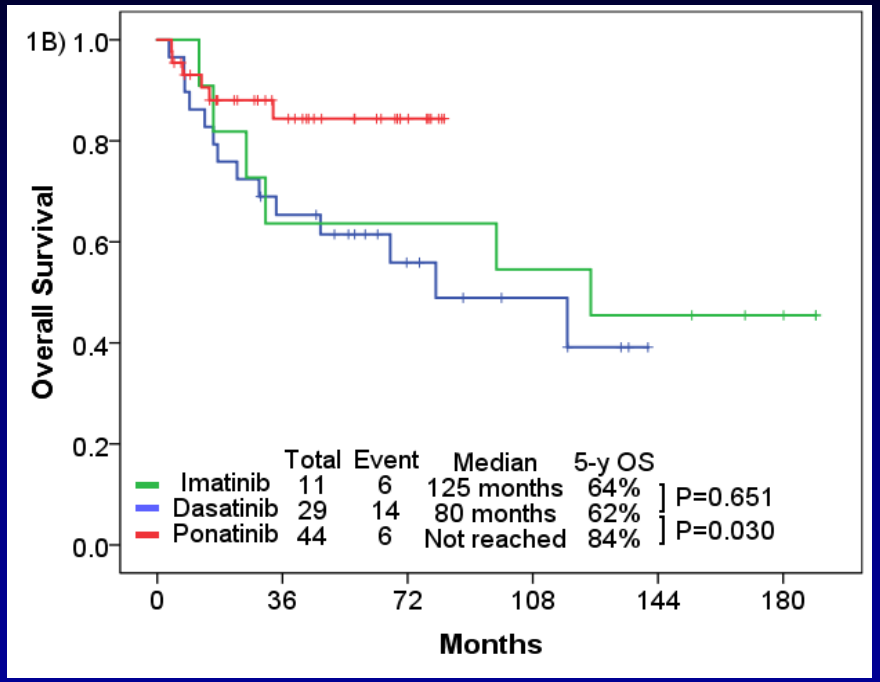
Short. *Blood.* 2016;128(4):504-507.

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)

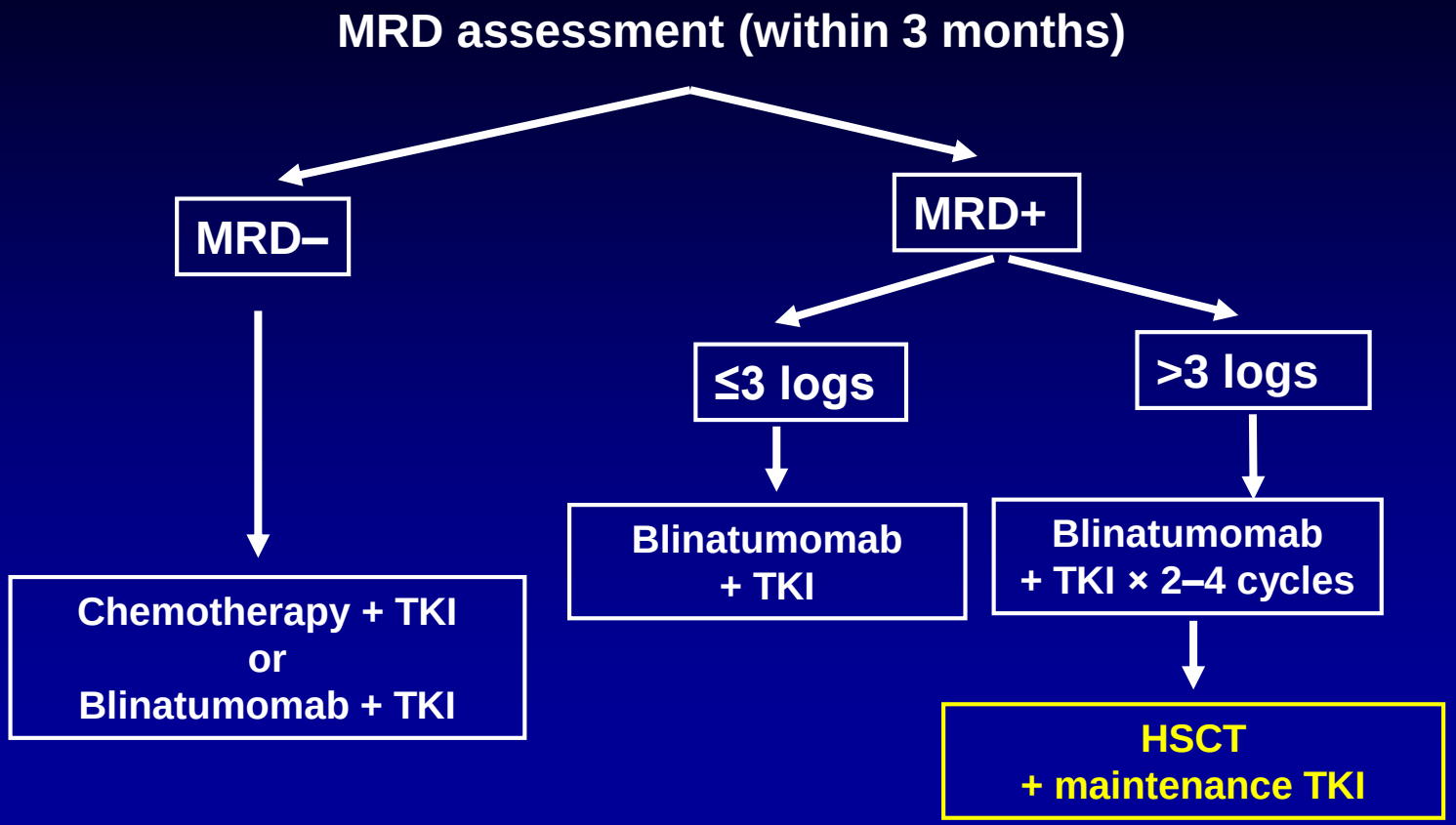
Sasaki. *Blood.* 2019;134:abstract 1296.

Two Evolving Strategies to Treat Ph+ ALL

Parameter	Hyper-CVAD + Ponatinib	TKIs With Minimal ChemoRx
% CR	90-100	90-100
% CMR	80	20
Allo-SCT required	Only if no CMR	In all
Outcome p190 vs p210	Same	P190 better
% 3-yr survival/DFS	70-80	40-50

Jabbour E, et al. *Lancet Oncol.* 2015;16:1547; Chiaretti, et al. *Blood.* 2015;126:abstract 81.

Indications for HSCT: Ph+ ALL



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

Blinatumomab and Inotuzumab in R-R Ph+ ALL

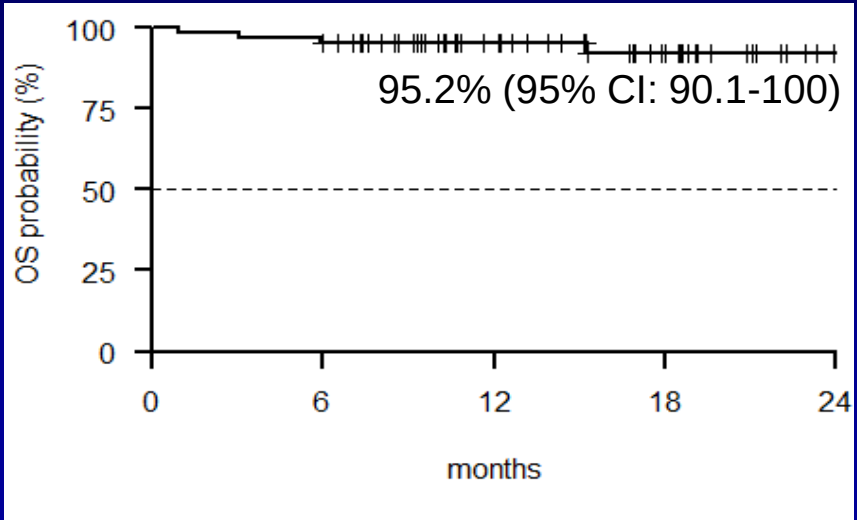
Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 **(36)**	25 **(66)**
MRD negative in CR, %	88	63
Median OS, mo	7.1	8.1
Later allo-SCT, %	44	32

Martinelli. *J Clin Oncol.* 2017;35:1795; Stock. Proceedings ASCO 2018

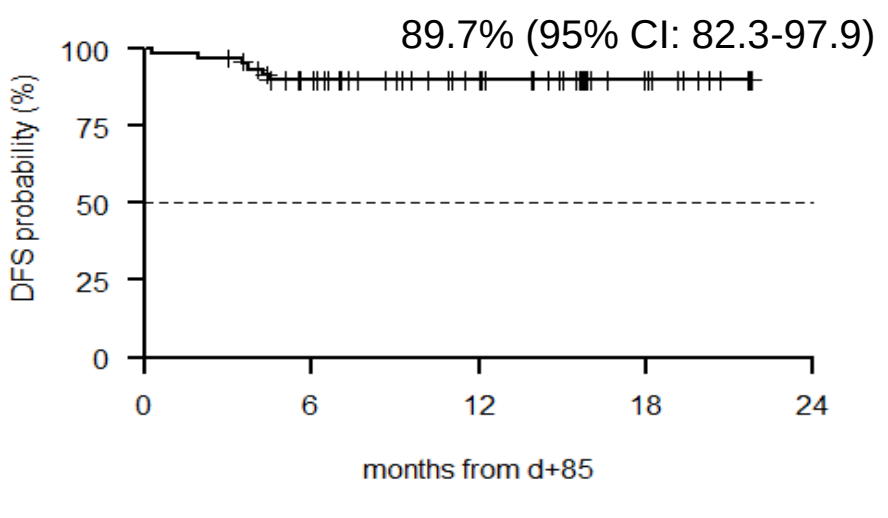
Dasatinib-Blinatumomab in Ph+ ALL

- 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

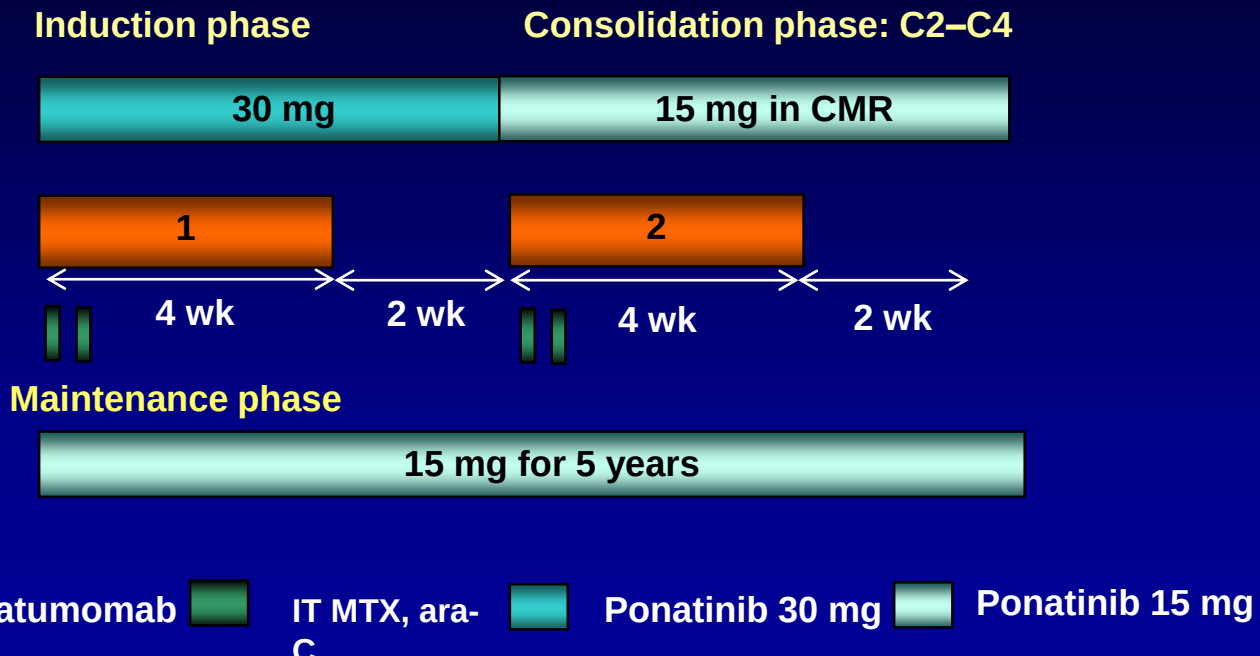


DFS



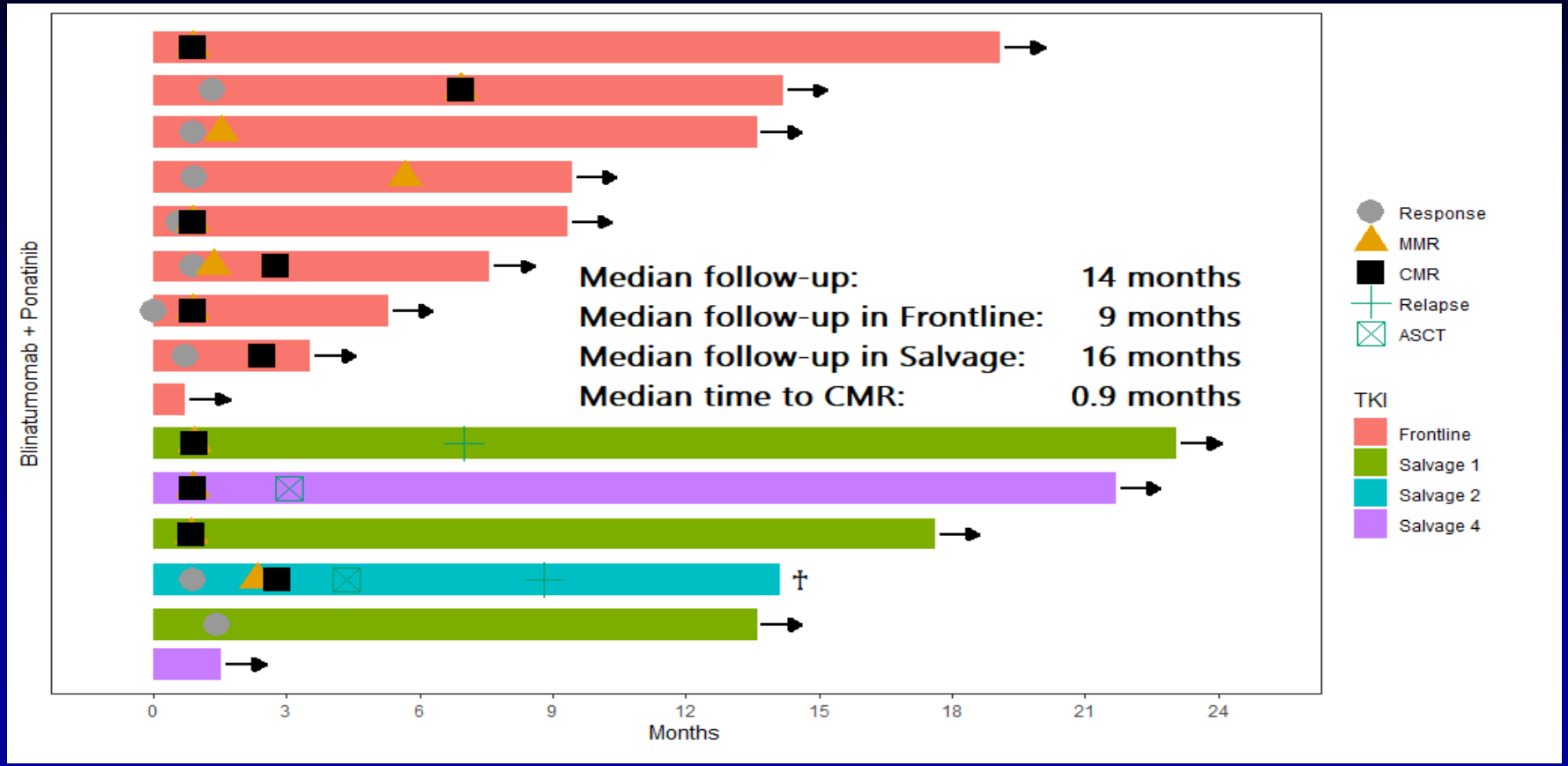
Chiaretti. *Blood.* 2019;134:abstract 615.

Blinatumomab-Ponatinib in Ph+ ALL



Assi. *Clin Lymphoma Myeloma Leuk.* 2017;17(12):897-901.

Blinatumomab + Ponatinib Swimmer Plot (N = 15)



Questions in Ph+ ALL

- Do we need allo-SCT? – not always, never?
  - Identify patients who can be cured without allo-SCT, eg, 3-mos CMR, others
- Ponatinib best TKI? – 3 mos-CMR 86%; 5-year OS rate 74%
  - Phase III low-dose CT + imatinib vs low-dose CT + ponatinib
- How much chemoRx – low-Intensity vs intensive chemo Rx?
  - Mini-HCVD-ponatinib-blinatumomab
- Can we cure Ph+ ALL without chemoRx or allo-SCT? – ponatinib + blinatumomab
- Duration of TKI maintenance
  - At least 5 years

Global Leukemia Academy

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

Patrick Brown

APTITUDE HEALTH®

Considerations in Adolescents and Young Adults (AYA) With Acute Lymphoblastic Leukemia (ALL)

Patrick Brown, MD

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

Learning Objectives

- Describe the AYA oncology patient, and recognize the challenges that have led to inferior outcomes in this group
- Understand that optimal AYA ALL outcomes require treatment with “pediatric-inspired” treatment regimens
- Know the difference in prevalence of sentinel genetic abnormalities in childhood vs AYA ALL
- Understand the importance of minimal residual disease (MRD) in risk stratification in AYA ALL
- Know that AYA patients are at higher risk of specific adverse events (AEs), and know the strategies to mitigate this risk

The AYA Oncology Patient – Key Phenotypic Features

- Do not “fit in” in either the peds or adult worlds, where environment and treatment intensities are tailored to median ages (10 y/o or 50 y/o)
- Un/underinsured, unlikely “primary care” relationship
- In transition to independence from parents
- In the midst of intense educational program
- Lack of firmly established career path
- Early stages of starting a family (engaged, newlywed, children planned or already arrived)

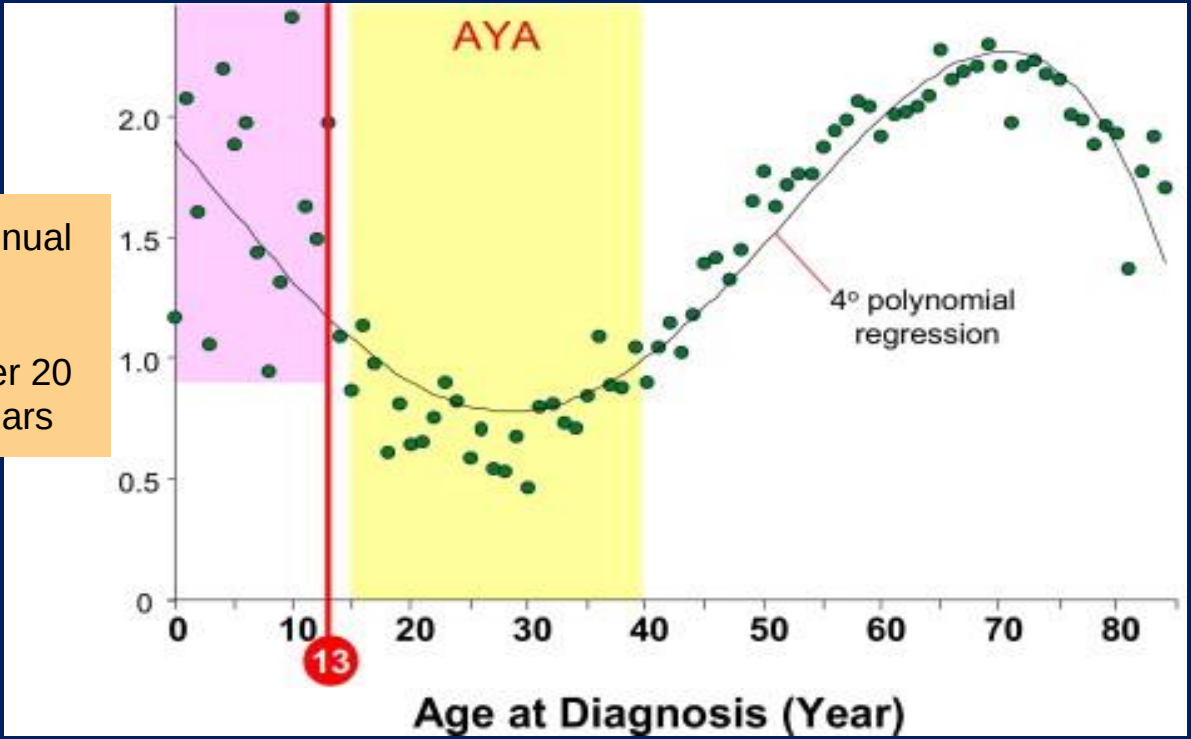
The AYA Oncology Patient – Medical Consequences of Phenotype

- Delayed diagnosis
- Low rates of clinical trial enrollment
- Lack of uniformity in treatment
- Poor adherence
- Enhanced concerns about fertility and other late effects
- Unique psychosocial hardships

Poor outcomes

AYA Deficit in Progress in Cancer Survival

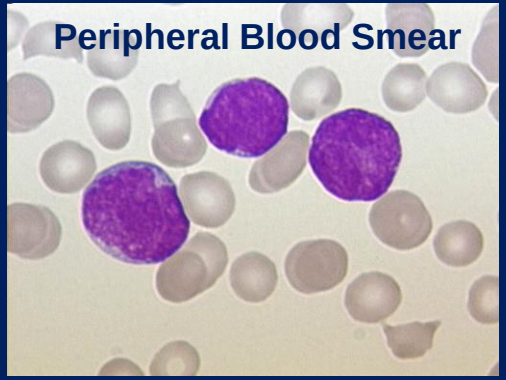
Average annual percentage change in survival over 20 previous years



Albritton, et al. *Semin Oncol.* 2009;36(5)478.

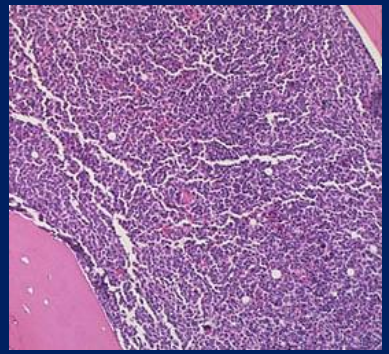
Case Presentation

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

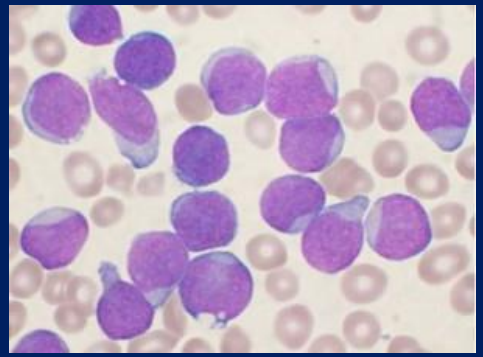


Suspected diagnosis: ALL

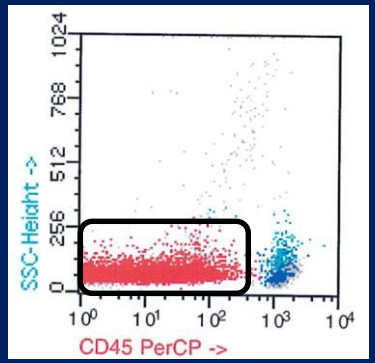
Case Presentation (continued)



Bone Marrow Biopsy



Bone Marrow Aspirate



Flow Cytometry Plots

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

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

- Normal echo, EKG

Diagnosis: B-Lymphoblastic Leukemia

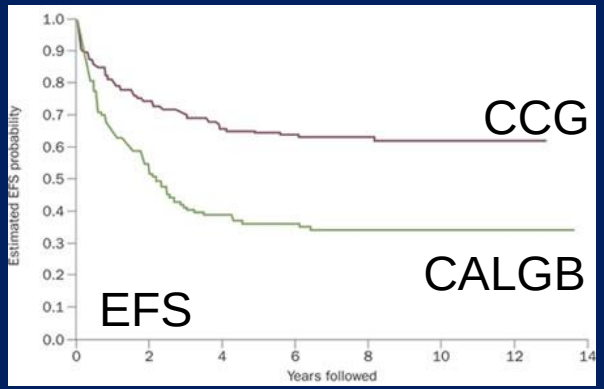
<u>Question 1</u>:

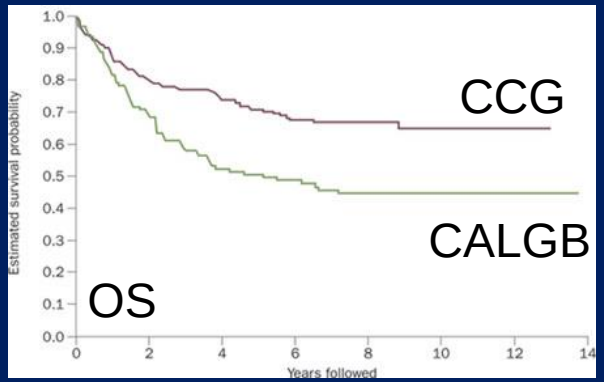
Which of the following factors is MOST important in deciding which ***initial ALL treatment regimen*** *should be used for this patient?*

Q

a. The level of expression of CD19 on the surface of the ALL blasts
b. The presence or absence of hepatosplenomegaly and lymphadenopathy
c. The age of the patient
d. Whether the patient is being treated by an adult oncologist or a pediatric oncologist
e. Whether the patient is being treated in an academic center or in a community hospital

AYA ALL: Superior Outcomes With Pediatric Protocols





Comparison of survival of patients ages 16–21 treated in CALGB (adult) or CCG (pediatric)

- Multiple subsequent prospective studies of “pediatric-inspired” regimens in “young adults” (variably defined) have demonstrated feasibility and better outcomes compared with historical controls

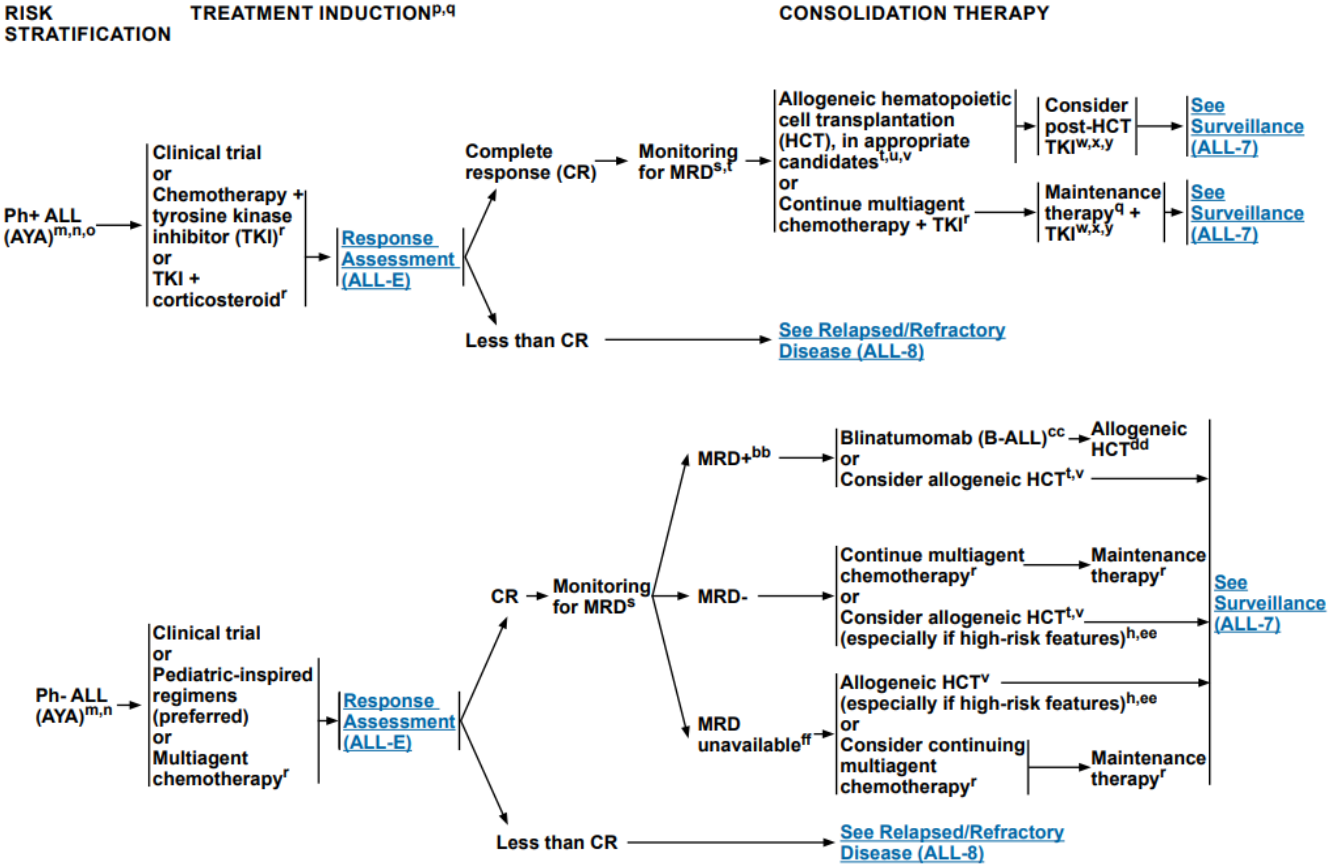
Stock W, et al. *Blood.* 2008;112:1646-1654.

Primacy of ***Ph Status*** and ***Age*** in NCCN Adult ALL Treatment Recommendations

Guidelines separated as follows

- Ph+ ALL (AYA)
- Ph+ ALL (Older Adults)
- Ph– ALL (AYA)
- Ph– ALL (Older Adults)

- "AYA" (NCI, NCCN): *age at diagnosis of 15 to 39 years*
- Wide recognition that age imperfectly defines of the "AYA oncology phenotype"


RISK STRATIFICATION
TREATMENT INDUCTION[p,q]
CONSOLIDATION THERAPY
Ph+ ALL (AYA)[m,n,o]
Clinical trial or Chemotherapy + tyrosine kinase inhibitor (TKI)[r] or TKI + corticosteroid[r]
Response Assessment (ALL-E)
Complete response (CR)
Monitoring for MRD[s,t]
Allogeneic hematopoietic cell transplantation (HCT), in appropriate candidates[t,u,v] or Continue multiagent chemotherapy + TKI[r]
Consider post-HCT TKI[w,x,y]
Maintenance therapy[q] + TKI[w,x,y]
See Surveillance (ALL-7)
See Surveillance (ALL-7)
Less than CR
See Relapsed/Refractory Disease (ALL-8)
Ph- ALL (AYA)[m,n]
Clinical trial or Pediatric-inspired regimens (preferred) or Multiagent chemotherapy[r]
Response Assessment (ALL-E)
CR
Monitoring for MRD[s]
MRD+[bb]
Blinatumomab (B-ALL)[cc] or Consider allogeneic HCT[t,v]
Allogeneic HCT[dd]
MRD-
Continue multiagent chemotherapy[r] or Consider allogeneic HCT[t,v] (especially if high-risk features)[h,ee]
Maintenance therapy[r]
MRD unavailable[ff]
Allogeneic HCT[v] (especially if high-risk features)[h,ee] or Consider continuing multiagent chemotherapy[r]
Maintenance therapy[r]
See Surveillance (ALL-7)
Less than CR
See Relapsed/Refractory Disease (ALL-8)

PRINCIPLES OF SYSTEMIC THERAPY[a]
INDUCTION REGIMENS FOR Ph-NEGATIVE ALL[b,h]

AYA Patients:

Preferred Regimens
• CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase[i] (ongoing study in patients aged <40 years)[19,h,j]
• COG AALL0232 regimen: daunorubicin, vincristine, prednisone, and pegaspargase[i] (patients aged ≤21 years)[20,h,j]
• COG AALL0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegaspargase;[i] nelarabine added to consolidation regimen[21,j]
• DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase[i] (ongoing study in patients aged <50 years)[22,h,j]

Other Recommended Regimens
• GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase,[i] and cyclophosphamide (patients aged <60 years), with rituximab for CD20-positive disease[23,h,j]
• PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase,[i] and cyclophosphamide (patients aged <30 years)[24,h,j]
• Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with or without rituximab for CD20-positive disease[25,h]
• USC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged 18–57 years)[26,h,j]
• Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase[27,h]

PRINCIPLES OF SYSTEMIC THERAPY[a]
INDUCTION REGIMENS FOR Ph-POSITIVE ALL[b,c]

Protocols for AYA Patients:

Other Recommended Regimens
• EsPhALL regimen: TKI[d] + backbone of the Berlin-Frankfurt-Münster regimen (cyclophosphamide, vincristine, daunorubicin, dexamethasone, cytarabine, methotrexate, pegaspargase, and prednisone)[1-3]
• TKI[d] + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[4–8]
• TKI[d] + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)[9-13]
• TKI[d,14,15] + corticosteroid[e]
• TKI[d] + vincristine + dexamethasone[16,e]
• CALGB 10701 regimen: TKI[d] + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)[17]

Case Presentation (continued)

- Initial treatment: standard induction for pediatric “high-risk” ALL
  - 4 weeks of vincristine, prednisone, PEG-asparaginase, daunorubicin, intrathecal methotrexate
- 7 days into treatment, genetic results are finalized

Question 2:

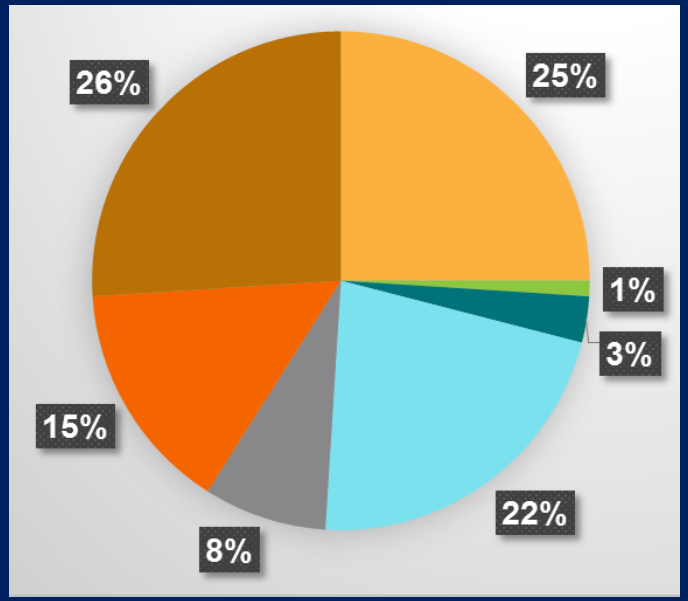
Of the following leukemia-specific genetic abnormalities, which is MOST likely to be present in this patient?

Q

a. 46,XX; FISH+ for ETV6-RUNX1 fusion
b. 46,XX,t(9;22)(q34;q11.2); FISH+ for BCR-ABL1 fusion; PCR+ for p190 BCR-ABL1
c. 52,XX,+4,+9,+10,+17,+18,+21 (high hyperdiploidy)
d. 46,XX,t(4;11)(q21;q23); FISH+ for KMT2A (MLL) rearrangement
e. 36,XX,-3,-7,-8,-9,-12,-14,-15,-18,-20,-21 (low hypodiploidy)

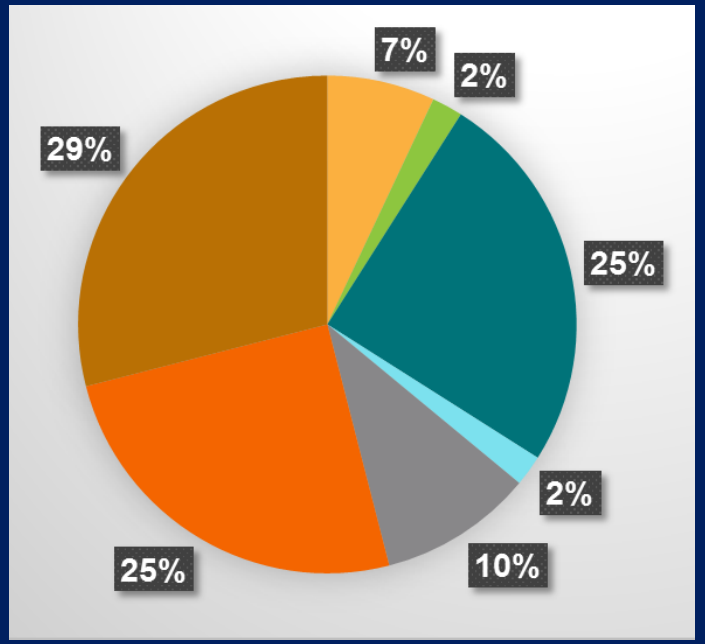
Frequency of Genetic Abnormalities by Age

Children



- Hyperdiploidy (>50)
- Hypodiploidy (<44)
- t(9;22)(q34;q11) BCR-ABL1
- t(12;21)(p13;q22) ETV6-RUNX1
- t(v;11q23) KMT2A-r
- BCR-ABL1-like
- Other

Adults



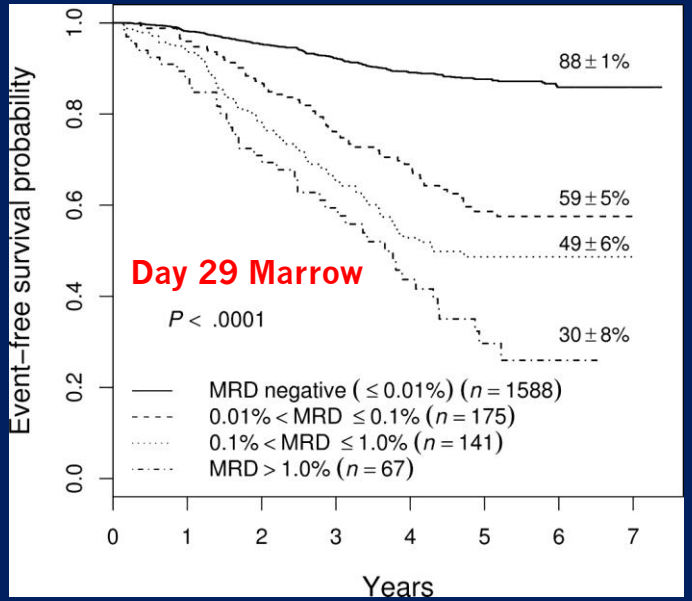
Case Presentation (continued)

- Patient confirmed to have diagnosis of B-ALL with BCR-ABL1 fusion
- Imatinib 400 mg daily added to induction chemotherapy beginning day 8 of induction
- End induction marrow
  - Complete morphologic remission
  - Flow cytometry for residual B-lymphoblasts and RT-PCR for BCR-ABL negative → no minimal residual disease (MRD negative)
- The patient's brother is determined to be HLA-identical

Minimal Residual Disease (MRD) in ALL

- State of the art for risk stratification based on early response to therapy
- MRD is defined as the presence of cells following chemotherapy below the level of morphologic detection, generally down to 1/10,000 cells (10^{-4})
- Flow cytometry and molecular (NGS, PCR) methods can be used to detect MRD
- In North America, flow is generally preferred over others, although NGS (ClonoSEQ) is gaining

MRD in ALL



Variable	Hazard Ratio	*P* Value
Day 29 marrow MRD	4.31	<.0001
NCI risk group	2.25	<.0001
Trisomy 4&10	.570	.0005
Tel-AML1	.778	.15
Day 8 marrow morphology	1.034	.79

- End induction MRD is a powerful and independent prognostic factor in ALL

Borowitz MJ, et al. *Blood.* 2008;111:5477.

Case Presentation (continued)

- Patient proceeded to consolidation chemotherapy, consisting of cyclophosphamide, cytarabine, PEG-asparaginase and mercaptopurine (6MP)
- 3 weeks into consolidation, patient developed severe abdominal pain radiating to the back, anorexia, and nausea
- Workup revealed elevated serum amylase and lipase and enlarged pancreas on abdominal ultrasound (acute pancreatitis) and steroids

<u>Question 3</u>:
Which of the following medications is MOST likely to be responsible for the acute pancreatitis in this patient?

Q

a. Cyclophosphamide
b. Cytarabine
c. 6MP
d. Vincristine
e. PEG-asparaginase

AYA ALL: Risk of Adverse Events

- L-asparaginase preparations (PEG, Erwinia)
  - Higher risk of toxicity in AYA compared with children (but less compared with older adults)
  - AEs: Pancreatitis, thrombosis (line-associated, sagittal sinus), hepatotoxicity, allergy
- Corticosteroids
  - High risk of osteonecrosis (hips, knees) in AYA patients relative to children and older adults
- Mitigation
  - Enhanced lab monitoring and high index of clinical suspicion
  - Anticoagulant prophylaxis for PEG-asparaginase (clinical trials ongoing)

Learning Objectives (How did we do?)

- Describe the AYA oncology patient, and recognize the challenges that have led to inferior outcomes in this group
- Understand that optimal AYA ALL outcomes require treatment with “pediatric-inspired” treatment regimens
- Know the difference in prevalence of sentinel genetic abnormalities in childhood vs AYA ALL
- Understand the importance of minimal residual disease (MRD) in risk stratification in AYA ALL
- Know that AYA patients are at higher risk of specific adverse events (AEs), and know the strategies to mitigate this risk

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Break

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

Patrick Brown

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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

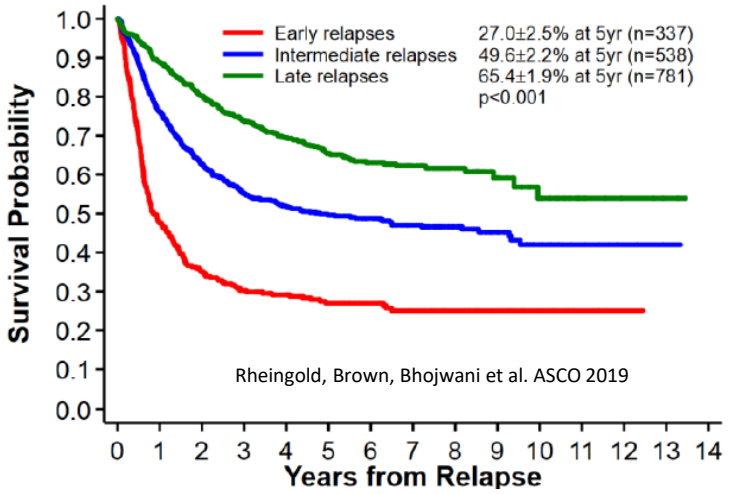
Patrick A. Brown, Lingyun Ji, Xinxin Xu, Meenakshi Devidas, Laura Hogan, Michael J. Borowitz, Elizabeth A. Raetz, Gerhard Zugmaier, Elad Sharon, Lia Gore, James A. Whitlock, Michael A. Pulsipher, Stephen P. Hunger, Mignon L. Loh

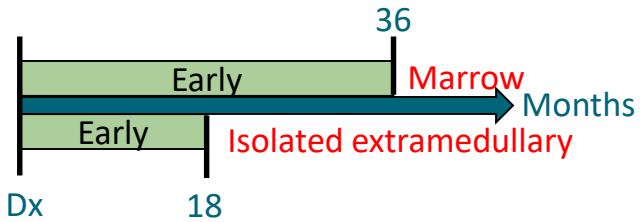
CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. *Blood.* 2019;134(suppl_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 -> 2nd 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





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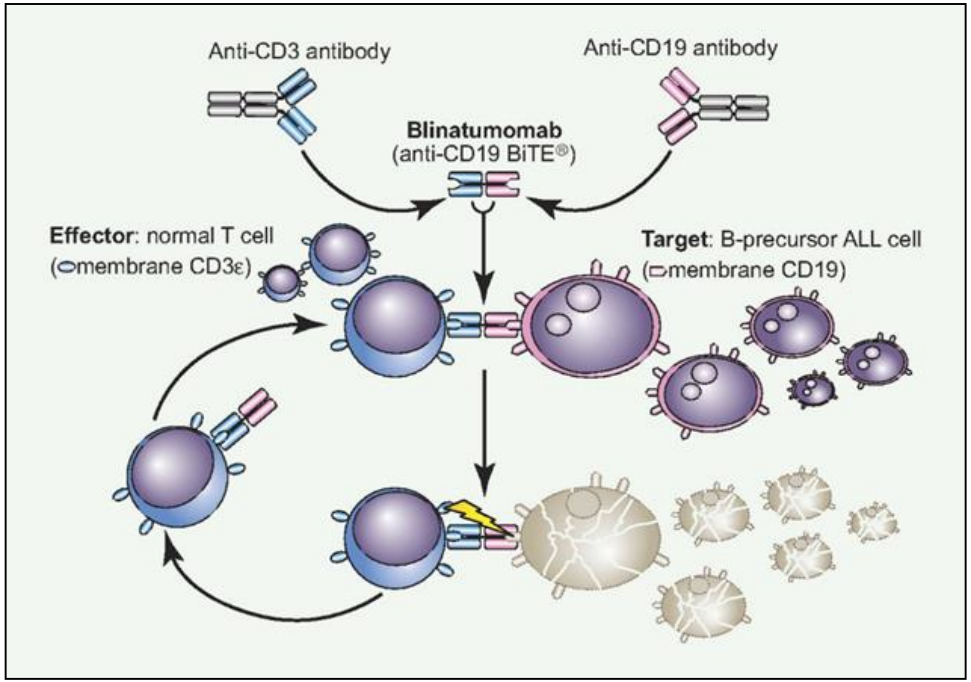
Brown PA, et al. *Blood.* 2019;134(suppl_2):LBA-1.

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

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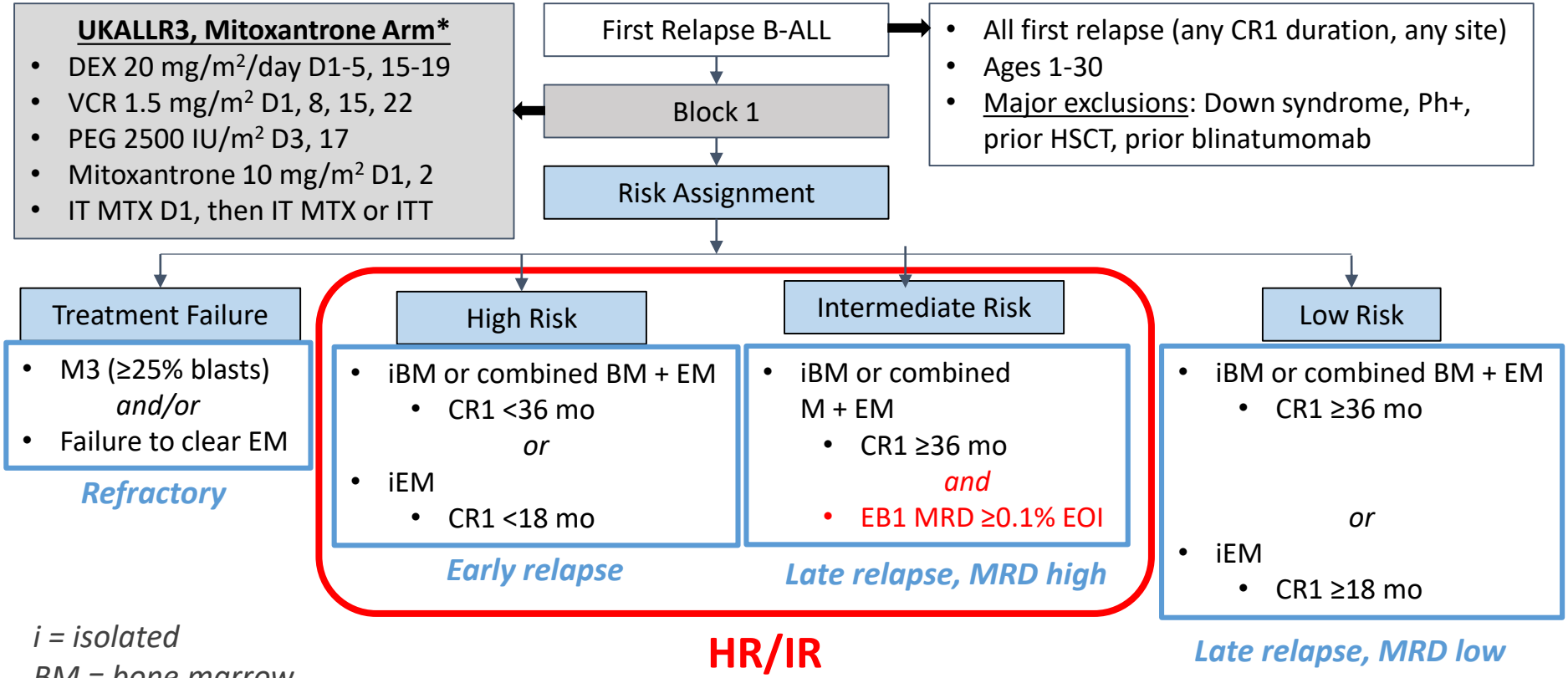
Brown PA, et al. *Blood.* 2019;134(suppl_2):LBA-1.



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(suppl_2):LBA-1.

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

Stratifications

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

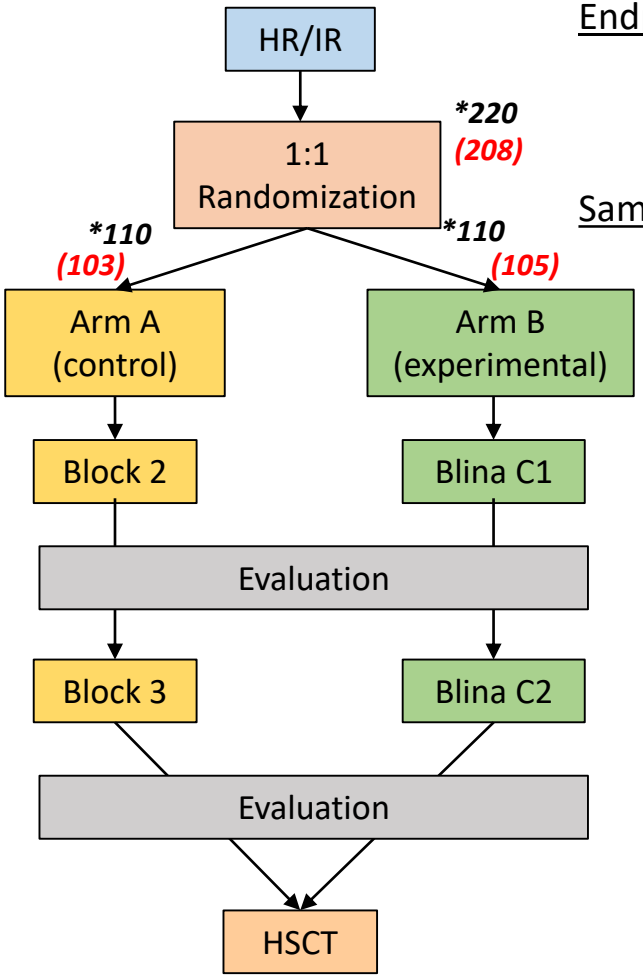
UKALLR3, Block 2*

- 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;376:2009-2017.



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(suppl_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

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

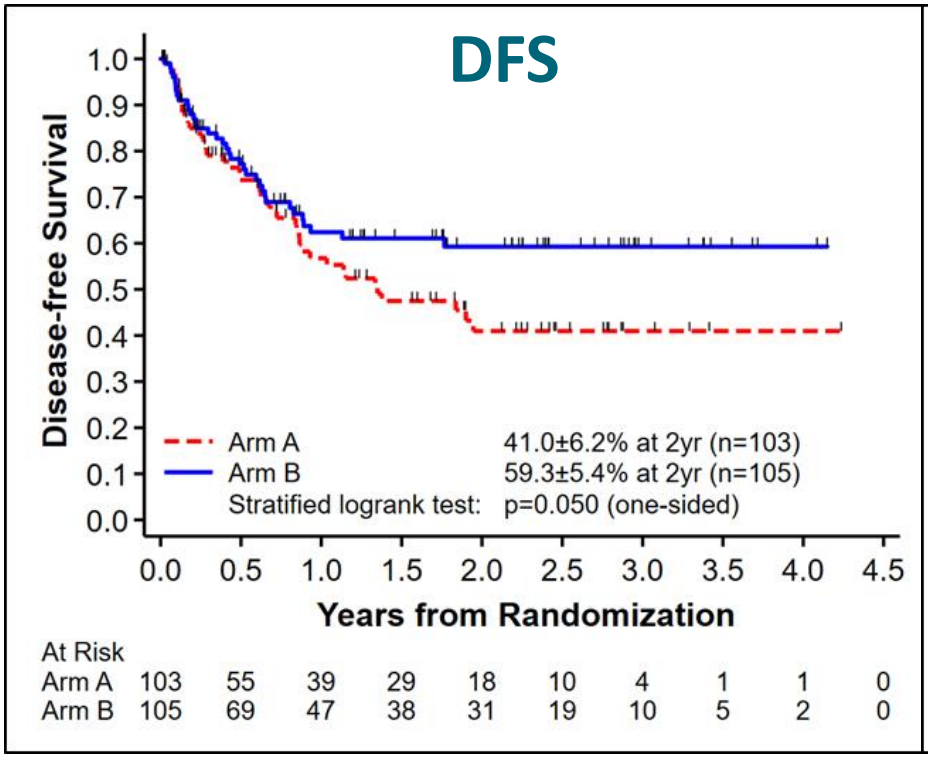
Randomization Stratification Factors

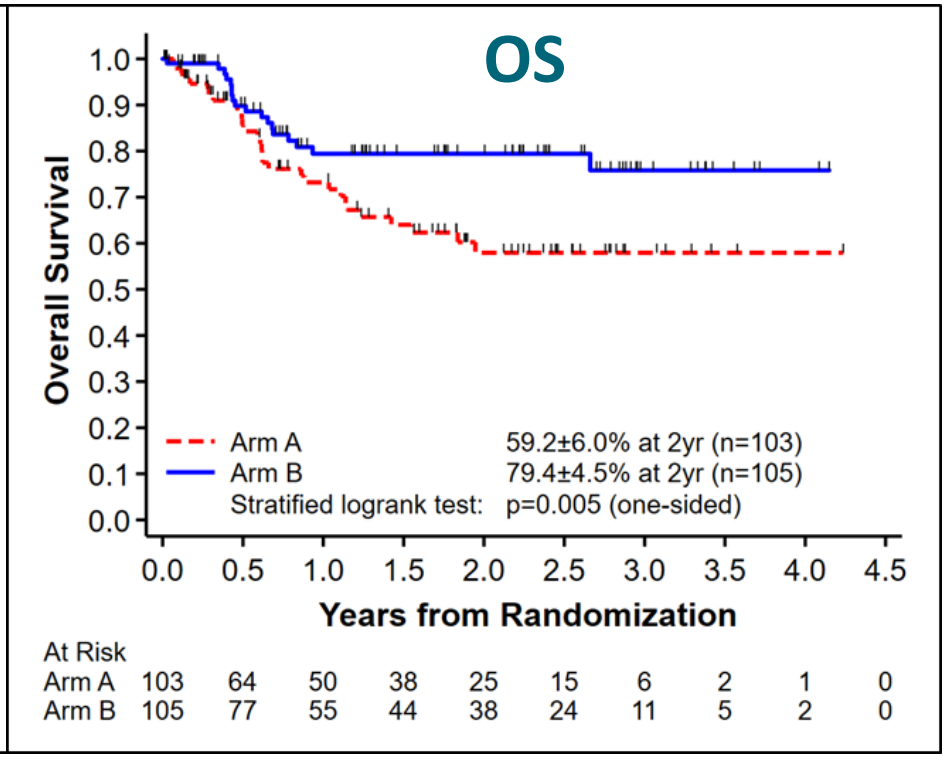
Stratification Factors	Arm A (n=103)	Arm B (n=105)
Risk Group Assignment After Block 1		
Intermediate risk (late relapse, MRD high)	34 (33%)	36 (34%)
High risk (early relapse)	69 (67%)	69 (66%)
High-Risk Subsets		
• Marrow, CR1 <18 months (very early)	18 (26%)	18 (26%)
• Marrow, CR1 18-36 months (early)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

CHILDREN'S ONCOLOGY GROUP

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

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



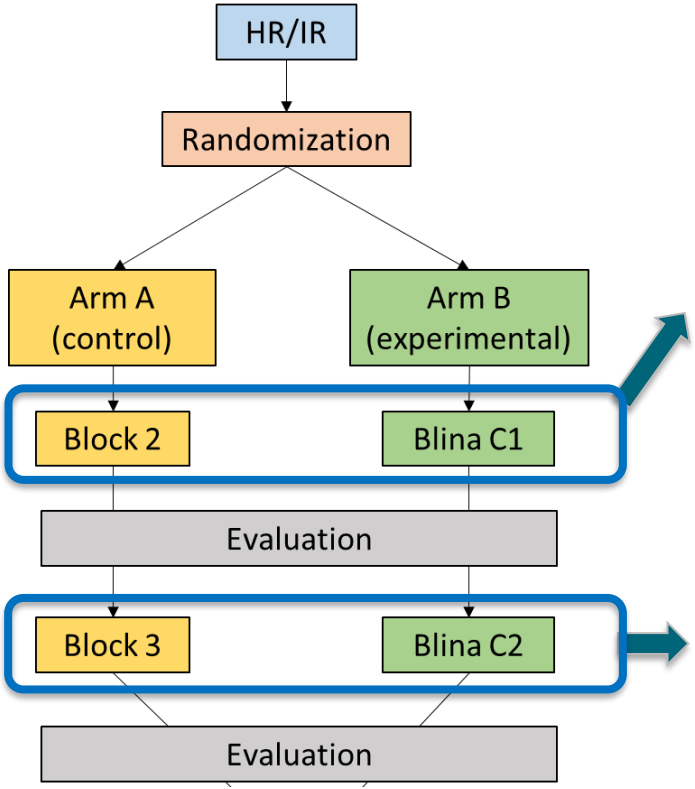


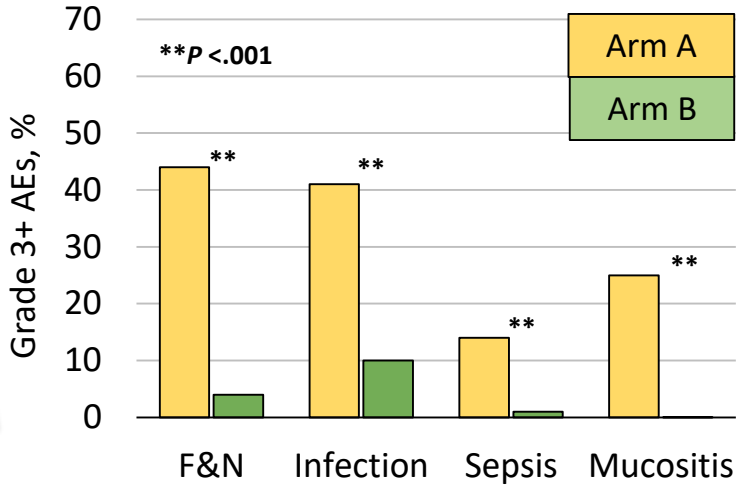
CHILDREN'S ONCOLOGY GROUP

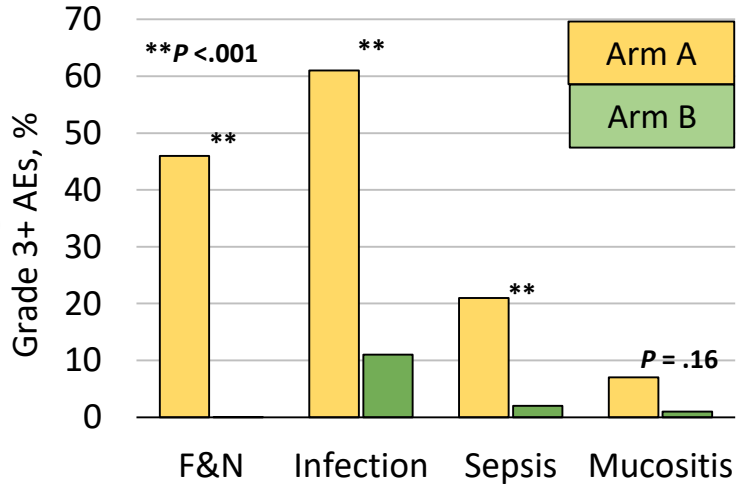
Median follow-up 1.4 years

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

Adverse Events







- *N = 4 postinduction 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)*

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

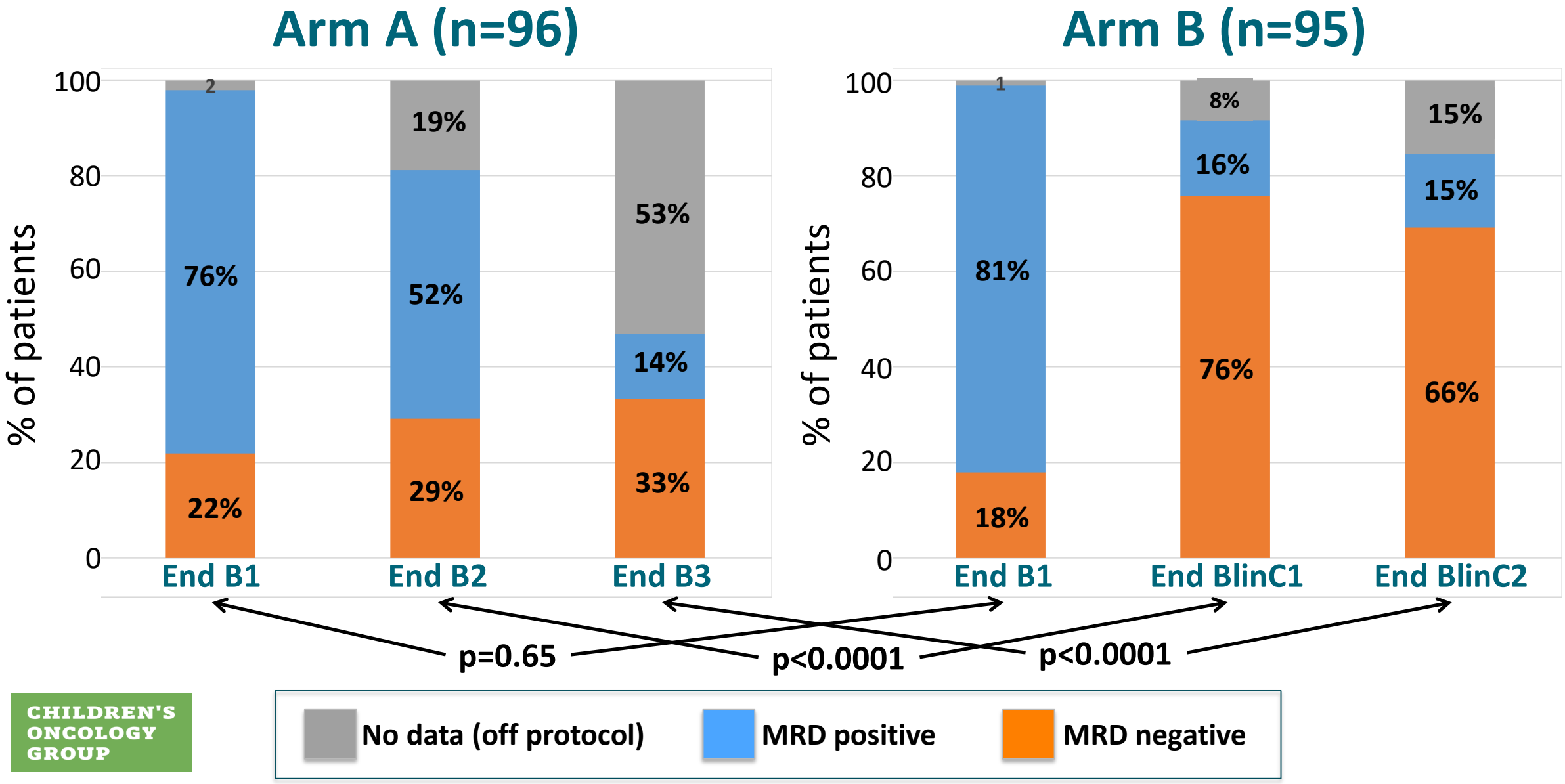
Blinatumomab-Related AEs on Arm B

	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%

CHILDREN'S ONCOLOGY GROUP

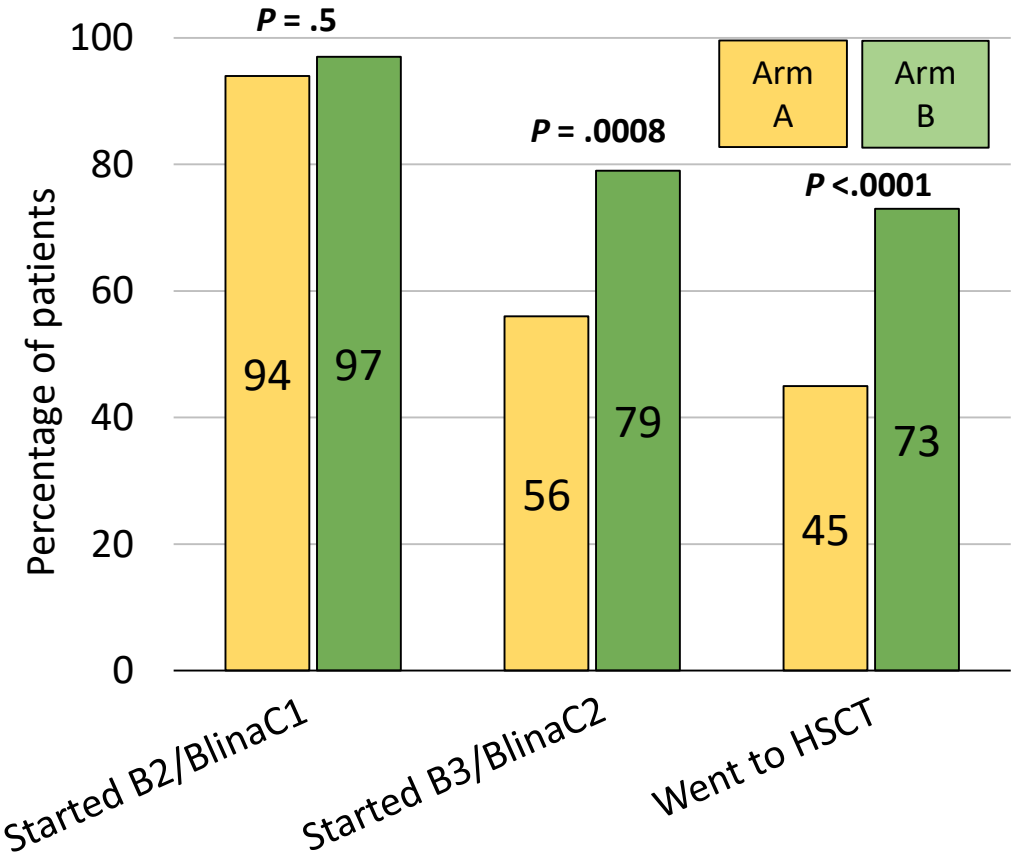
Brown PA, et al. *Blood.* 2019;134(suppl_2):LBA-1.

MRD Clearance (for iBM and BM+EM)



CHILDREN'S ONCOLOGY GROUP

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(suppl_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

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

Multiple Choice Question 1

Q

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

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
  - Kala Kamdar
  - Mignon Loh
  - Jen McNeer
  - Maureen O'Brien
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  - Sue Rheingold
  - Teena Bhatla
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  - Richard Tower
- **Lab/Path**
  - Mike Borowitz
  - Andrew Carroll
  - Fady Mikhail
  - Julie Gastier-Foster
- **Rad Onc**: Stephanie Terezakis
- **Pharmacy**
  - Brooke Bernhardt
  - Olga Militano
- **CRA**: Christopher Henchen
- **Nursing**
  - Deb Schissel
  - Susan Zupanec
- **Research Coordinator**: Susan Conway, Don Sortillon, Naira Setrakian
- **Protocol Coordinator**: Rachel Vasquez

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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?

Global Leukemia Academy

Panel Discussion on the Role of HSCT

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Experience of HSCT in the Region

Eduardo Rego

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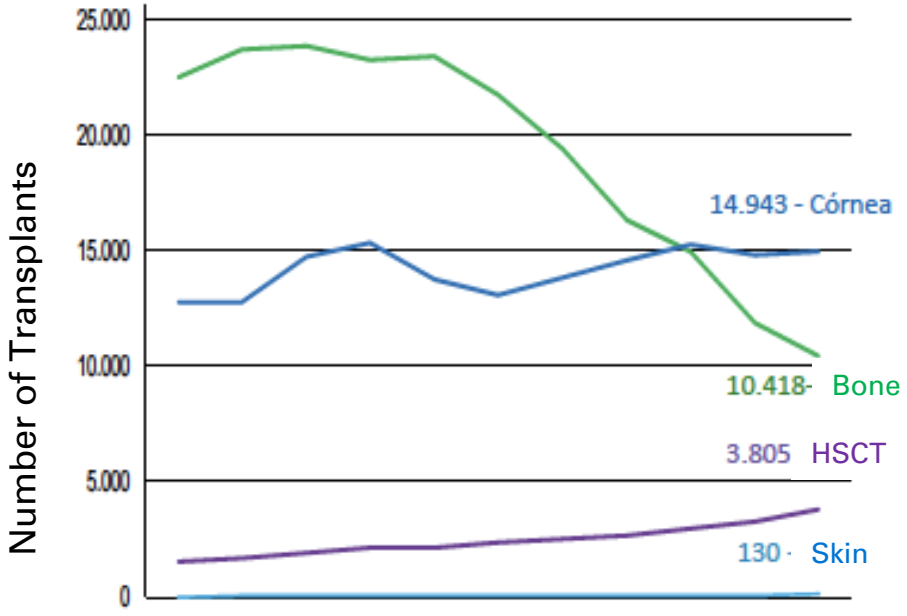
HSCT IN BRAZIL

Eduardo M. Rego
University of São Paulo
Oncologia D'Or

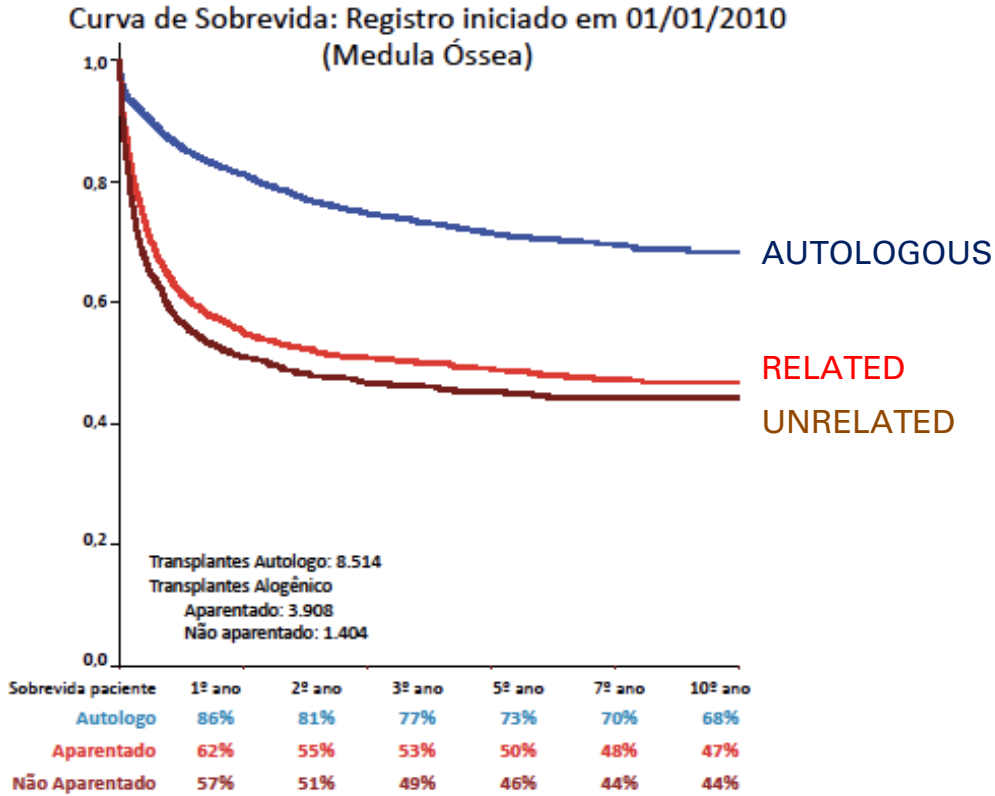
Number of Transplants per Year (2009–20190



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Bone	22.503	23.647	23.815	23.211	23.348	21.681	19.408	16.293	14.945	11.860	10.418
Cornea	12.724	12.778	14.726	15.280	13.744	13.065	13.830	14.531	15.262	14.809	14.943
HSCT	1.550	1.712	1.870	2.095	2.153	2.379	2.506	2.642	2.930	3.237	3.805
Skin	17	26	21	30	23	28	28	49	33	62	130

ais de Transplantes (Córnea); Banco de Tecidos (Pele e Ossos) Medula Óssea (Equipes de Transplantes)

Overall Survival



Sobrevida paciente	1º ano	2º ano	3º ano	5º ano	7º ano	10º ano
Autologo	86%	81%	77%	73%	70%	68%
Aparentado	62%	55%	53%	50%	48%	47%
Não Aparentado	57%	51%	49%	46%	44%	44%

Country-Level Macroeconomic Indicators Predict Early Post-Allogeneic Hematopoietic Cell Transplantation Survival in Acute Lymphoblastic Leukemia: a CIBMTR Analysis

Effect of Human Expenditure per Capita and Human Development Index on the Number of HSCT

Health Expenditure Per Capita (USD)

Category	Number of Transplants
Quartile 4 (>$5904)	8714
Quartile 3 ($2508-$5093)	864
Quartile 2 ($797-$2507)	1413
Quartile s (<$797)	249

Human Development Index

Category	Number of Transplants
Quartile 4 (>0.913)	8937
Quartile 3 (0.8806-0.912)	1092
Quartile 2 (0.780-0.8805)	528
Quartile 1 (<0.780)	698

Brazil's HDI = 0.76
Brazil HEPC= US $1318.00

Effect of Human Expenditure per Capita and Human Development Index on 100-day Overall Survival Following Allogeneic HCT for ALL*

Main Effect: Health Expenditure per Capita (USD)

Category	N	HR	95% CI	p-value
Quartile 4 (>$5094)	8714	1.00		0.0150
Quartile 3 ($2508-$5093)	864	1.25	0.97-1.62	0.0872
Quartile 2 ($797-$2507)	1413	1.45	0.82-2.55	0.2032
Quartile 1 (<$797)	249	1.56	1.11-2.18	0.0098

Main Effect: Human Development Index

Category	N	HR	95% CI	p-value
Quartile 4 (>0.913)	8937	1.00		<0.0001
Quartile 3 (0.8806-0.912)	1092	1.10	0.85-1.41	0.48
Quartile 2 (0.780-0.8805)	528	1.02	0.56-1.84	0.95
Quartile 1 (<0.780)	698	2.19	1.66-2.87	<0.0001

In all multivariable models, other statistically significant associations were seen for the following variables: age, ALL subtype, time from diagnosis to HCT, KPS, conditioning regimen intensity, and year of treatment

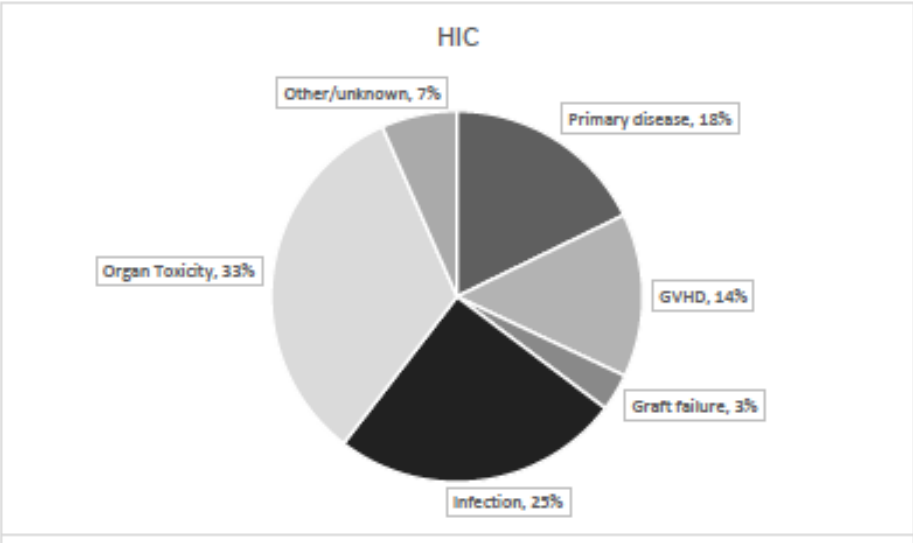
Wood, et al. *Biol Blood Marrow Transplant*. 2018;24(9):1928-1935.

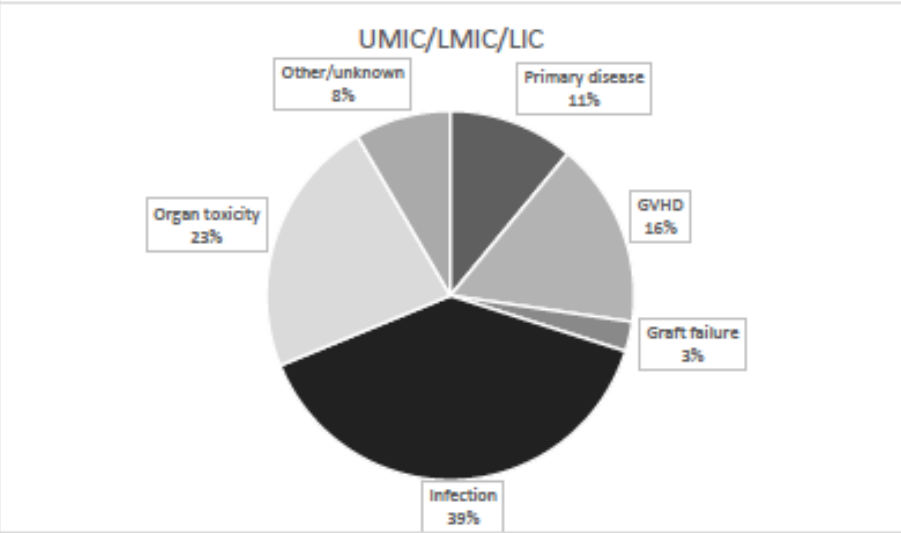
Q.

Regarding causes of death in the first 100 days after 100 days of HSCT, which statement is true?

a. The leading cause of death among patients who submit to HSCT for ALL in high-income countries (HIC) is GVHD
b. The leading cause of death among patients who submit to HSCT for ALL in intermediate-income countries is organ toxicity
c. There is no difference in the incidence of death due to graft-failure between HIC and low-income countries (LIC)
d. Unknown causes of death are approx 2-fold higher in LIC/MIC compared with HIC

Causes of Death by Country-Level GNI Grouping





Wood, et al. *Biol Blood Marrow Transplant*. 2018;24(9):1928-1935.

QUESTION 1: DO PATIENTS HAVE ACCESS TO STEM CELL TRANSPLANT IN YOUR REGION?

a. Yes
b. No
c. It depends on their financial situation

QUESTION 2: WHAT PROPORTION OF YOUR PATIENTS WITH NEWLY DIAGNOSED ALL ARE TRANSPLANT ELIGIBLE?

a. 0%–20%
b. 21%–40%
c. 41%–60%
d. 61%–80%
e. 81%–100%

QUESTION 3: WHAT PROPORTION OF YOUR TRANSPLANT-ELIGIBLE PATIENTS WILL RECEIVE TRANSPLANT?

a. 0%–20%
b. 21%–40%
c. 41%–60%
d. 61%–80%
e. 81%–100%

Global Leukemia Academy

Pros and Cons of HSCT, COVID-19 Impact and Measures

Aaron Logan

APTITUDE HEALTH®

UCSF Helen Diller Family Comprehensive Cancer Center

Pros and Cons of Hematopoietic Cell Transplantation in ALL

Aaron Logan, MD, PhD
UCSF Division of Malignant Hematology and Blood and Marrow Transplantation

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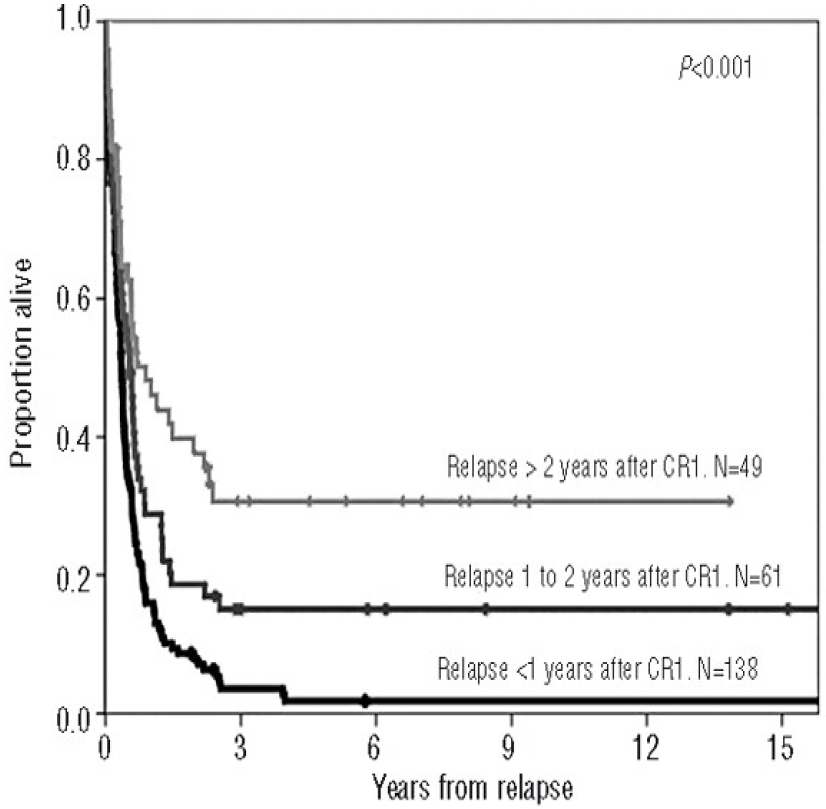
@hemedoc

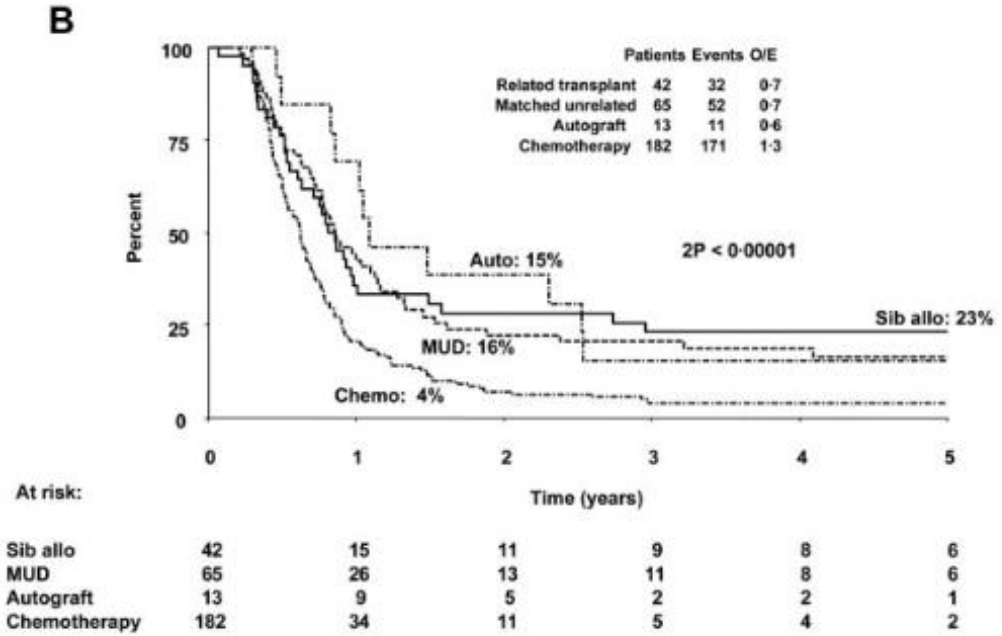
Relapsed/Refractory ALL is associated with poor prognosis



Oriol A, et al. *Haematologica*. 2010;95:589-596.

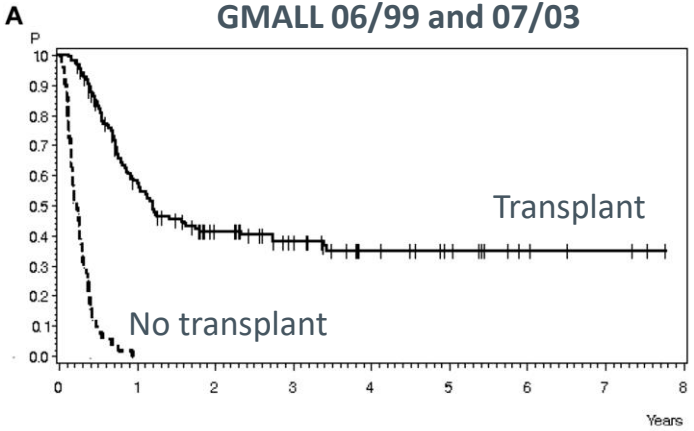
Transplant improves survival in relapsed ALL

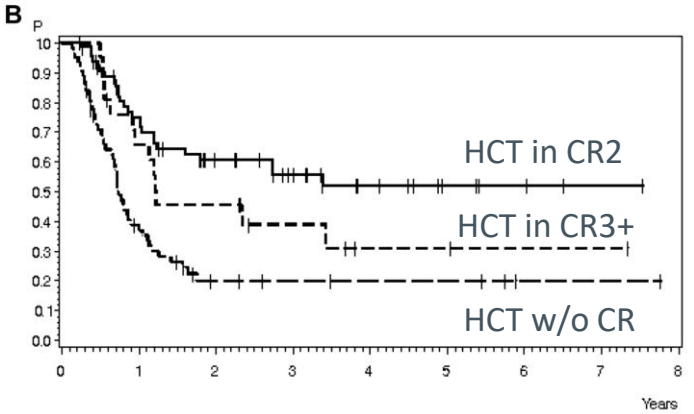
UKALL12/ECOG 2993



Fielding AK, et al. *Blood*. 2007;109:944-950.

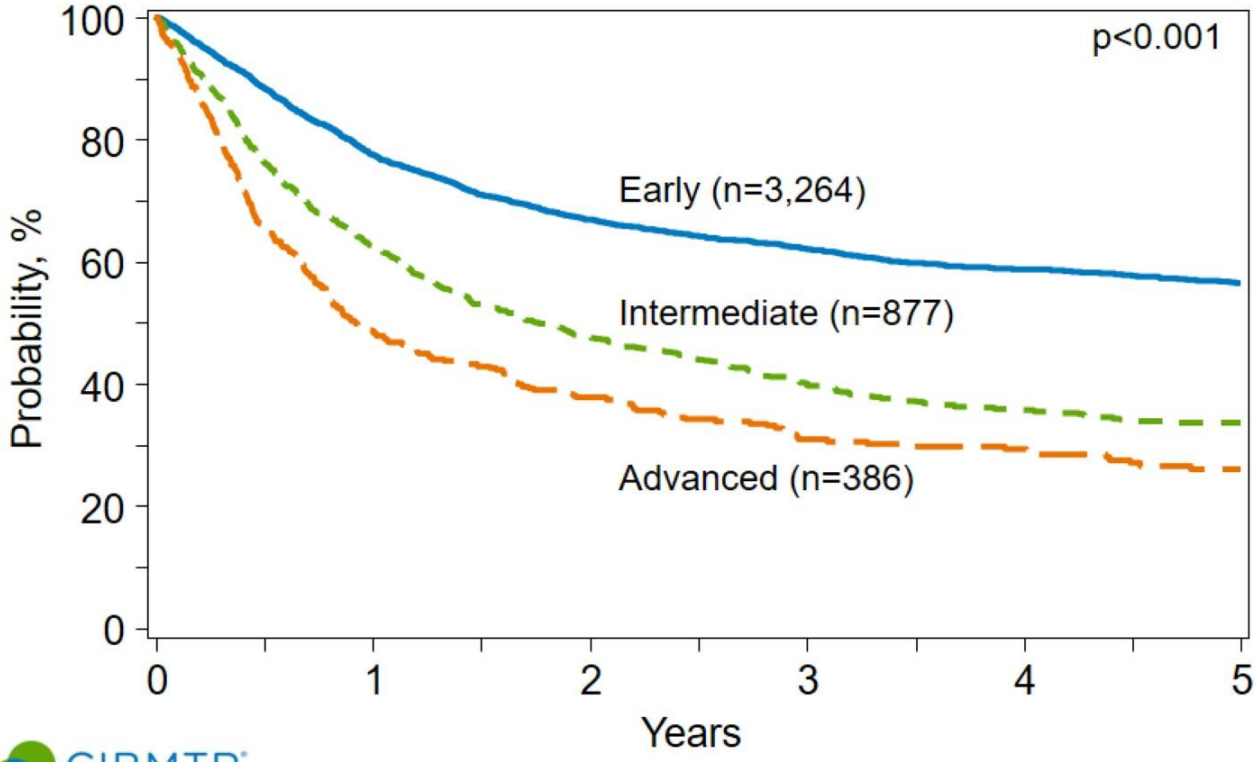
GMALL 06/99 and 07/03





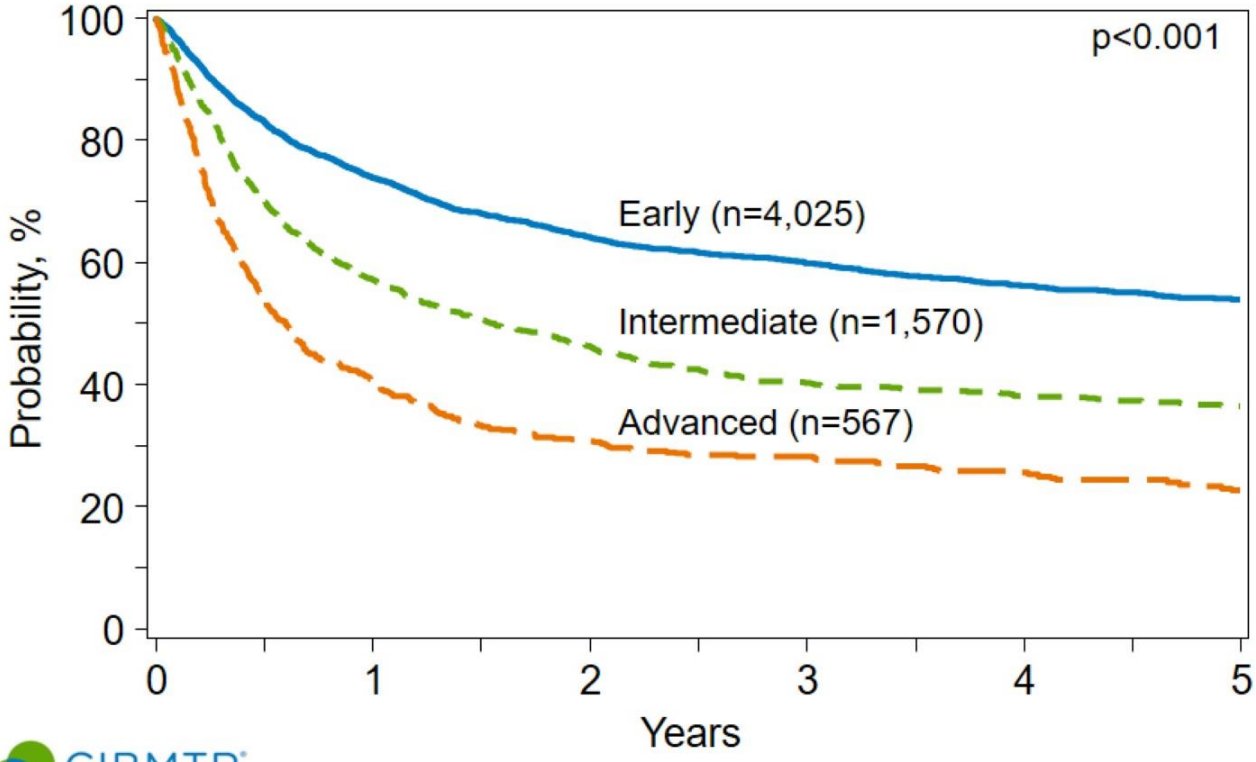
Gökbuget N, et al. *Blood.* 2007;110: abstract 12.

Survival after HLA-Matched Sibling Donor HCT for ALL, Age ≥18 Years, 2007-2017



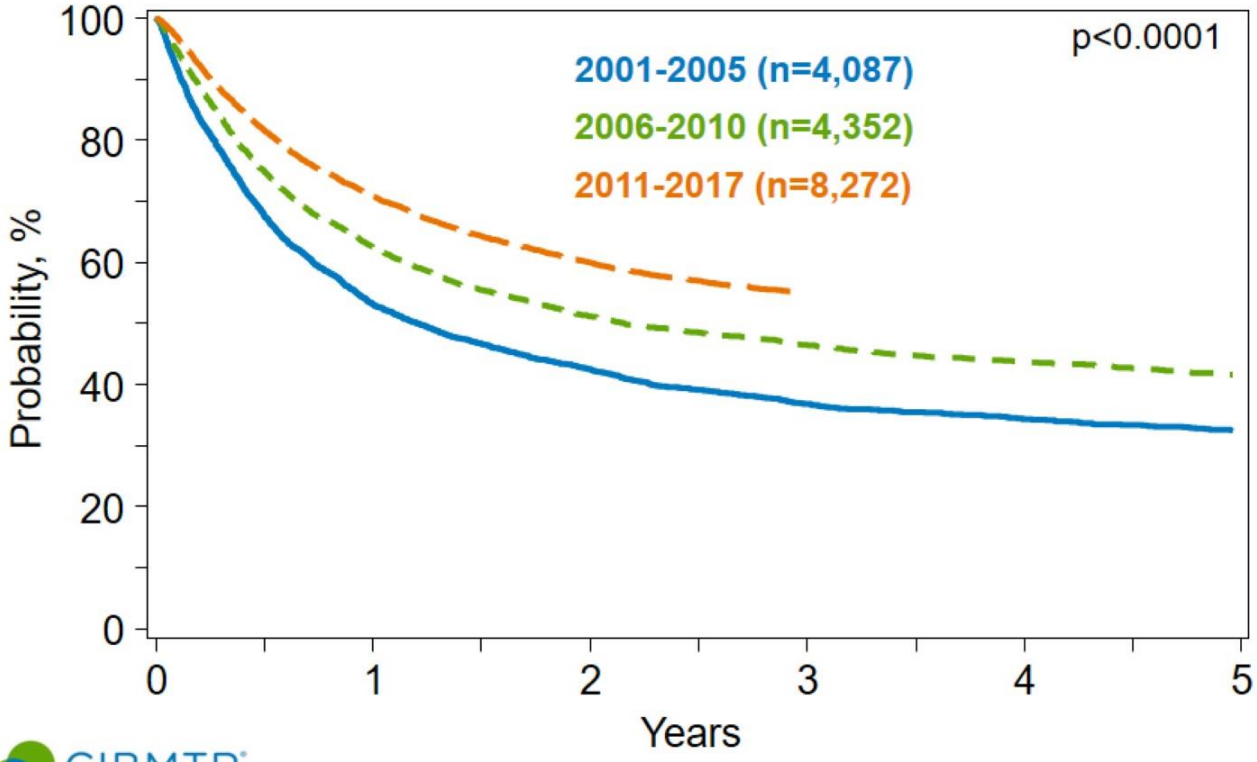
CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Survival after Unrelated Donor HCT for ALL, ≥18 Years, 2007-2017



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Trends in Survival after Allogeneic HCT for ALL, ≥18, 2001-2017



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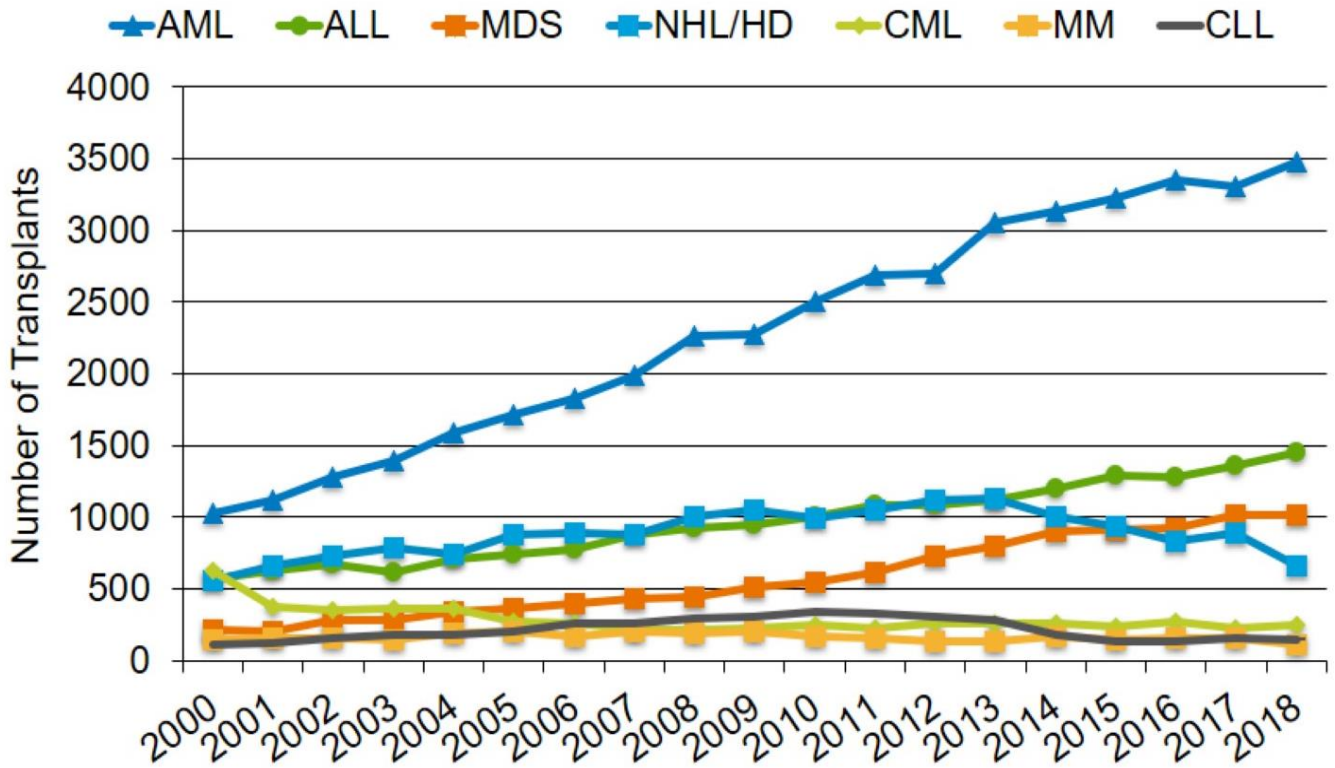
Selected Disease Trends for Allogeneic HCT in the US



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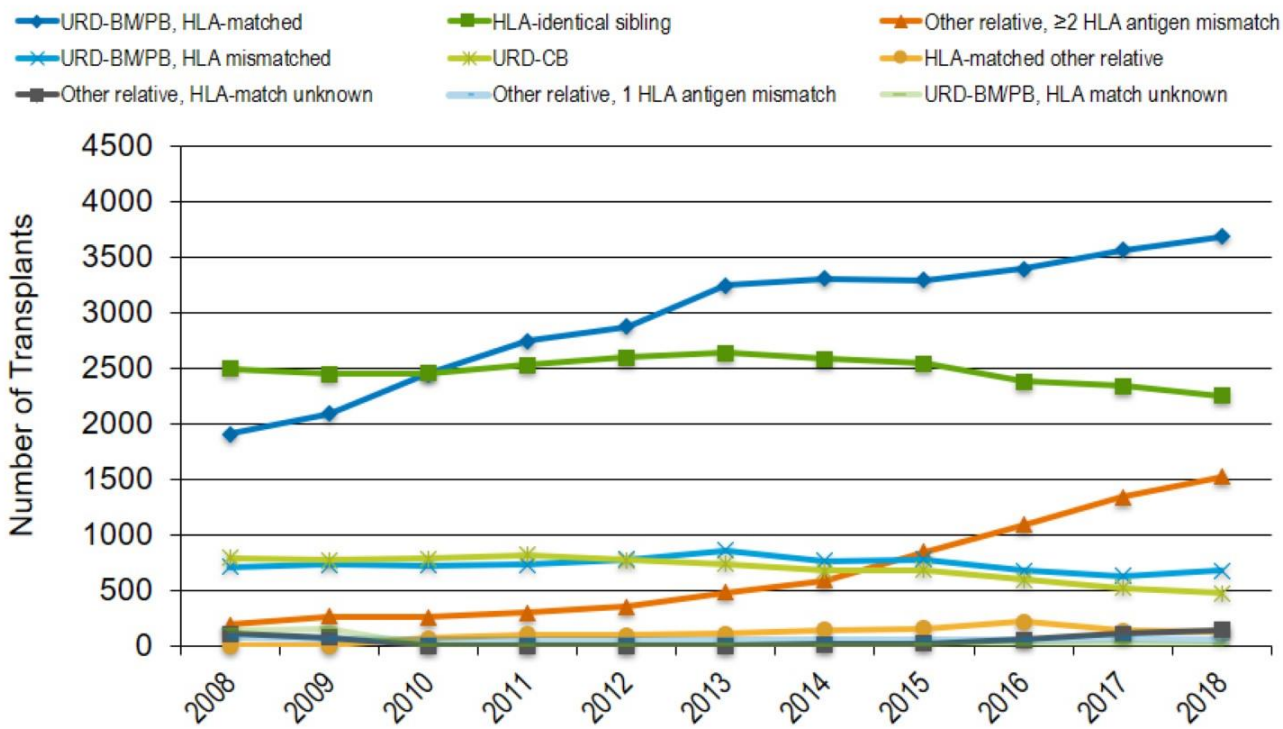
Allogeneic HCT Recipients in the US, by Donor Type



MUD

Matched related

HaploHCT

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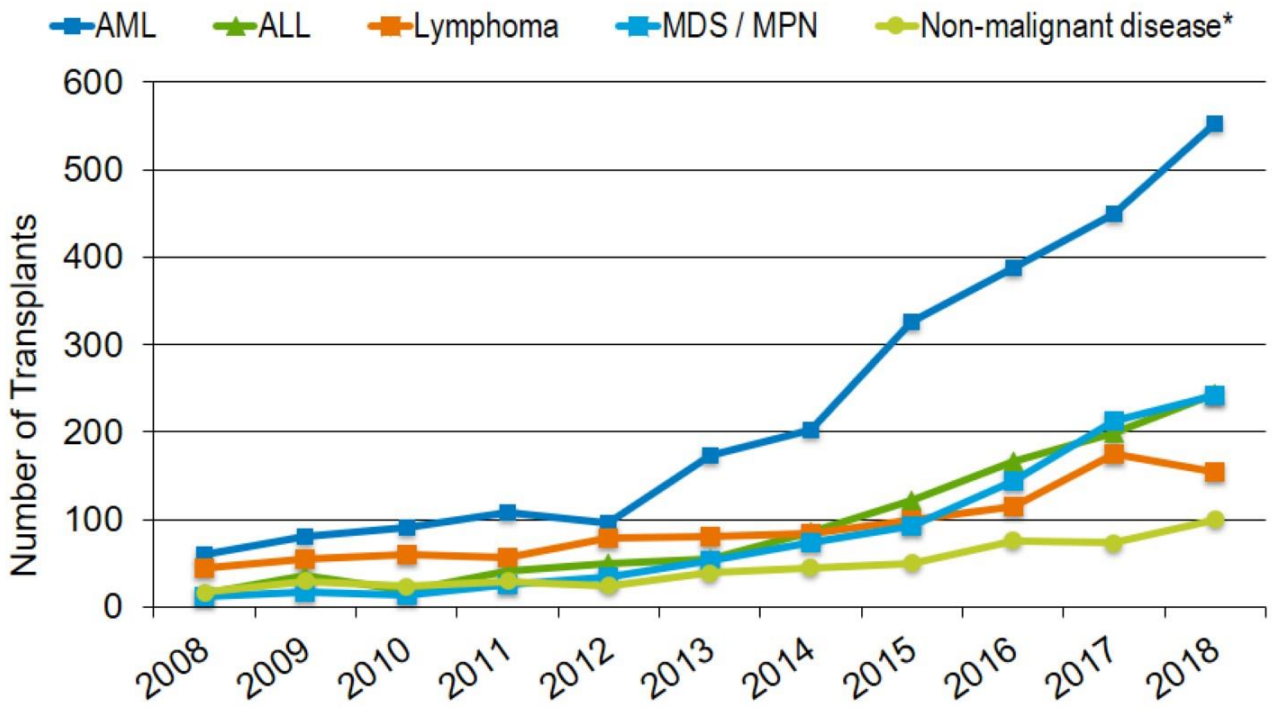
Haploidentical HCT Recipients in the US, by Disease



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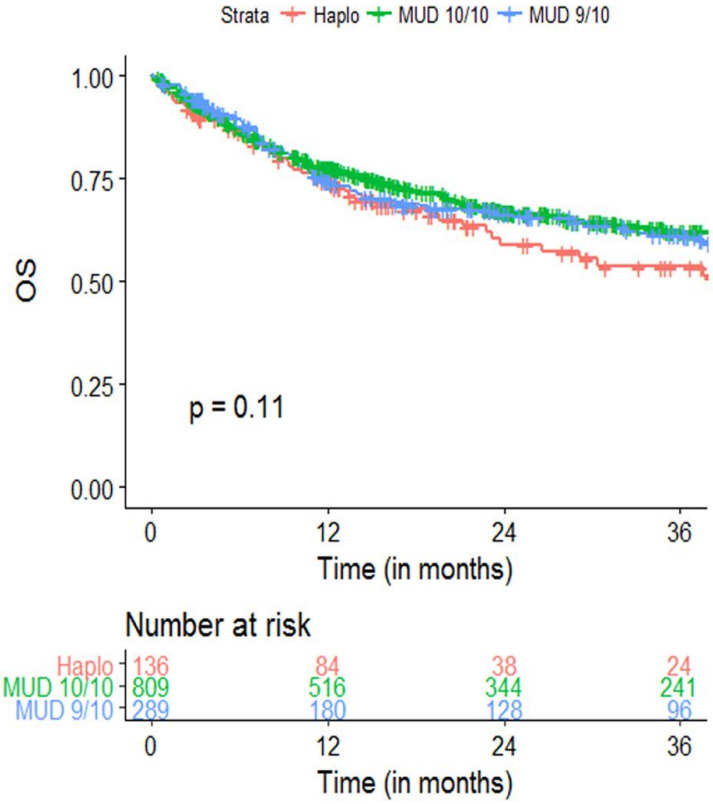
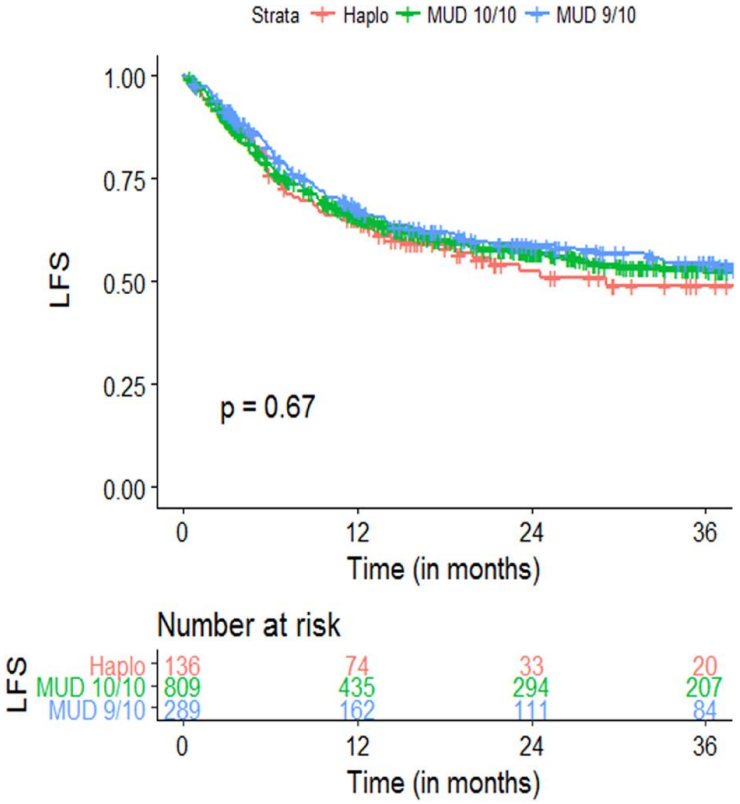
*Not including aplastic anemia.

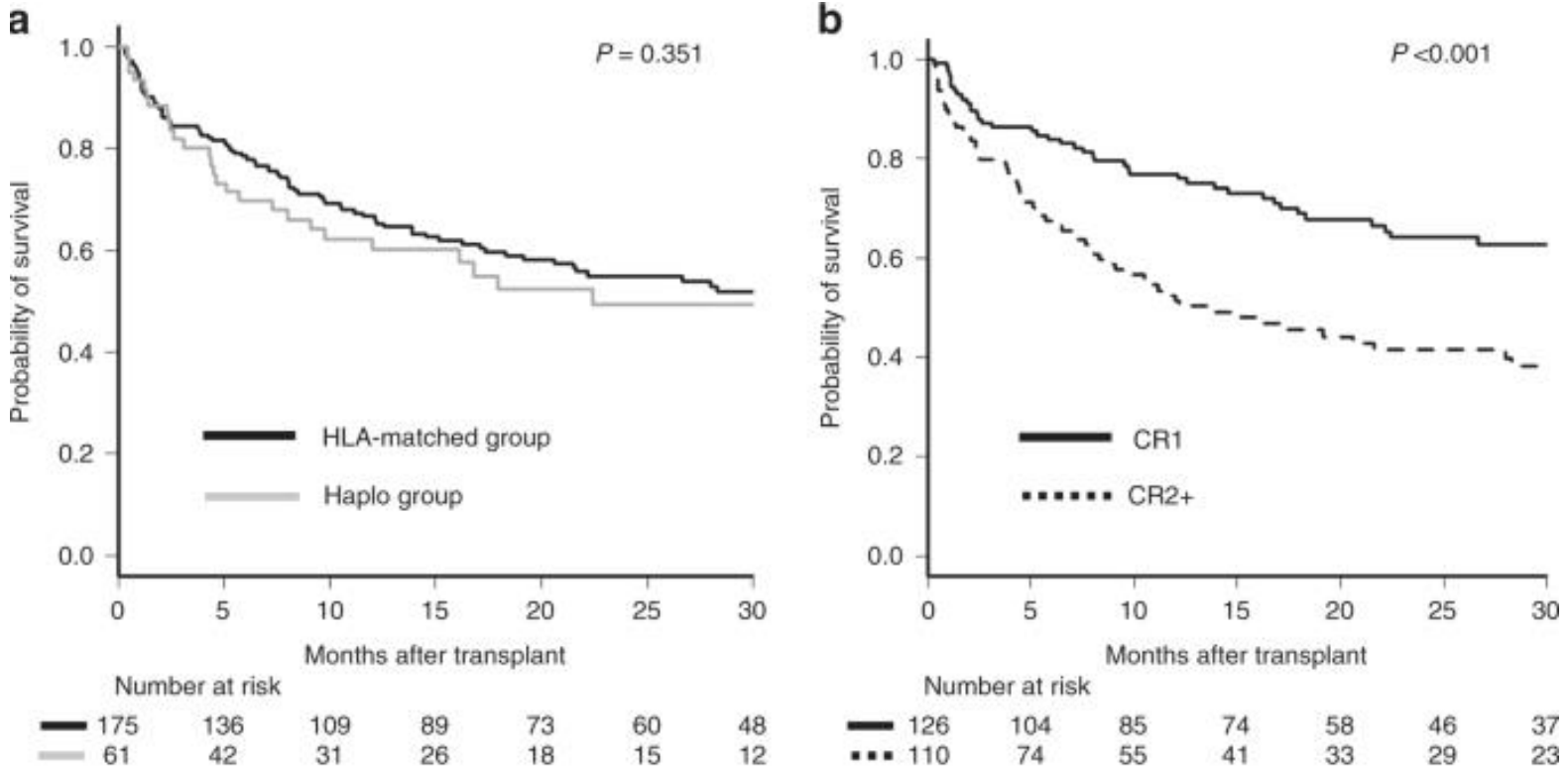
In ALL CR1, HaploHCT associated with outcomes similar to MUD: EBMT





Shem-Tov N, et al. *Leukemia*. 2020;34:283-292.

HaploHCT for ALL associated with favorable outcomes in Argentina



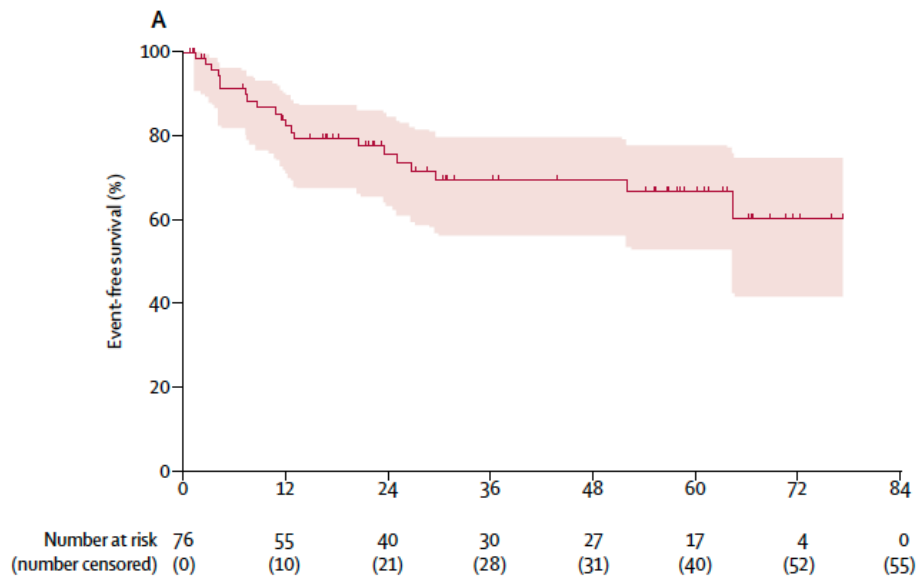
Basquiera AL, et al. *Bone Marrow Transplant.* 2020;55:400-408.

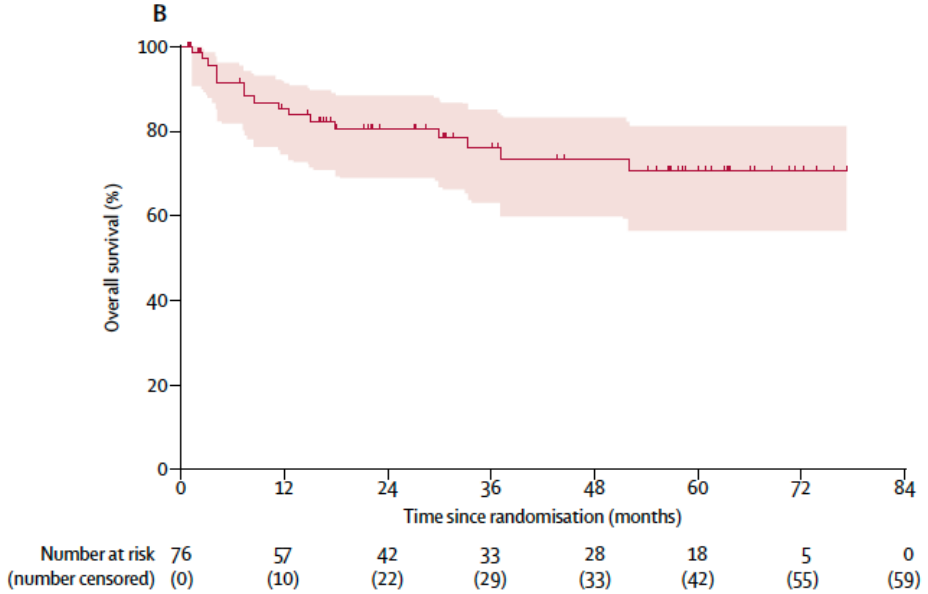
Indications for alloHCT in ALL

- Ph+ (? — probably can avoid in most using ponatinib)
- Ph-like lesions
- *MLL/KMT2A* rearrangements
- MRD >10^{-4} after 1–3 cycles of chemotherapy
- All in CR2+

HyperCVAD + ponatinib for Ph+ ALL: Long-term results

<20% went to alloHCT





Jabbour E, et al. *Lancet Haematol*. 2018;5:e618-e627.

Indications for alloHCT in ALL

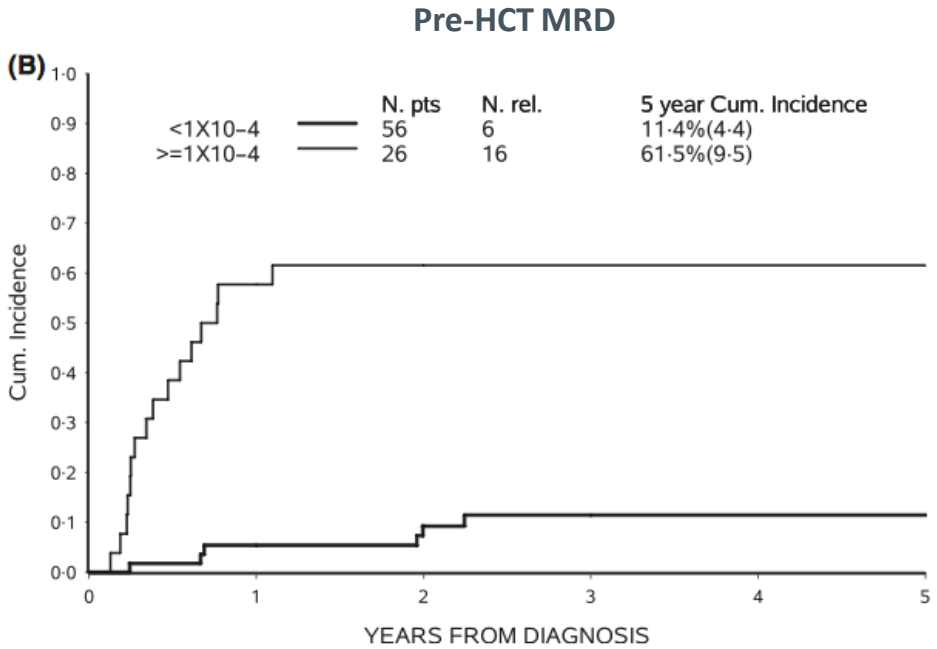
- Ph+ (? — probably can avoid in most using ponatinib)
- Ph-like lesions
- *MLL/KMT2A* rearrangements
- MRD >10^{-4} after 1–3 cycles of chemotherapy
- All in CR2+

MRD status pre-HCT predicts outcome of transplant

N = 82, age <1–20
MRD by ASO-PCR
Median f/u 4.9 yr

HCT in CR1 if
- Day +78: >5 × 10^{-4} MRD
- Induction failure
- Ph+, MLL+
- T-lin w/WBC >100K

HCT for all CR2+

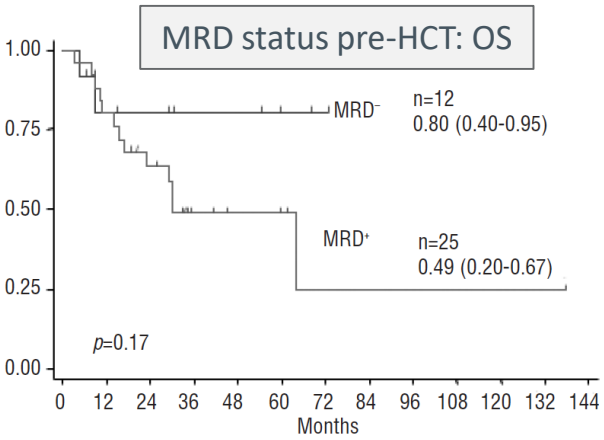


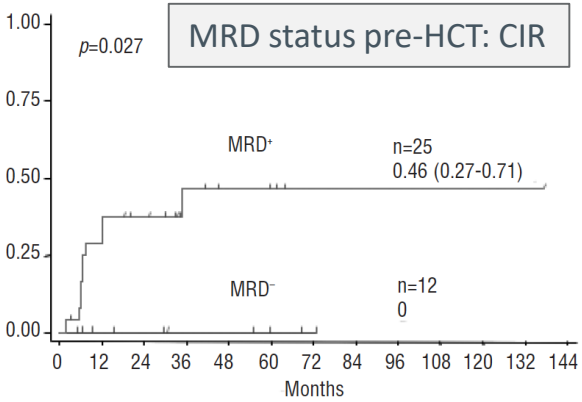
Balduzzi A, et al. *Br J Haematol*. 2014;164:396-408.

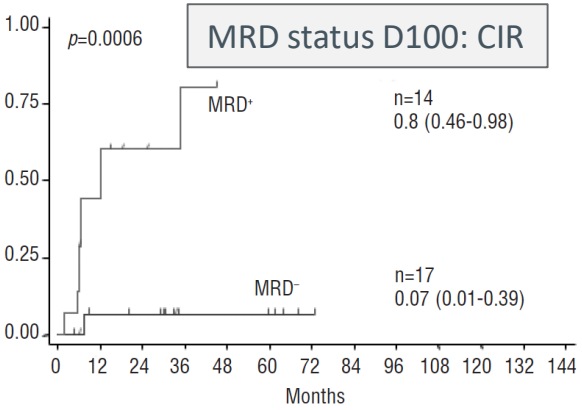
MRD status pre/post-HCT predicts RFS and OS

N = 43, age 18–63
MAC alloHCT in CR1

MRD quant: TCR/Ig ASO-PCR or BCR/ABL or MLL/AF4 Q-PCR

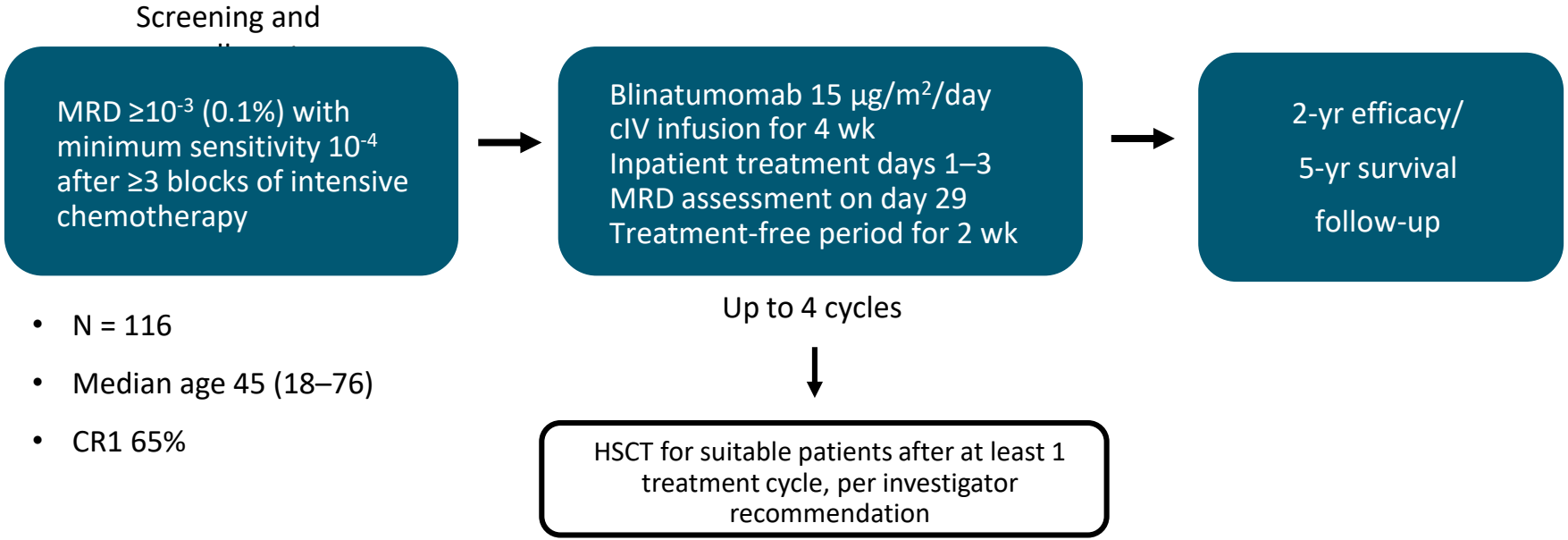






Spinelli O, et al. *Haematologica*. 2007;92:612-618.

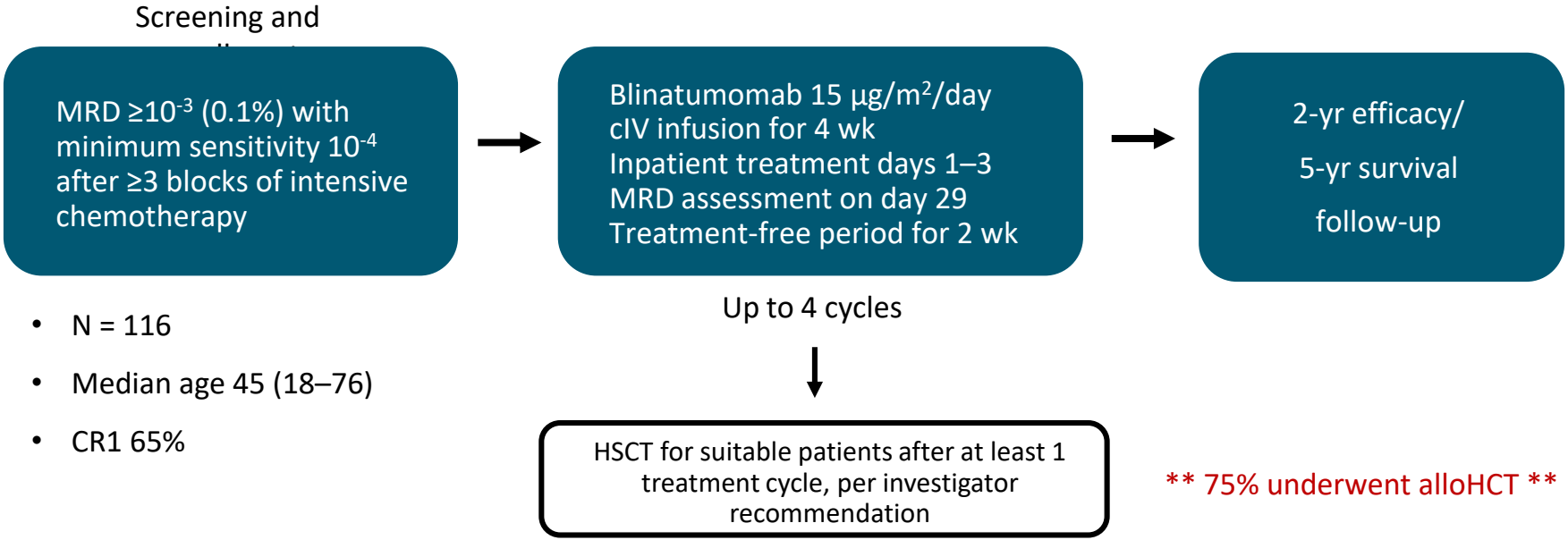
Blinatumomab BLAST trial: Preemption of B-ALL relapse using MRD-directed treatment



- N = 116
- Median age 45 (18–76)
- CR1 65%

Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

Blinatumomab BLAST trial: Preemption of B-ALL relapse using MRD-directed treatment

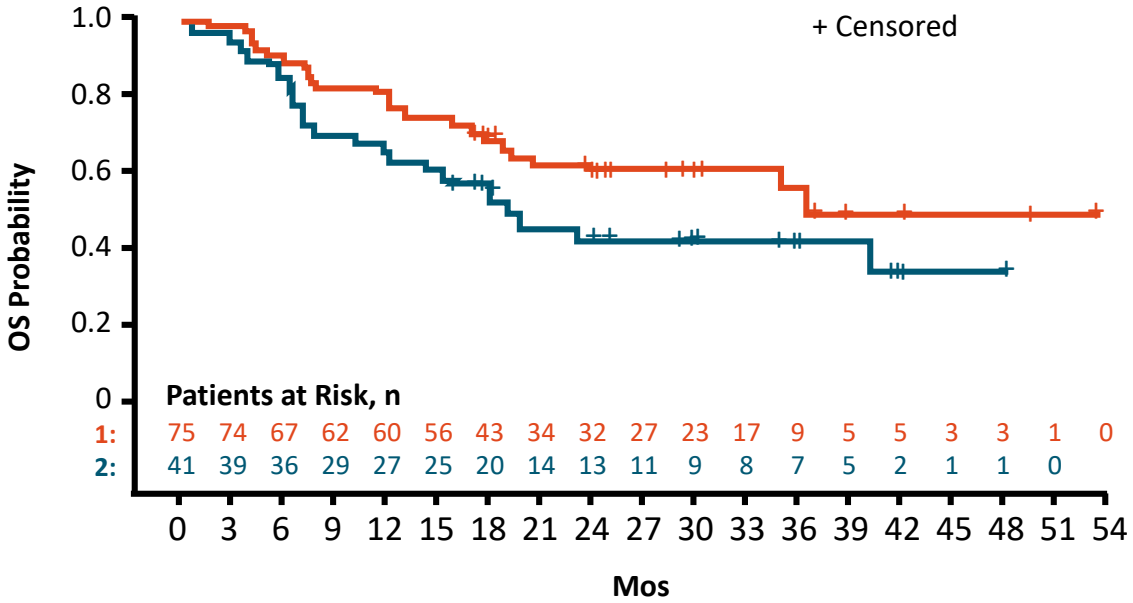


- N = 116
- Median age 45 (18–76)
- CR1 65%

** 75% underwent alloHCT **

Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

Blinatumomab BLAST trial: Preemption of B-ALL relapse using MRD-directed treatment – results

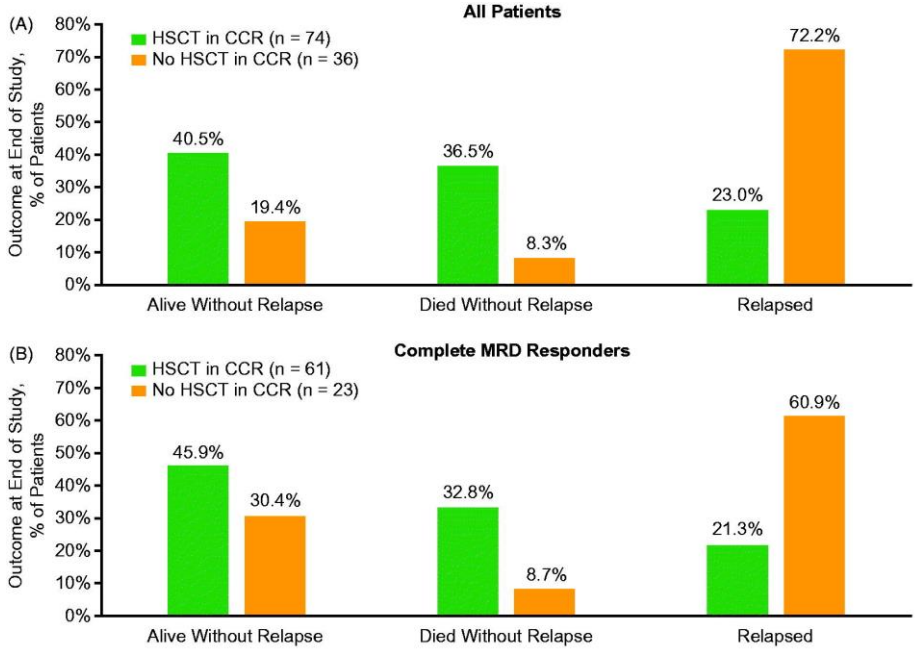


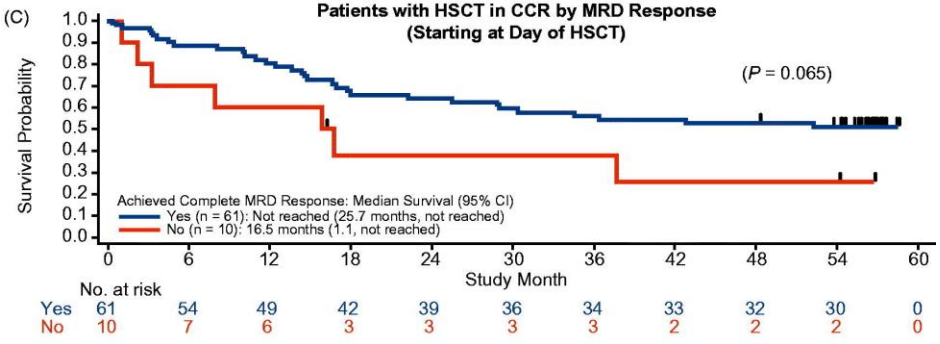
1: Patients in 1st CR (n = 75); median: 36.5 (95% CI: 20.6-NR)

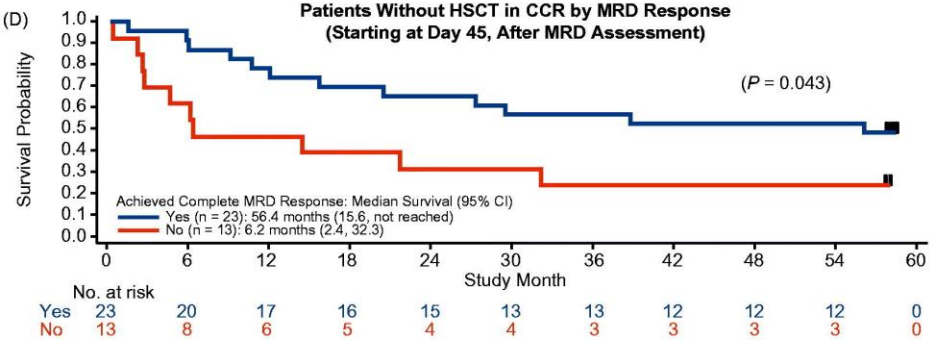
2: Patients in 2nd or 3rd CR (n = 41); median: 19.1 (95% CI: 11.9-NR)

Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

Blinatumomab BLAST trial: Long-term outcomes

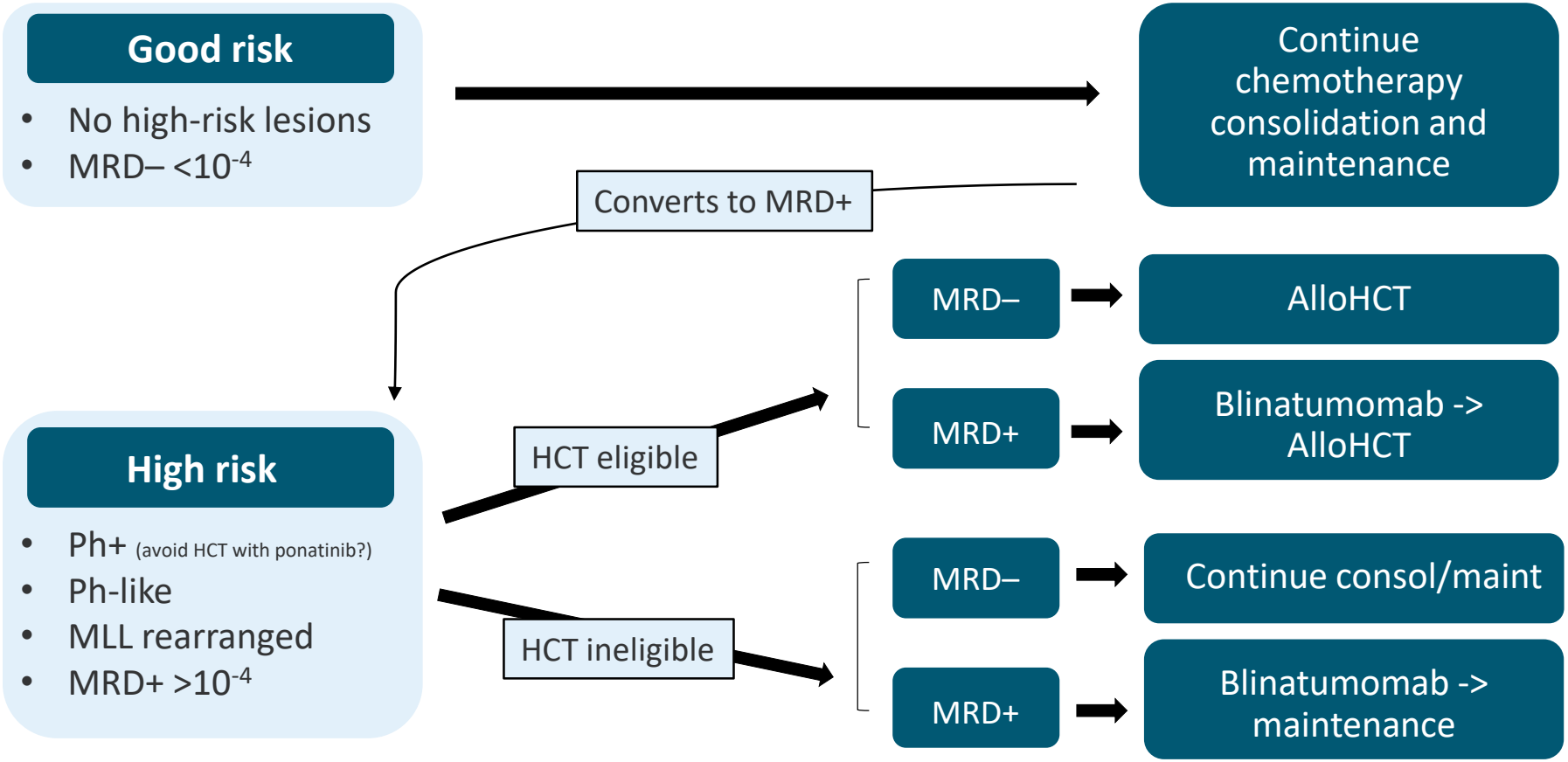






Gökbuget N, et al. *Leuk Lymphoma*. 2020;Jul 3:1–9; epub ahead of print.

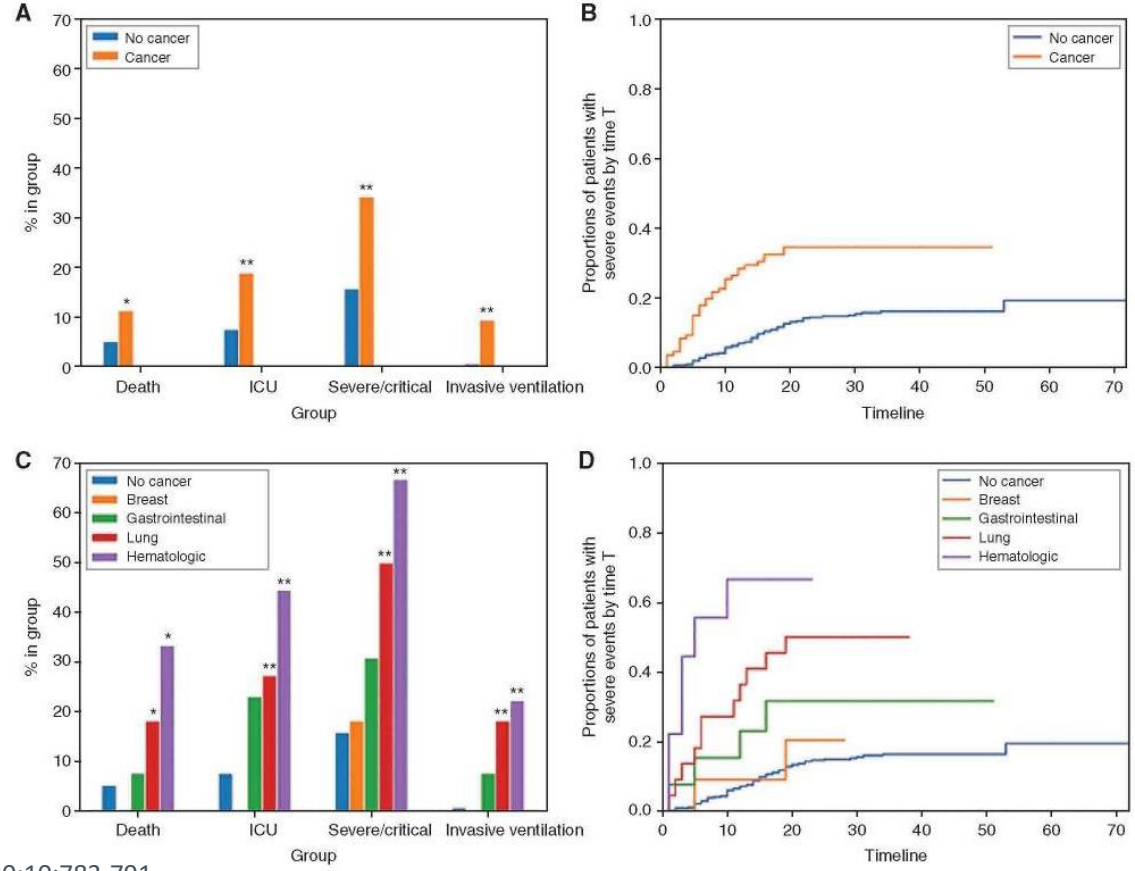
Management of adult ALL patients in first complete remission



Pros and cons of HCT in ALL: Summary

- The substantial toxicities of transplant require judicious use of this treatment modality; however, there is not yet a therapy to replace transplant for high-risk patients
- All patients with relapsed ALL should be considered for alloHCT
- For patients in CR1, alloHCT may be considered for those with MRD >10^{-4} after 1–3 cycles of therapy or high-risk genetic lesions (eg, Ph-like, MLL)
- Patients with Ph+ ALL may be able to avoid alloHCT with ponatinib
- The presence of MRD prior to alloHCT is associated with high relapse risk. Blinatumomab as bridge to HCT should be considered

Considerations for ALL patients in COVID-19 era



Dai M, et al. *Cancer Discov*. 2020;10:783-791.

Considerations for ALL patients in COVID-19 era

- COVID-19 testing recommended prior to starting chemotherapy cycles. Patients presenting with newly diagnosed ALL and COVID positivity with mild-moderate symptoms should receive standard therapy with curative intent. In those with respiratory failure, consider dexamethasone-vincristine to temporize
- In general, it is prudent to NOT delay alloHCT, given the logistics involved and curative nature of the therapy for those with high-risk disease
- Treatment for ALL must be timely and uninterrupted, since relapsed disease is difficult to recapture. Consider blinatumomab as bridge to transplant if delay needed
- The ramifications of SARS-CoV-2 infection during the course of immunotherapies such as blinatumomab and CAR T cells remain to be determined
- ALL patients may not develop protective immunity to SARS-CoV-2 from natural infection or vaccination (when available)

Considerations for ALL patients in COVID-19 era

www.hematology.org/covid-19

- COVID-19 and Aggressive Non-Hodgkin Lymphoma (Version 3.0; last updated June 15, 2020)
- COVID-19 and Acute Lymphoblastic Leukemia - Adult (Version 1.1; last reviewed June 4, 2020)
- COVID-19 and Acute Lymphoblastic Leukemia - Pediatric (Version 2.0; last updated June 15, 2020)
- COVID-19 and Acute Myeloid Leukemia (Version 1.2; last reviewed June 4, 2020)
- COVID-19 and Chronic Lymphocytic Leukemia (Version 2.0; last updated June 9, 2020)
- COVID-19 and Chronic Myeloid Leukemia (Version 1.2; last updated July 20, 2020)
- COVID-19 and Hodgkin Lymphoma (Version 3.0; last updated June 15, 2020)
- COVID-19 and Indolent Lymphomas (Version 3.0; last updated June 15, 2020)
- COVID-19 and Myelodysplastic Syndromes (Version 3.1; last updated June 8, 2020)
- COVID-19 and Myeloproliferative Neoplasms (Version 3.0; last updated July 20, 2020)
- COVID-19 and Multiple Myeloma (Version 1.2; last updated July 21, 2020)
- COVID-19 and HCT (Version 1.0; last updated July 20, 2020)

Thank you!

Global Leukemia Academy

Panel Discussion on the Role of HSCT: Discussion and Voting

APTITUDE HEALTH®

Q

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-vs-host disease
d) All of the above
e) None of the above

Global Leukemia Academy

Debate on CD19-Targeted Approaches

APTITUDE HEALTH®

Q

Question 1

EM: baseline questions for this session

What is your preferred ALL treatment choice in salvage if all these therapies were made 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 nonbulky 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 bispecifics 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

Patrick Brown

APTITUDE HEALTH®

Debate on CD19-targeted approaches:

CAR T cells

Patrick Brown, MD

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

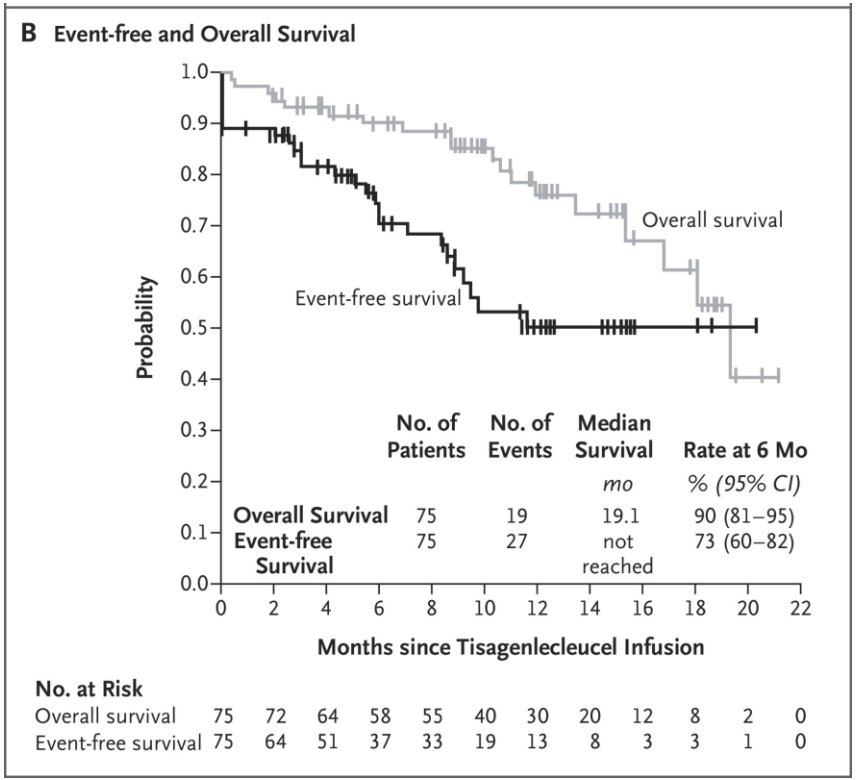
Setting up the debate: Some factors to be considered . . .

	CAR T	BiTE	ADC
Initial response rate			
Durability of response			
Need for HSCT as consolidation			
Adverse event profile			
Ease of administration			
Timing of administration			
Resource intensity			
Others?			

Response rates and survival in relapsed/refractory B-ALL

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

Survival in R/R ALL

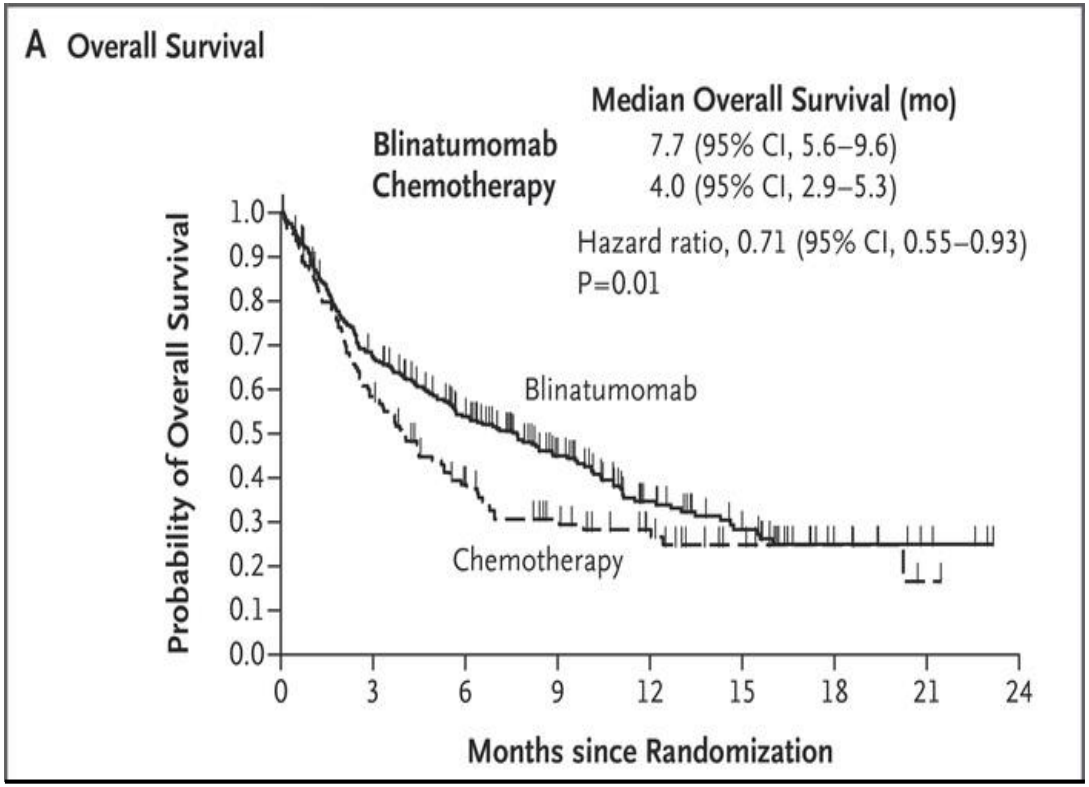


Durable survival improvement, but long-term EFS is in the 50% range; failures include

- Failed manufacture
- No response
- Loss of B-cell aplasia +/– CD19+ relapse
- CD19 escape

Maude SL, et al. *N Engl J Med*. 2018;378:439-448.

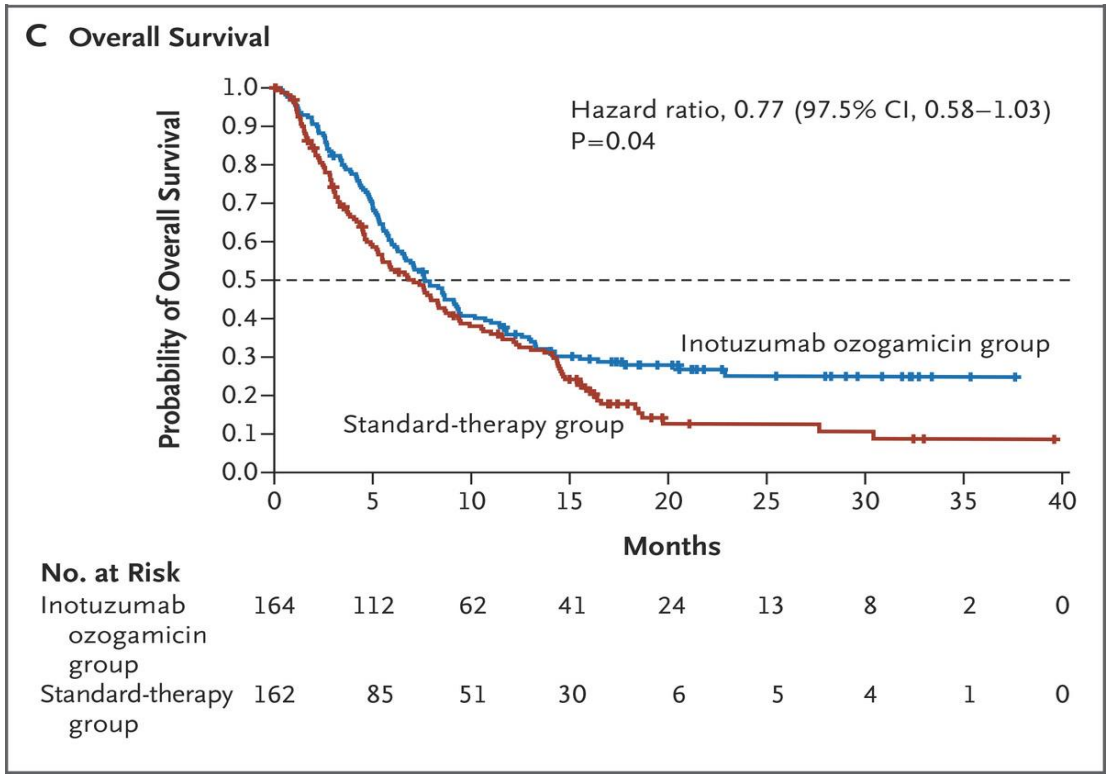
Survival in R/R ALL



Blina: improved survival initially, but not durable

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

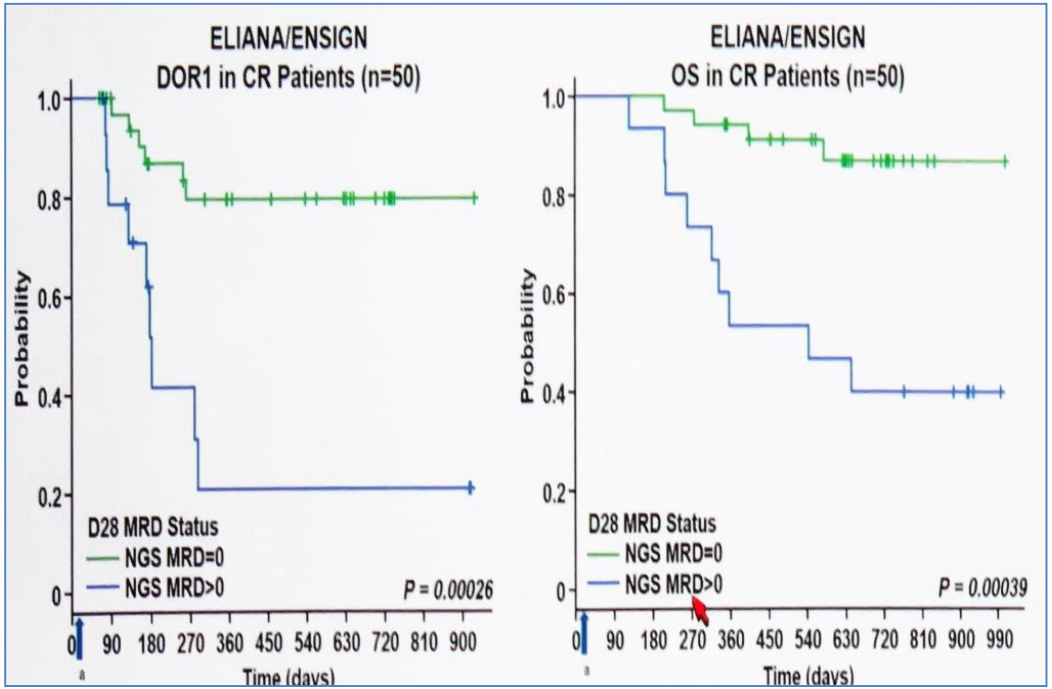
Survival in R/R ALL

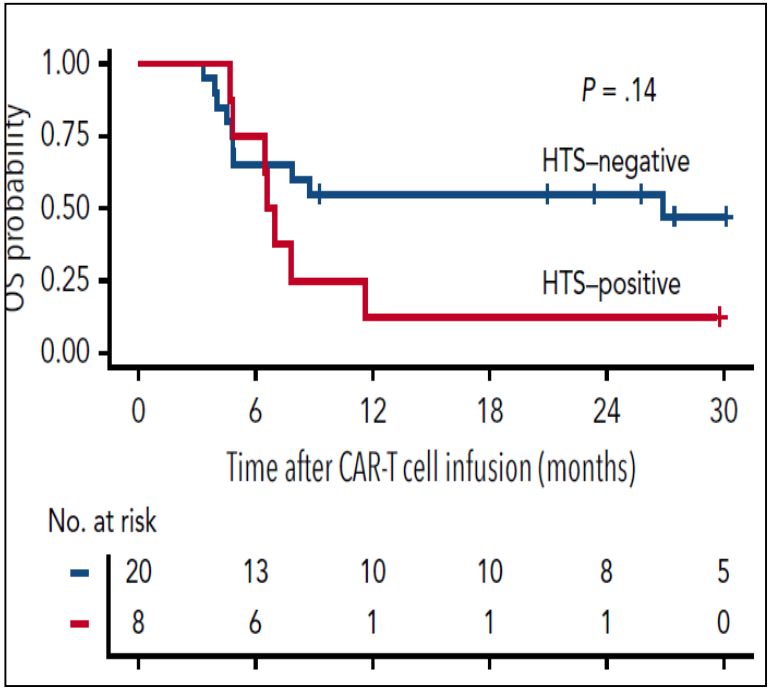


Ino: improved survival initially, but not durable

Kantarjian H, et al. *N Engl J Med*. 2016;375:740-753.

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





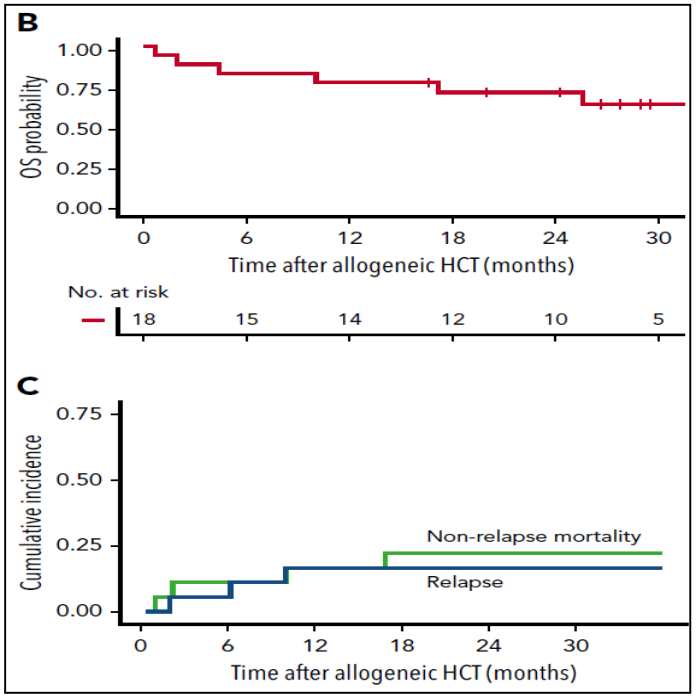
Median OS: 26.9 vs 6.8 months

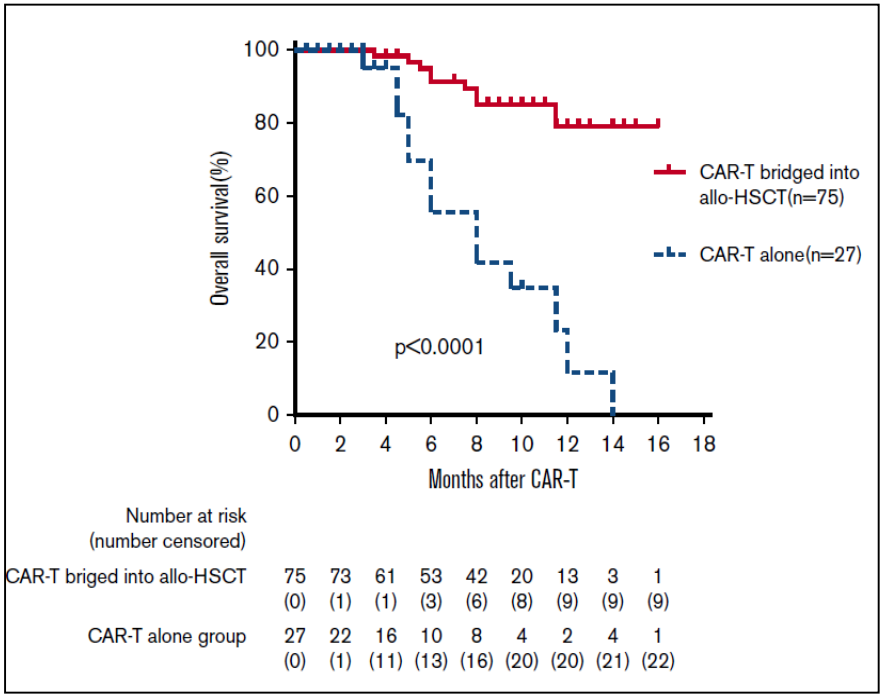
Pulsipher MA, et al. ASH 2018. Abstract 1551.

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;133:1652-1663.

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

Adverse events in relapsed/refractory B-ALL

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Blinatumomab	BiTE	CD19	44%/33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	$180K
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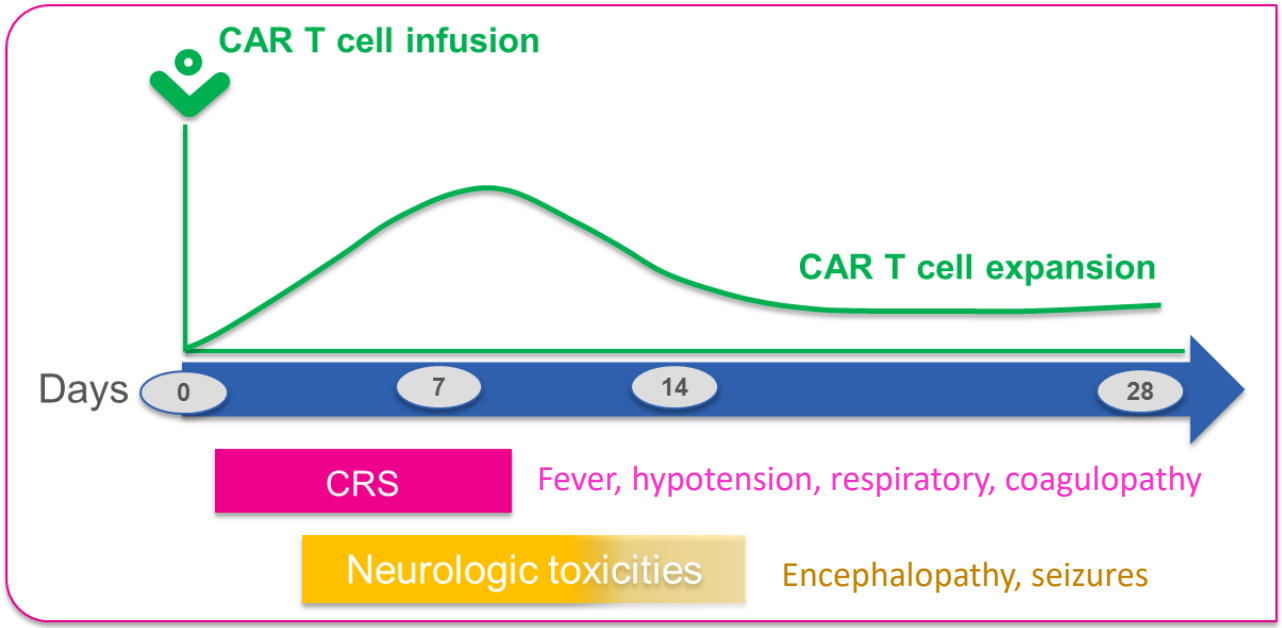
AEs after CAR T cells or blinatumomab

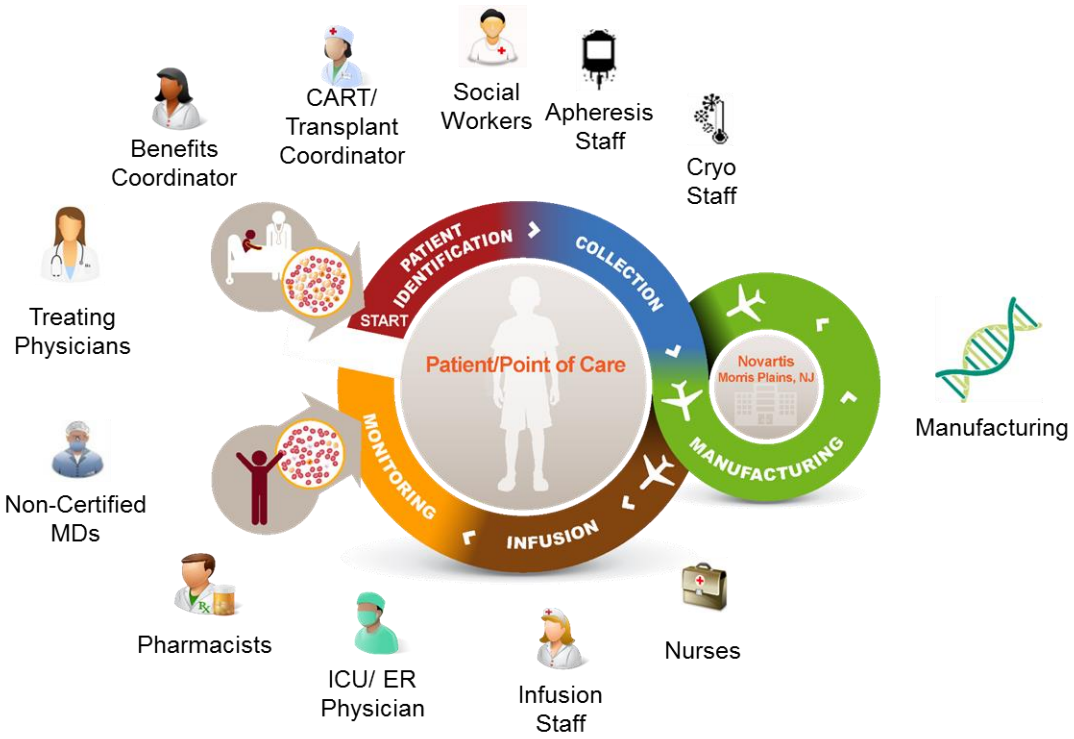


- CRS 40%–80% (20%–40% Gr3+), Neuro 10%–30% (5%–10% Gr3+)

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

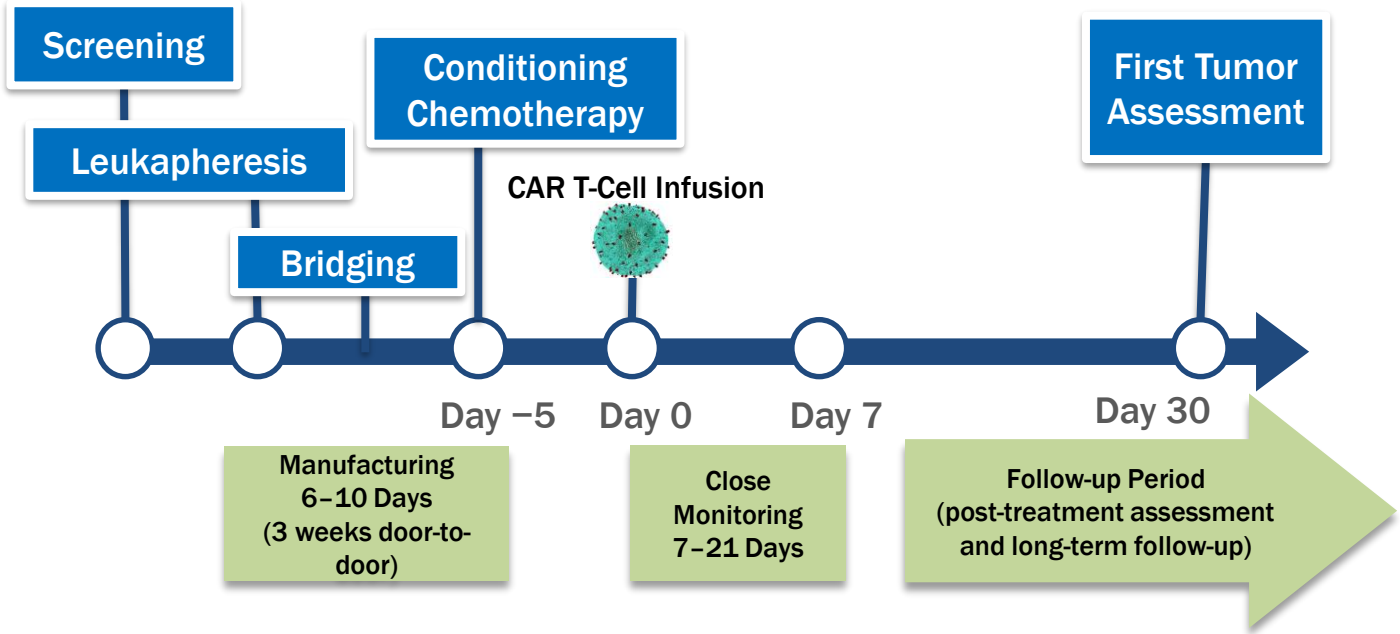
Adapted from/courtesy of Novartis.

CAR T-cell process:
A multistep treatment process involving many stakeholders



Adapted from/courtesy of Novartis.

CAR T-cell treatment schema



Adapted from/courtesy of Kite.

CAR T cells: Putting the plan into practice

- Insurance approval
- Schedule pheresis
  - Surgery – Shiley catheter
  - Pheresis team
  - Cell therapy laboratory
- Local housing
- Appropriate central venous access
- Bridging chemotherapy
- CAR T-cell infusion
- Follow-up

Setting up the debate: Some factors to be considered . . .

	CAR T	BiTE	ADC
Initial response rate	√		
Durability of response	√		
Need for HSCT as consolidation	?		
Adverse event profile	?		
Ease of administration	X		
Timing of administration	X		
Resource intensity	X		
Others?			

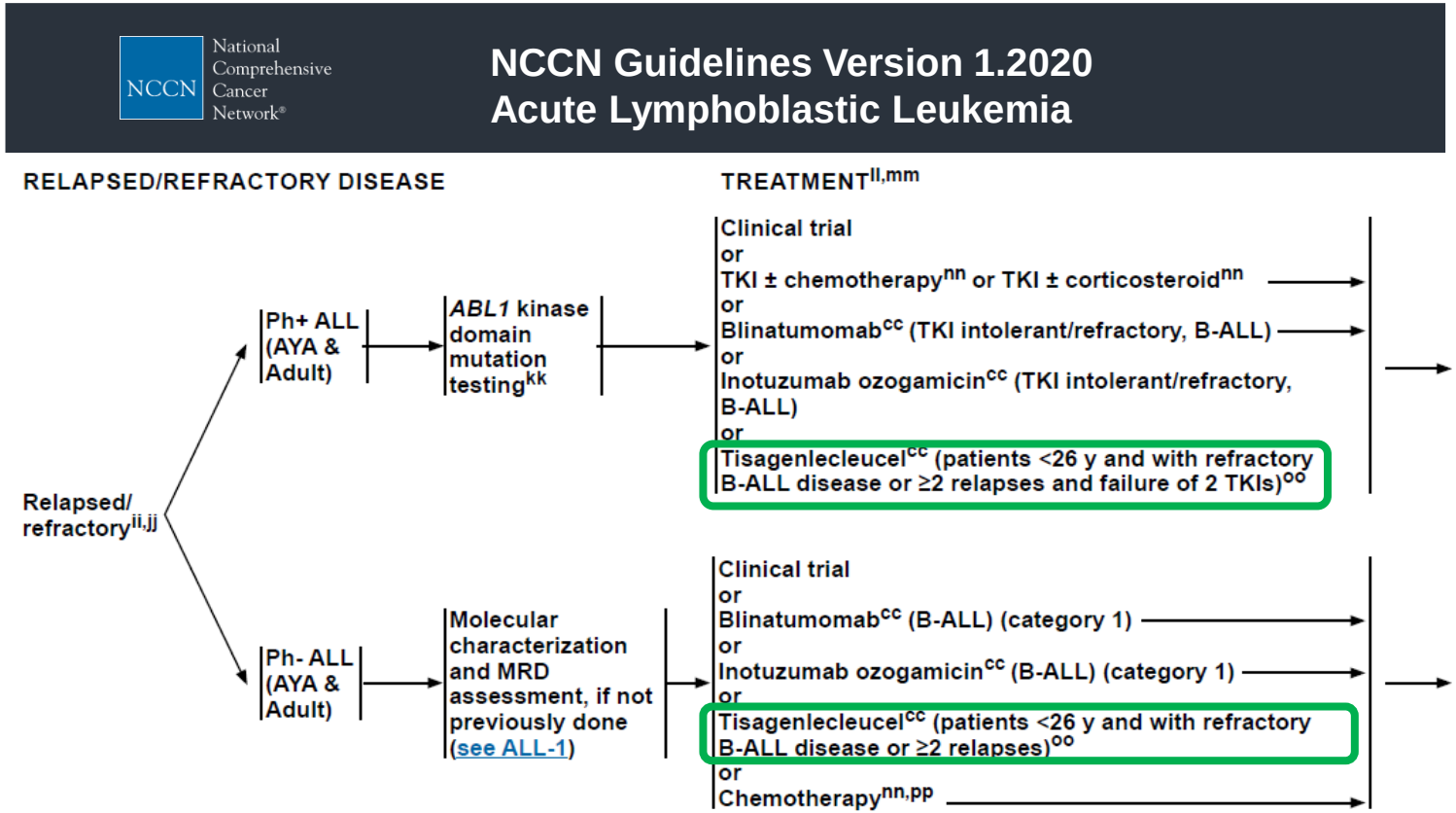
Overcoming failures

- Failure to manufacture (CAR): infants, heavily pretreated
  - Optimizations (earlier pheresis, improved ex vivo techniques)
  - Universal CAR T cells (using TALEN/CRISPR gene editing)
    - ***Would also address ease/access**
- Failure to engraft or lack of persistence (CAR)
  - Optimizations
    - Co-stimulatory domains (4-1BB vs CD28, for example)
    - T-APCs
    - Fully humanized CAR T cells
  - Checkpoint inhibitors (anti–PD-1, PD-L1)
- Antigen escape: multi-antigen targeting

Can use of immunotherapy in ALL be expanded?

- For B-ALL, earlier in disease course?
  - First relapse?
  - First remission with persistent MRD?
  - Upfront?
- T-ALL/Lly?

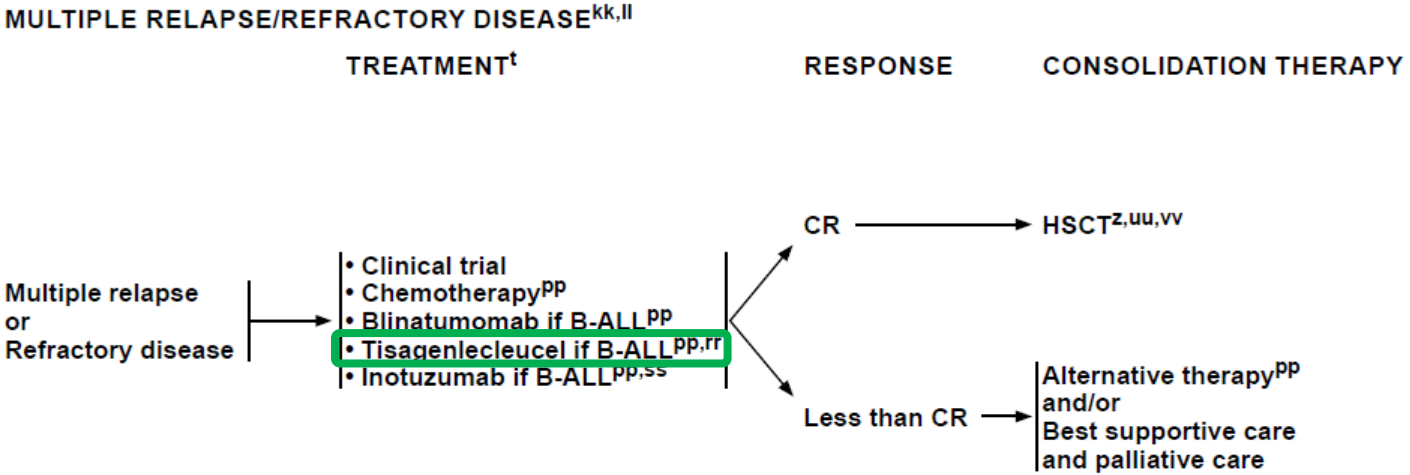
Where are CAR T cells in NCCN adult ALL guidelines?



Where are CAR T cells in NCCN pediatric ALL guidelines?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



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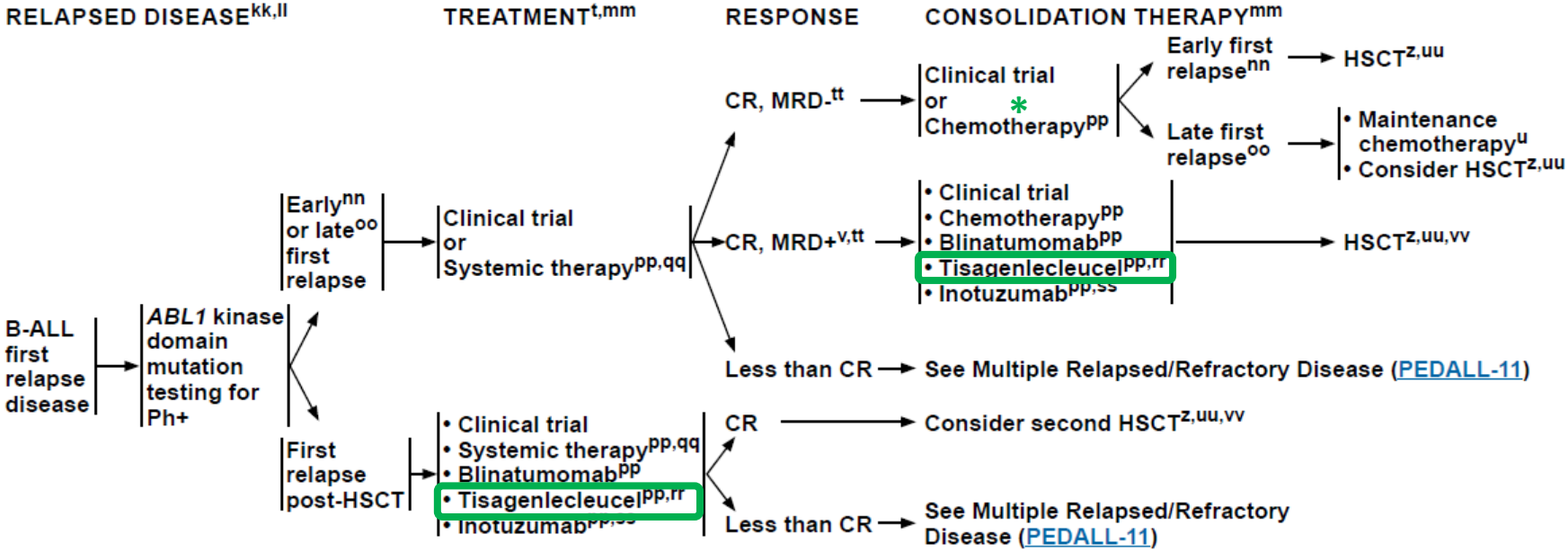
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



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National Comprehensive Cancer Network®

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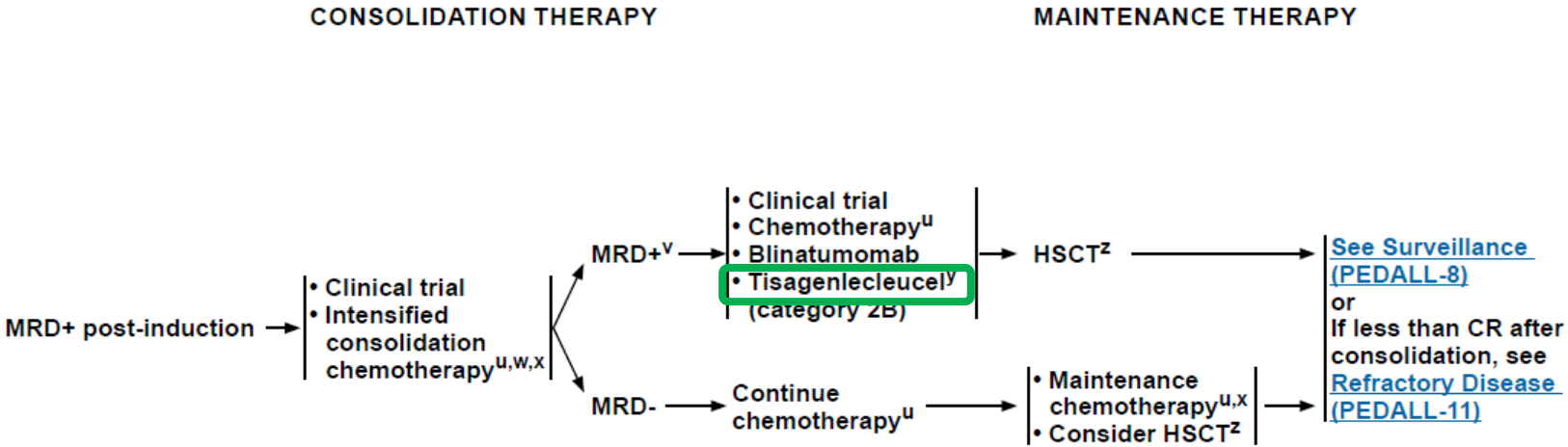

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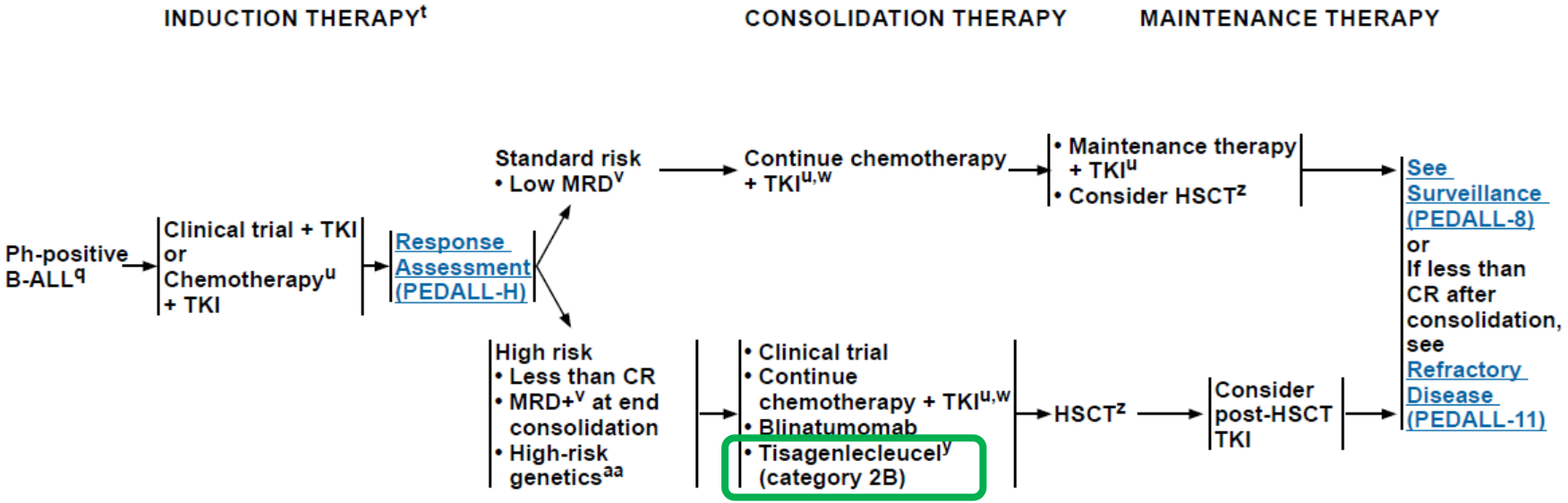


Global Leukemia Academy

Debate on CD19-Targeted Approaches: Monoclonal Antibodies and Bispecifics

Elias Jabbour

APTITUDE HEALTH®

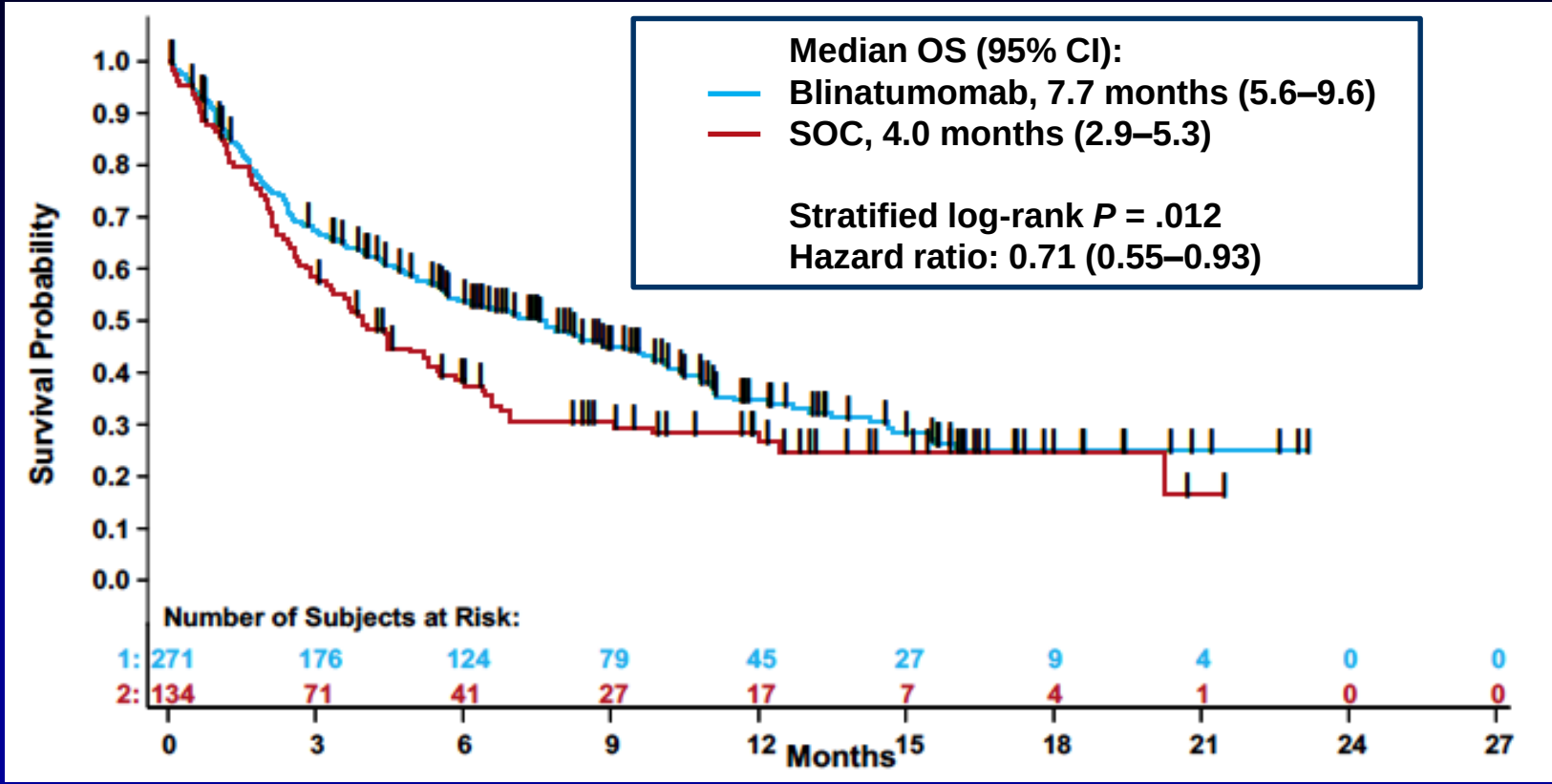
Historical Results in R-R ALL

- **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

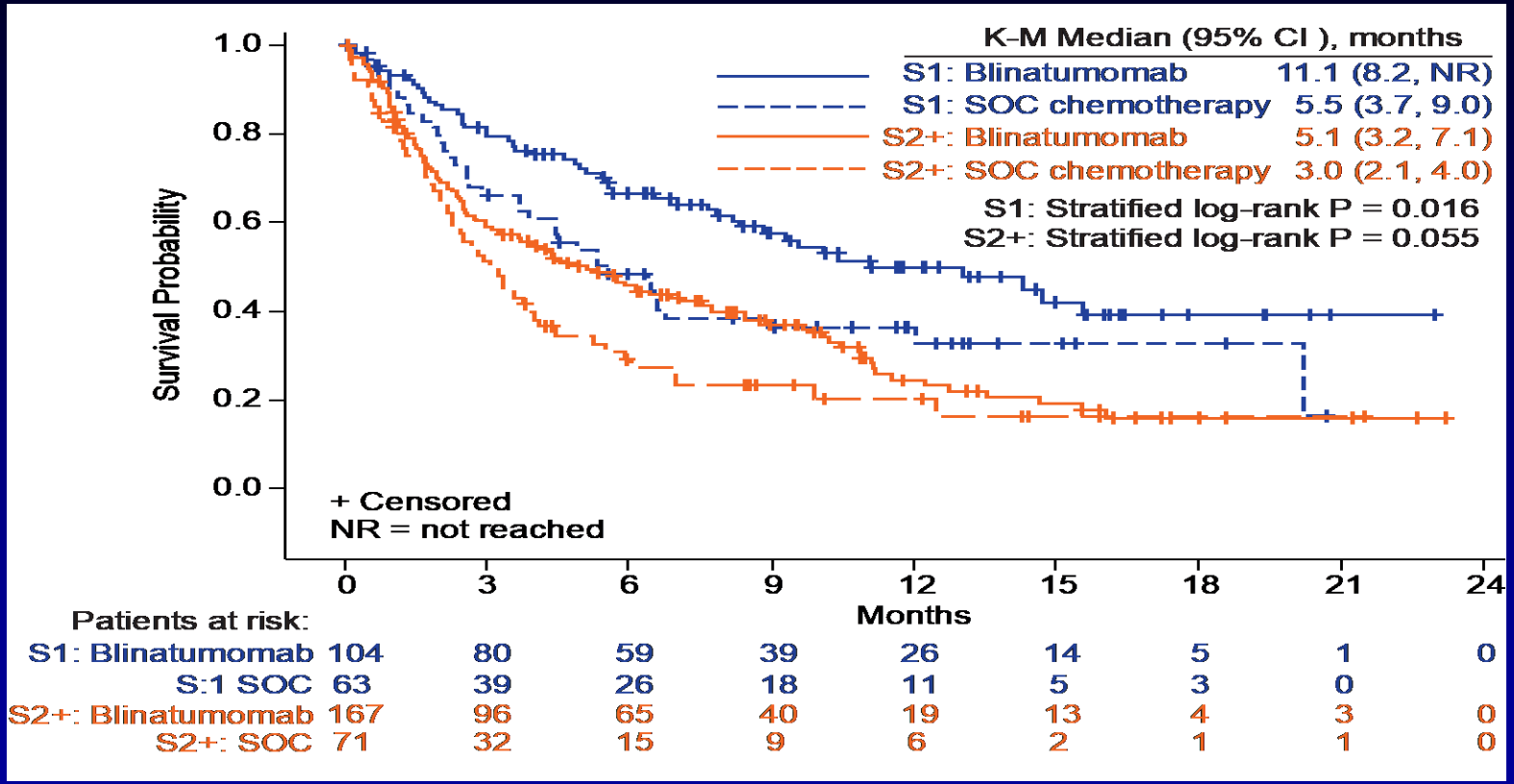
Gökbuget N, et al. *Haematologica*. 2016;101:1524-1533.

Blinatumomab vs Chemotherapy in R-R ALL



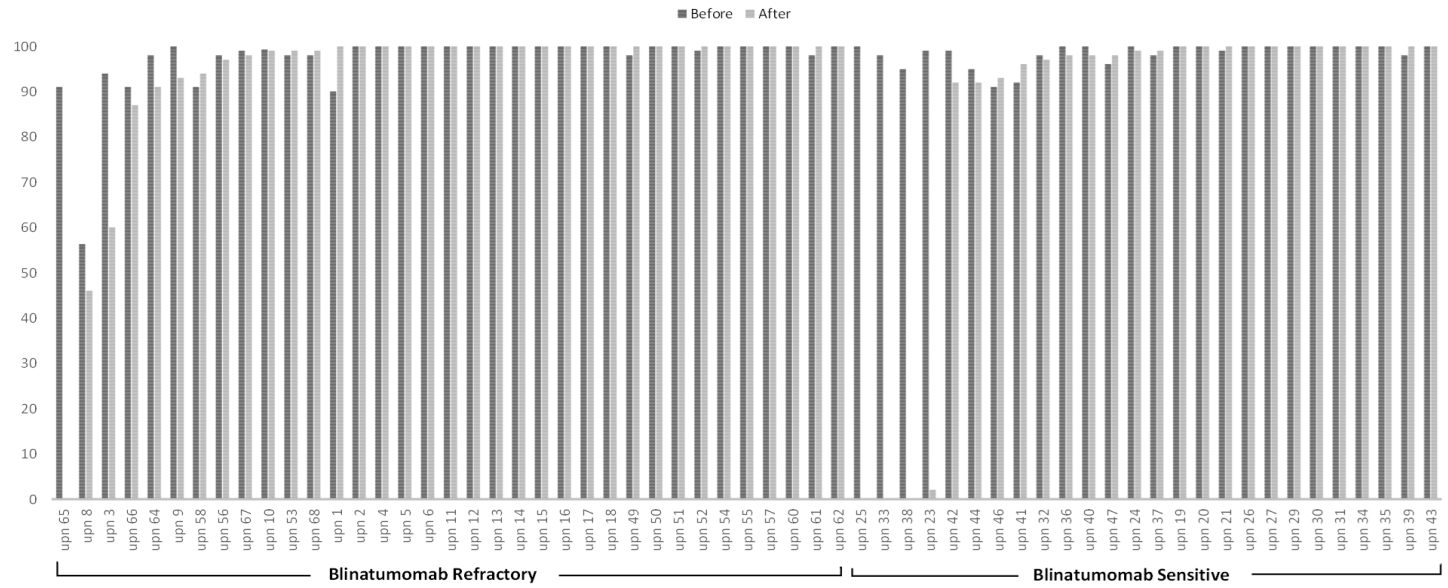
Kantarjian. *N Engl J Med.* 2017;376:836-847.

Phase III TOWER Study: Survival by Salvage



Dombret. *Leuk Lymphoma.* April 2019.

CD19 (%) Expression Before and After Blinatumomab Therapy

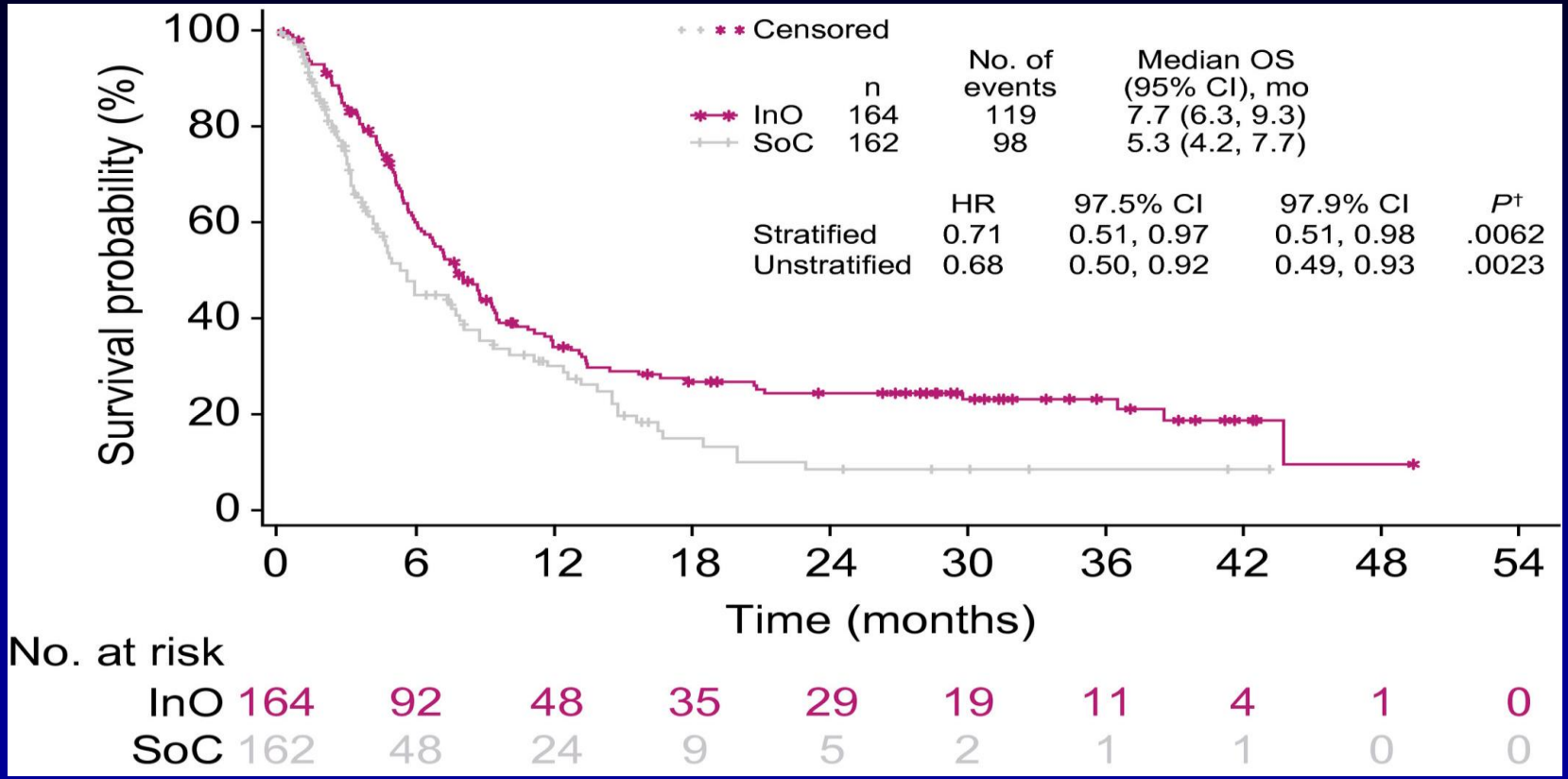


61 patients evaluated for immunophenotype; 56 (92%) had CD19+ disease

- **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 alloSCT 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 alloSCT
- **5 VOD (10.4%):** all post-SCT: 5/19 (26%)

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

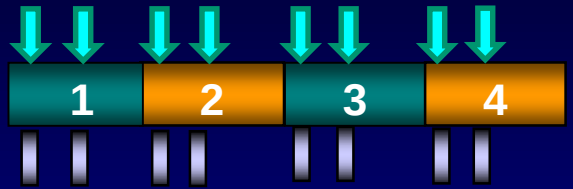
Mini-HCVD–Ino–Blina in ALL: Design

- Dose-reduced hyperCVD 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

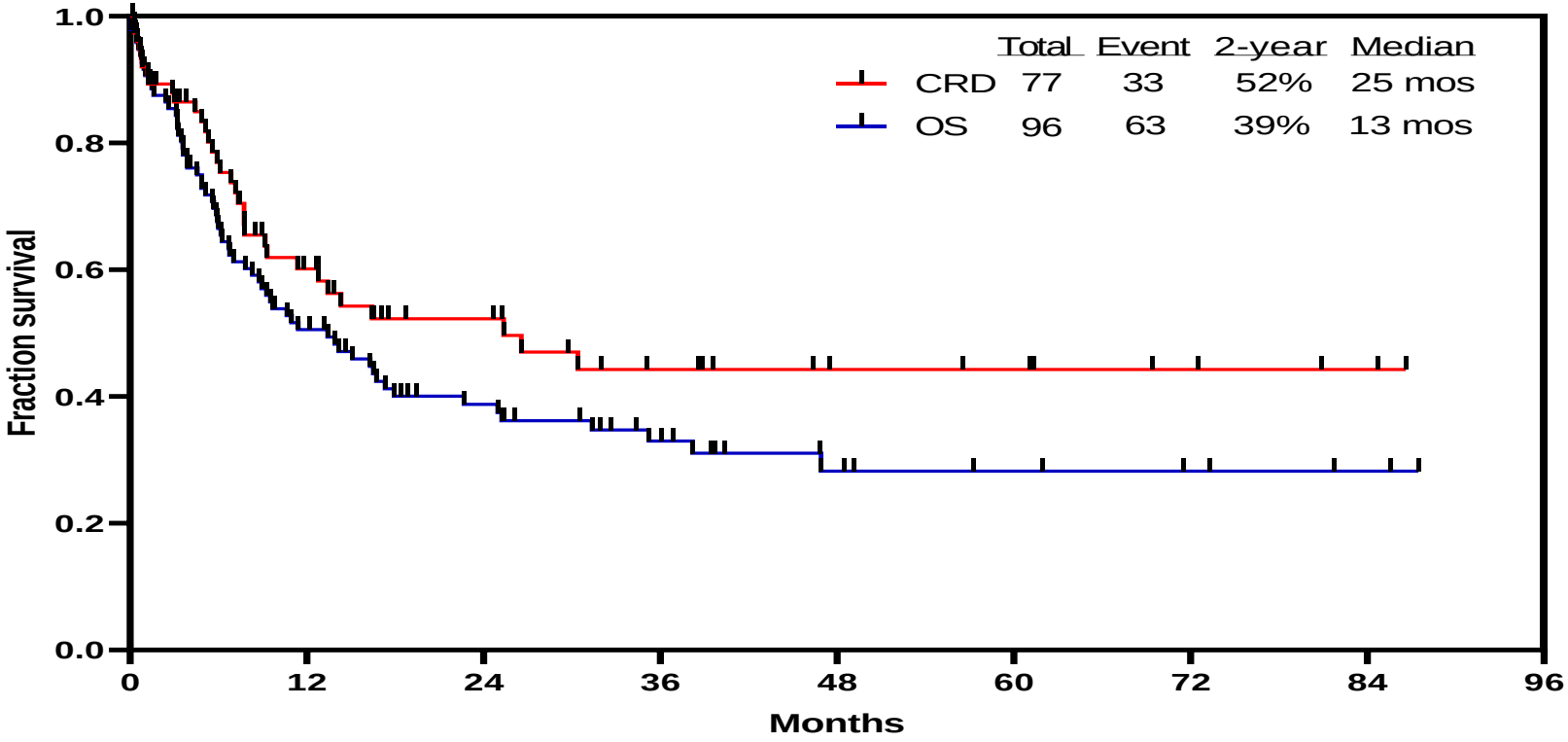
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Sasaki K, et al. *Blood.* 2018;132:abstract 553.

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

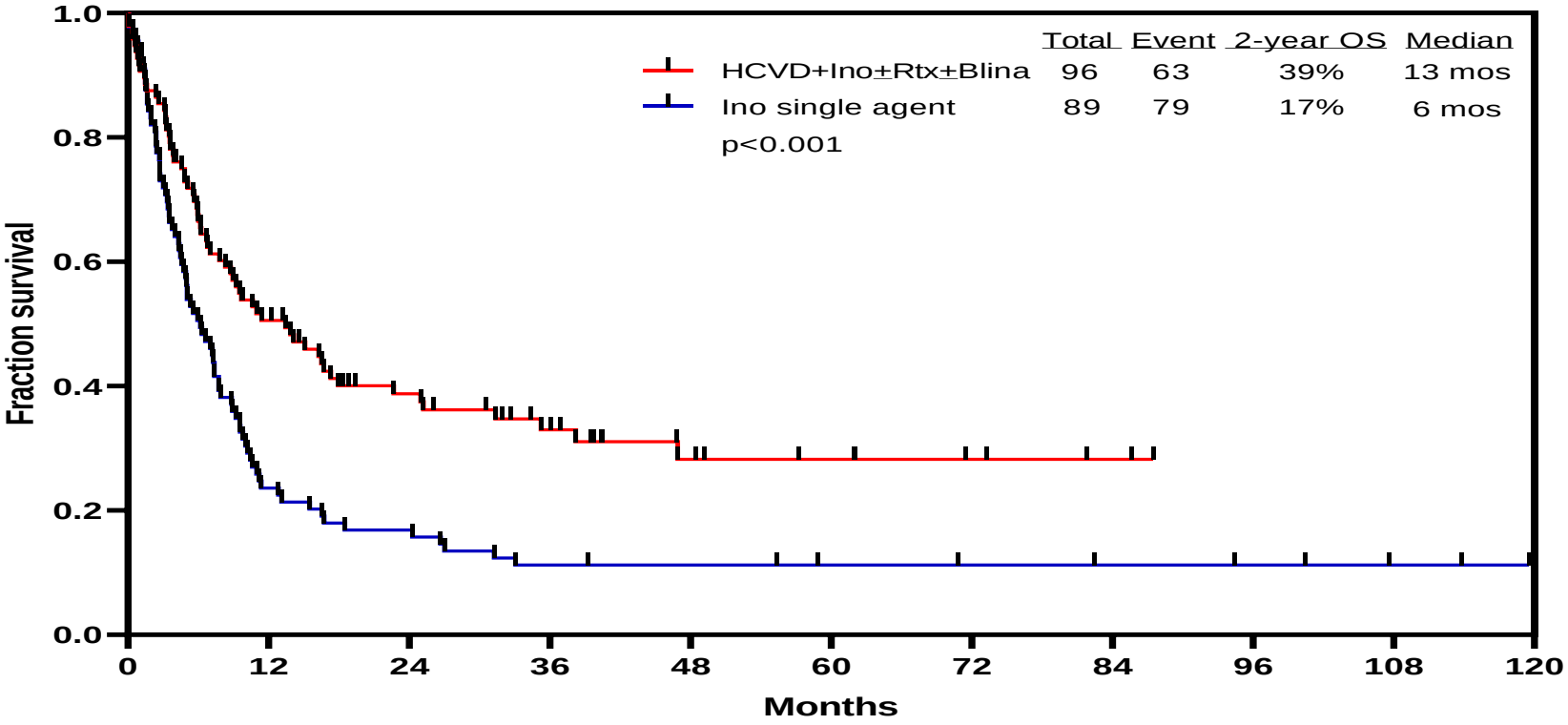
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055.

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



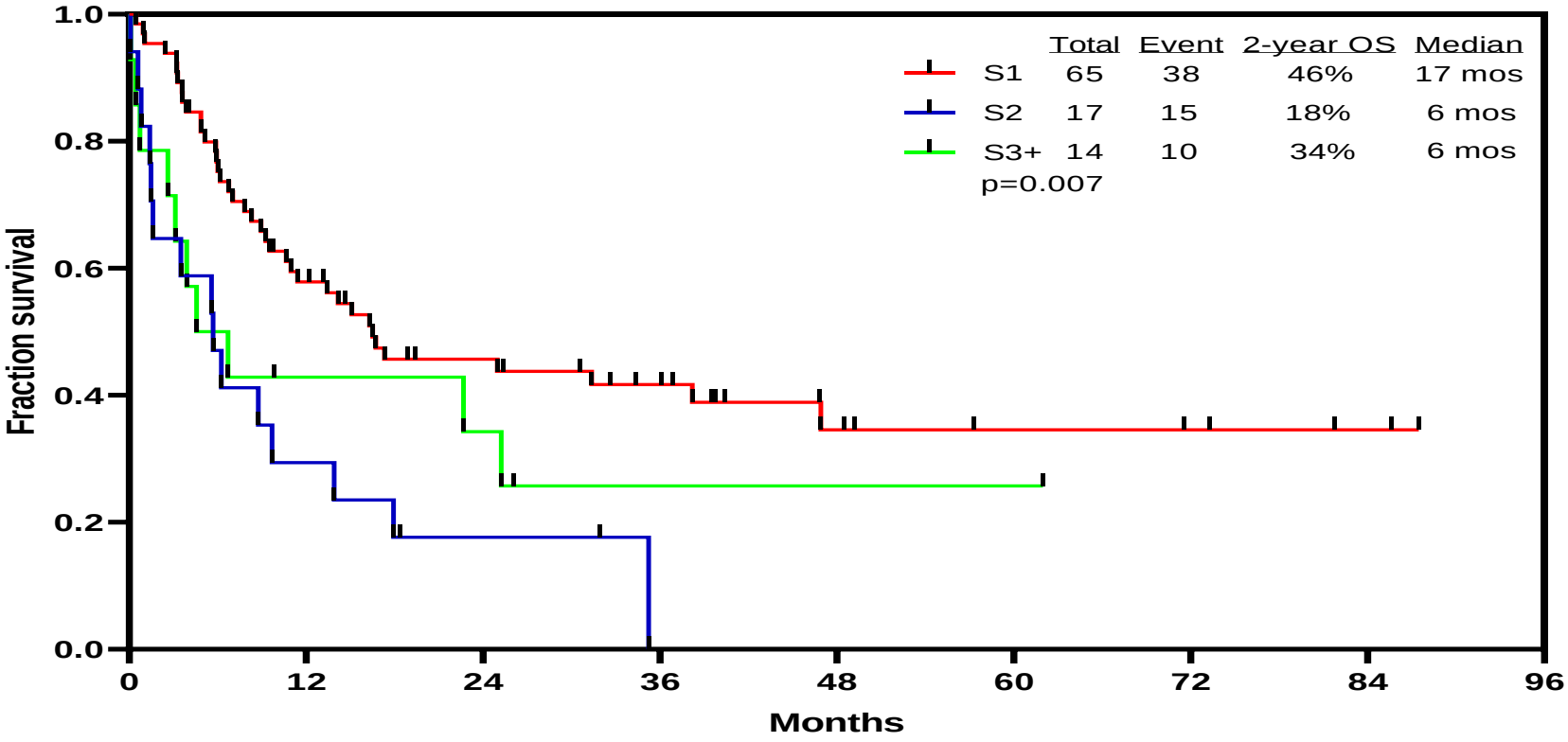
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Sasaki K, et al. *Blood.* 2018;132(suppl):553.

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

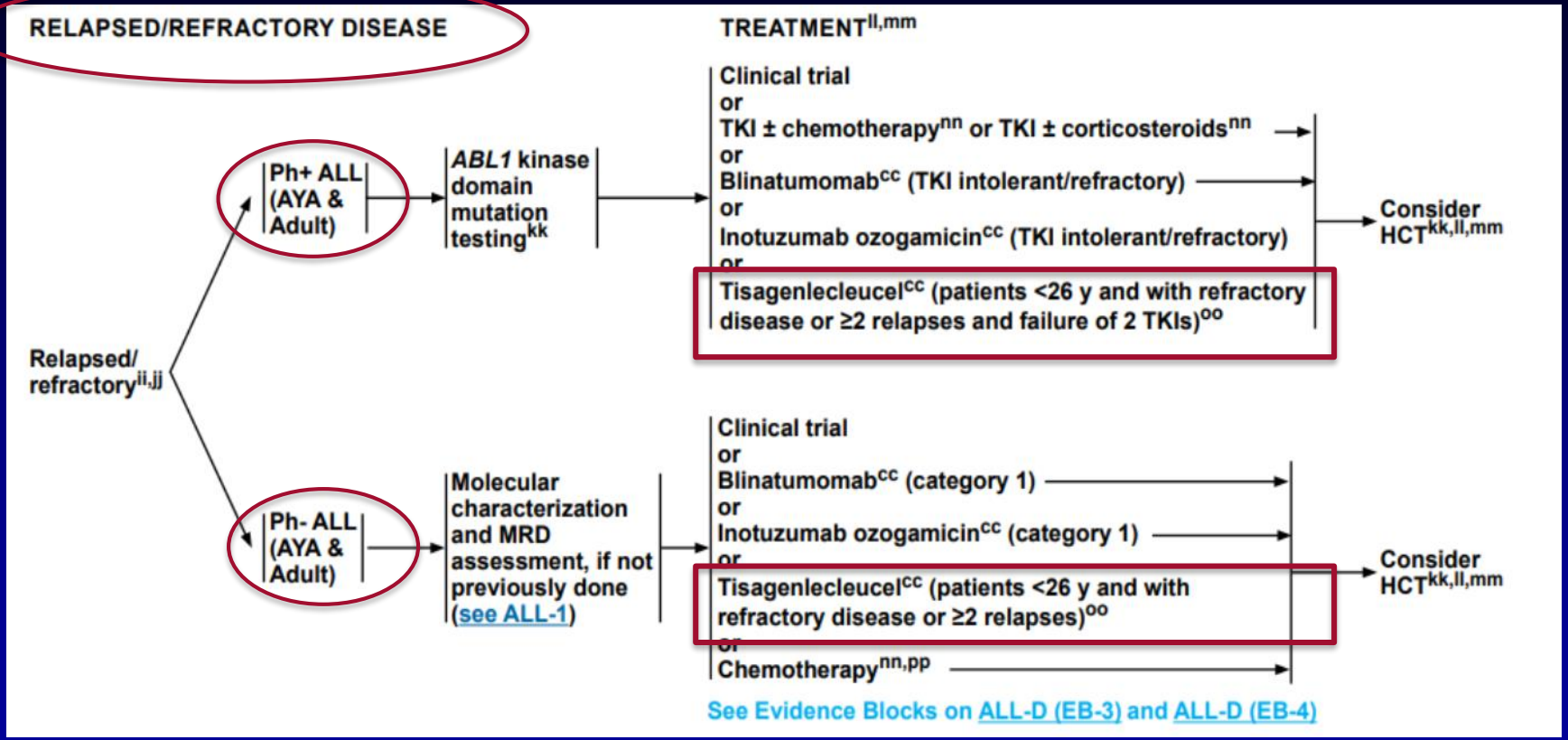


Sasaki. *Blood.* 2018;132:abstract 553; Jabbour E. *JAMA Oncol.* 2018;4:230.

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%)

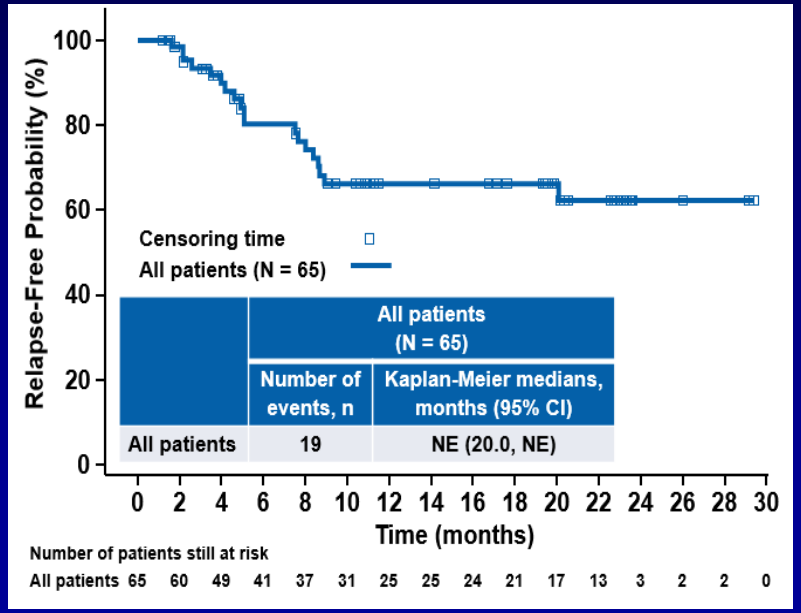
Where Does CAR T-Cell Therapy Stand?

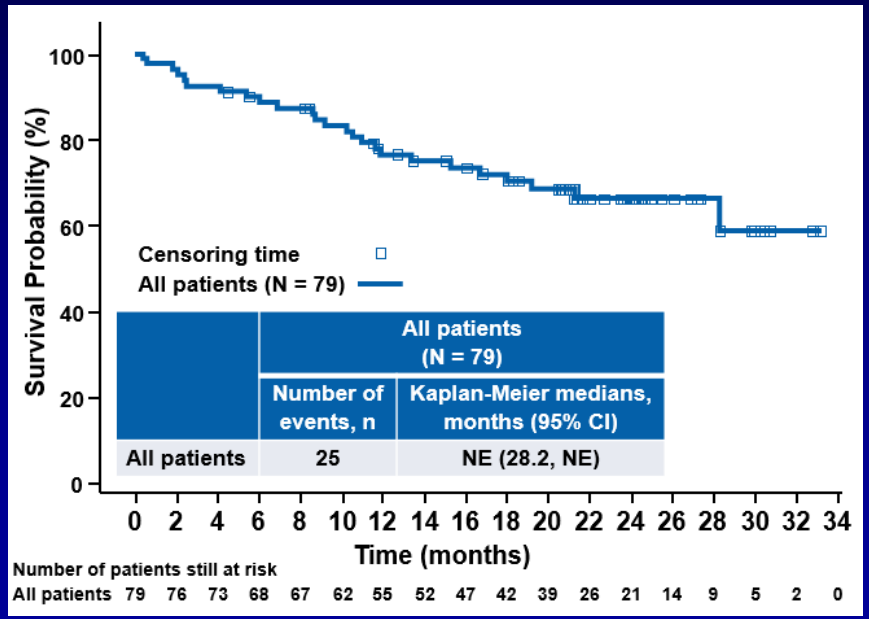


NCCN Guidelines ALL version 1.2020: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

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%. Grade 3–4 CRS 49%. ICU 48%

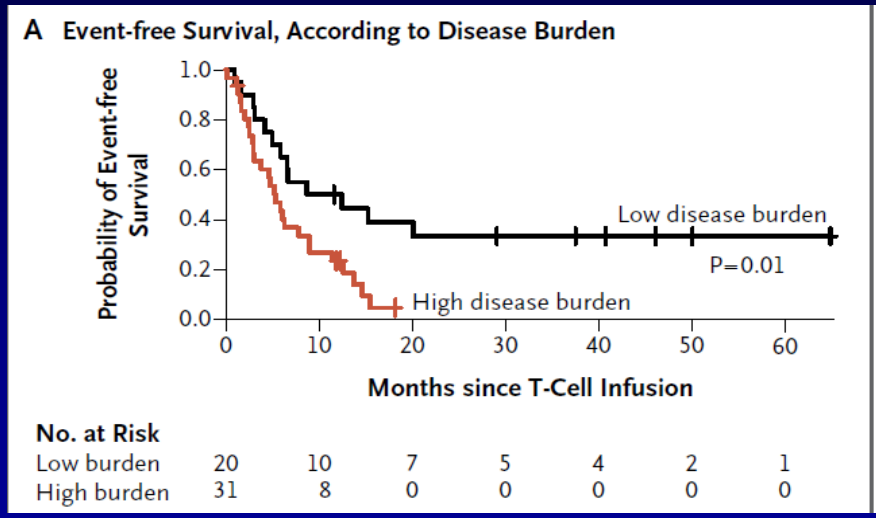


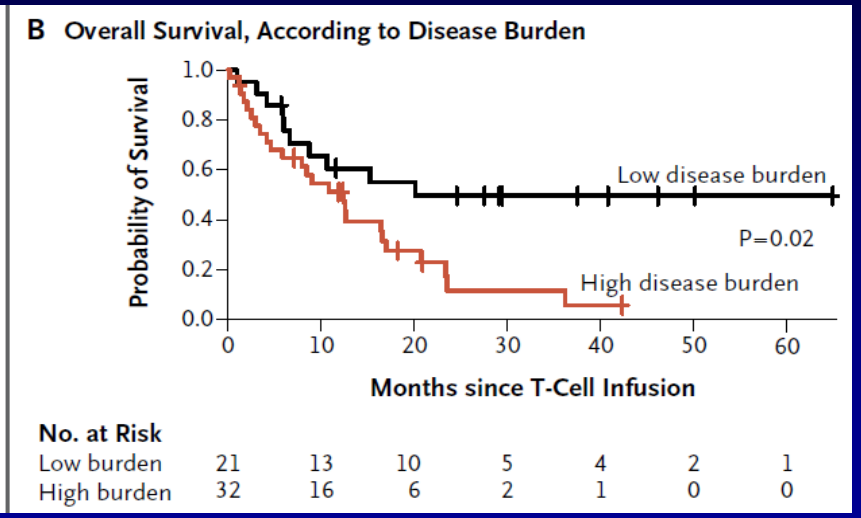


Grupp. EHA 2019. Abstract S1618.

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®

Q

Question 1

EM: postdiscussion questions for this session: should be comparative

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

a) CAR T therapies

b) Monoclonal antibodies or bispecifics

Q

Question 2

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

a) Yes

b) No

c) I do not know

Q

Question 3

EM: postdiscussion questions for this session: should be comparative

What advantages do you see in bispecifics 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®

Q

Question 1

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

a) No, I am seeing about the same number of new cancer patients per month

b) Yes, I am seeing fewer new cancer patients per month

c) Yes, I am seeing more new cancer patients per month

Q

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?

a) Yes

b) 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, el at. *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 candidates 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		
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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.

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

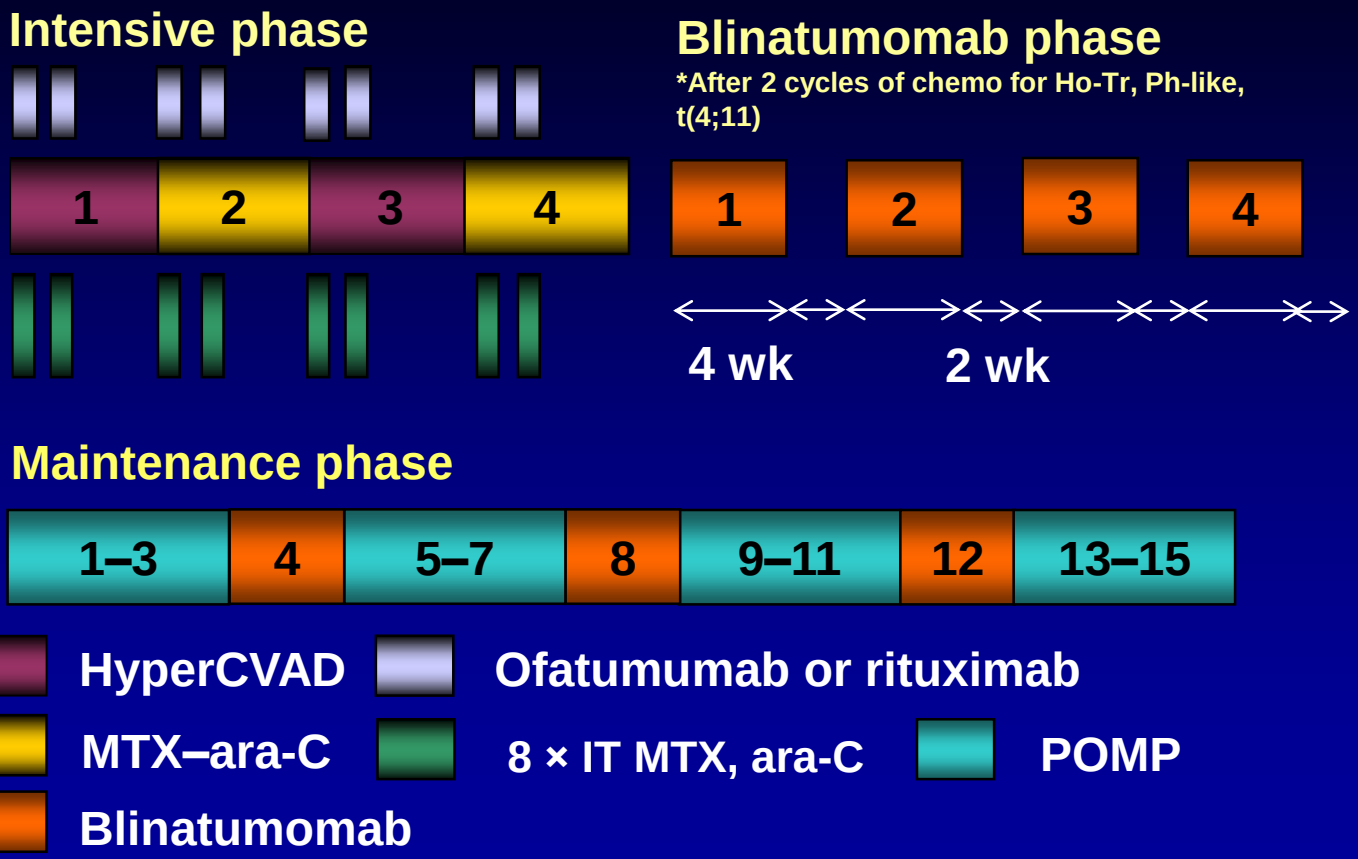
Treating ALL in the Time of COVID-19

Type				
ALL	Induction/ Consolidation	Ph–	<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+	• 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+		• 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.

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

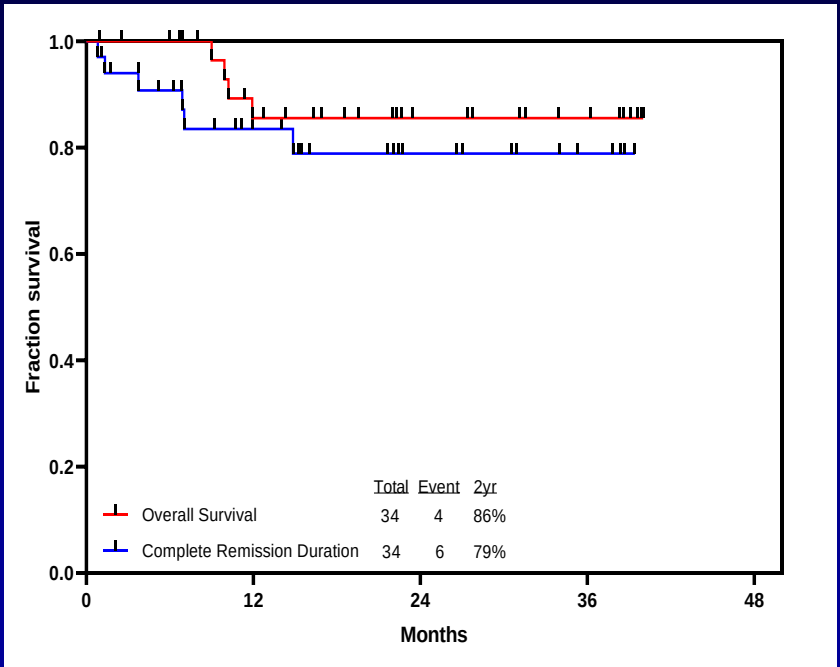


Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

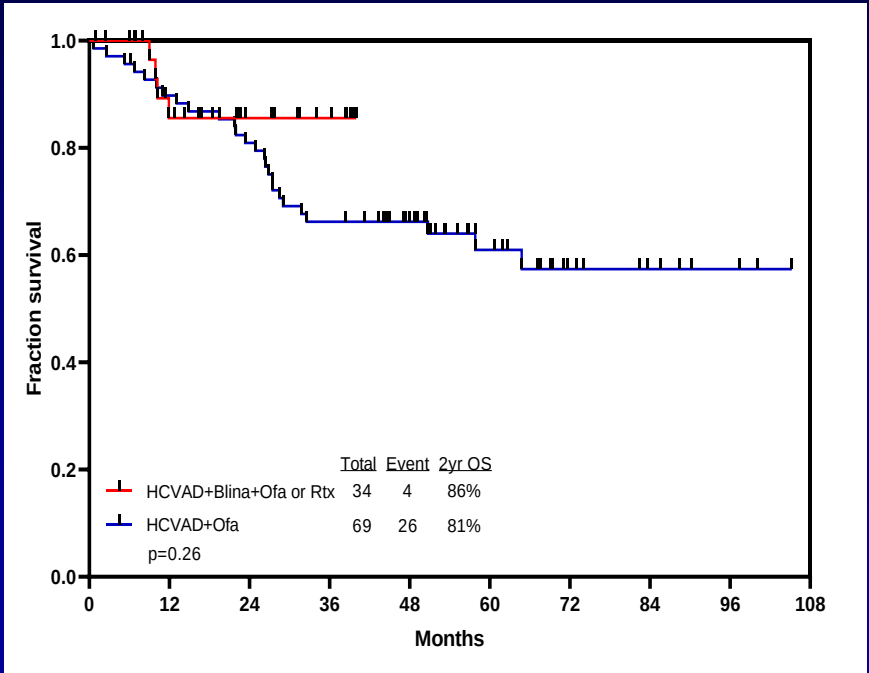
HyperCVAD + Blinatumomab in FL B-ALL (N = 34)

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

CRD and OS Overall

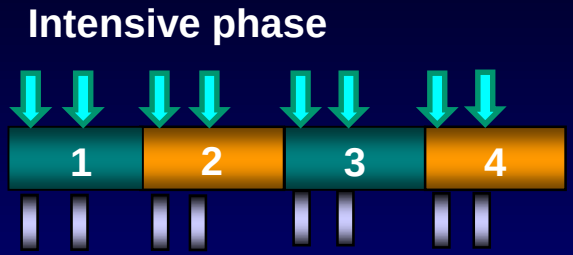


OS – HCVAD-Blina vs O-HCVAD



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)**

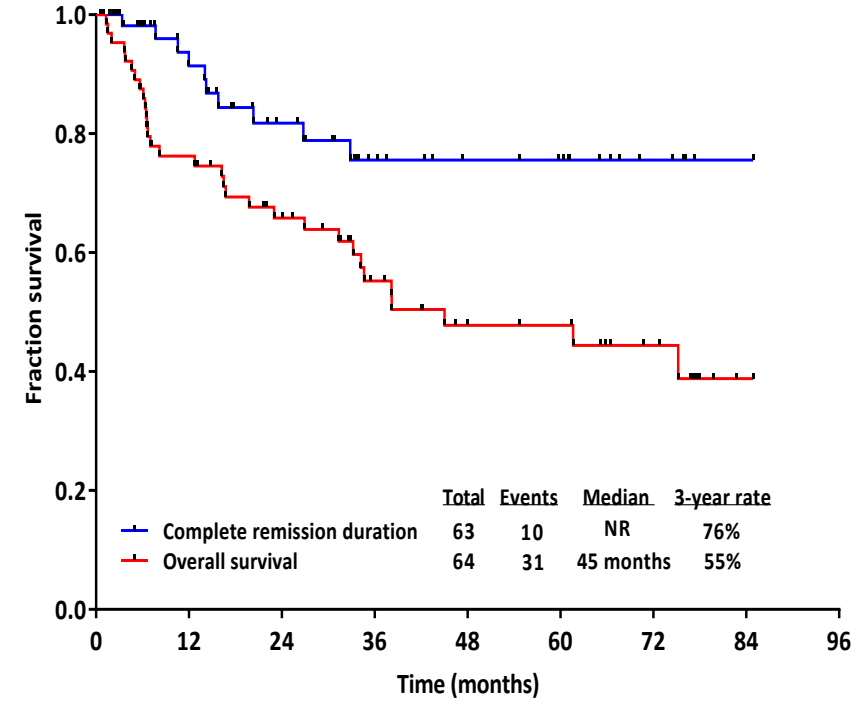
Response (N = 59)	N (%)
ORR	**58 (98)**
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	**0**

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

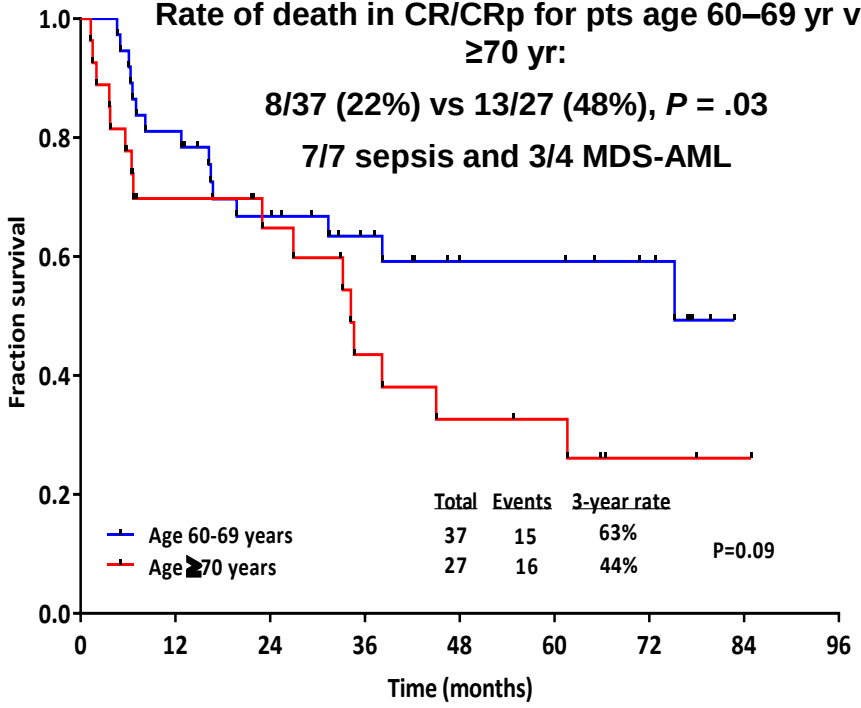
Short. *Blood.* 2019;134:abstract 823.

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

CRD and OS overall



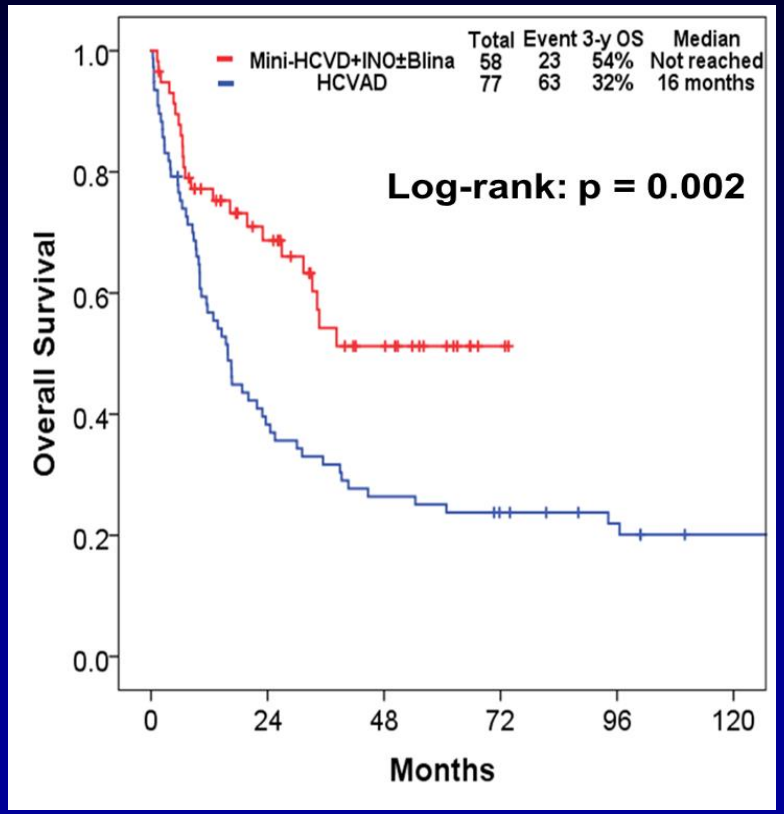
OS by age



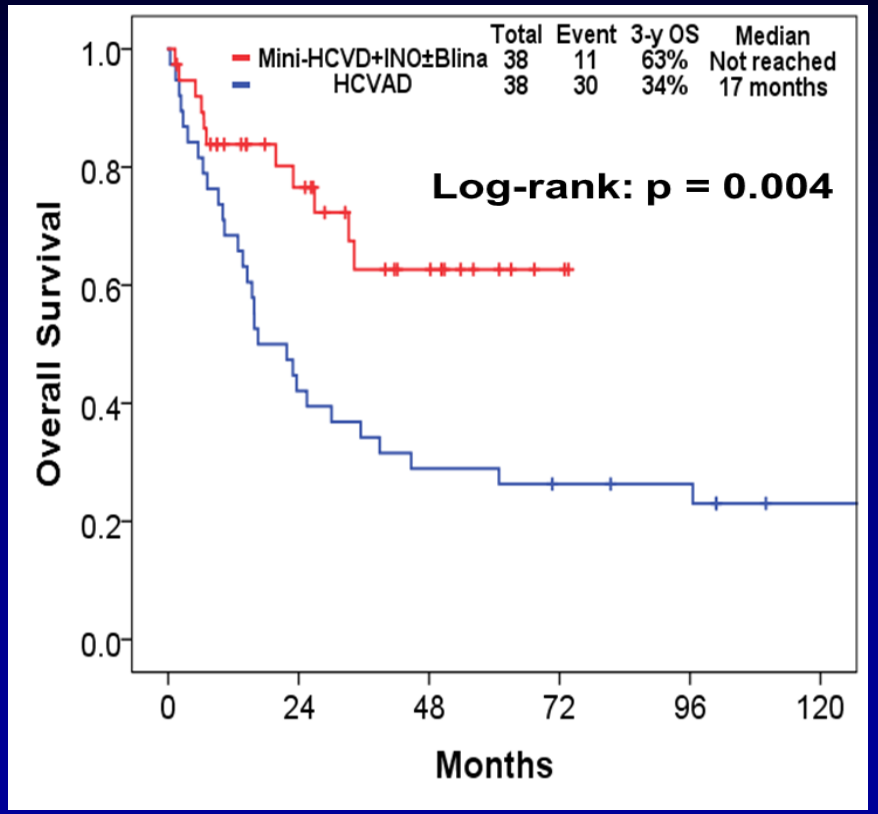
Short. *Blood.* 2019;134:abstract 823.

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

Prematched

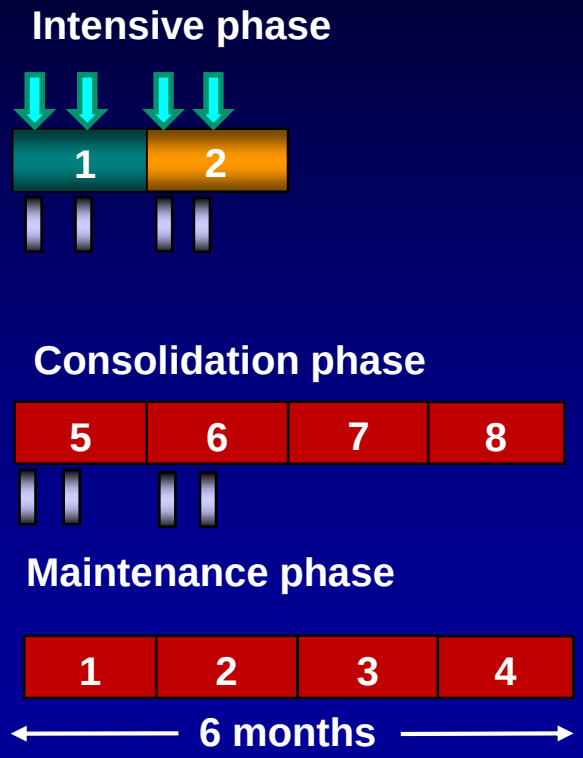


Matched



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

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



Mini-HCVD

Mini-MTX–cytarabine

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Blinatumomab

POMP

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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.

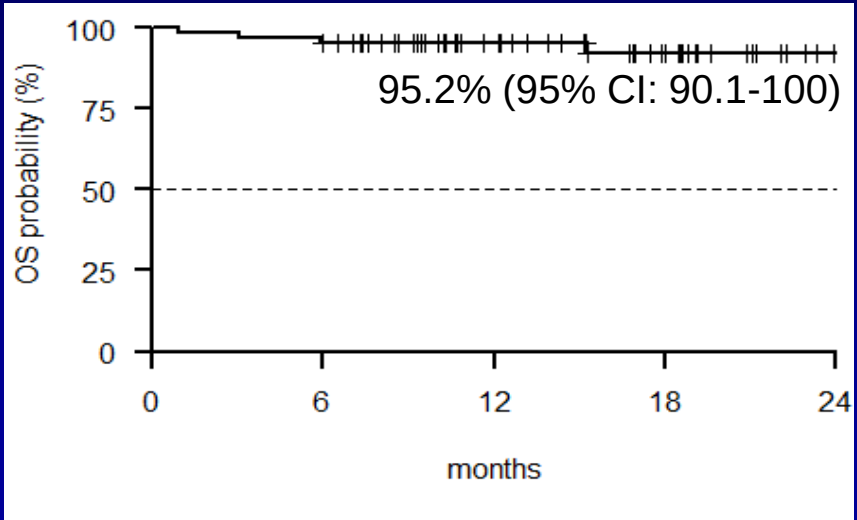
Treating ALL in the Time of COVID-19: Advantage of These Regimens

- 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

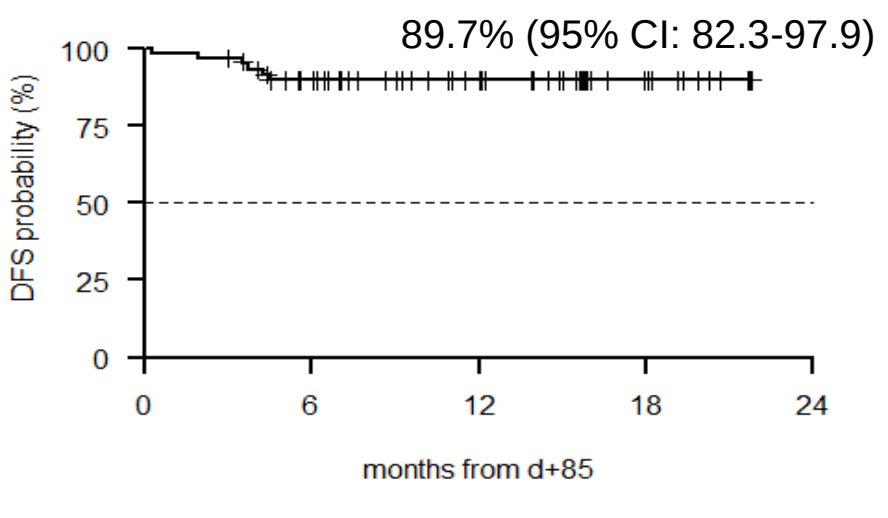
Dasatinib-Blinatumomab in Ph+ ALL

- 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

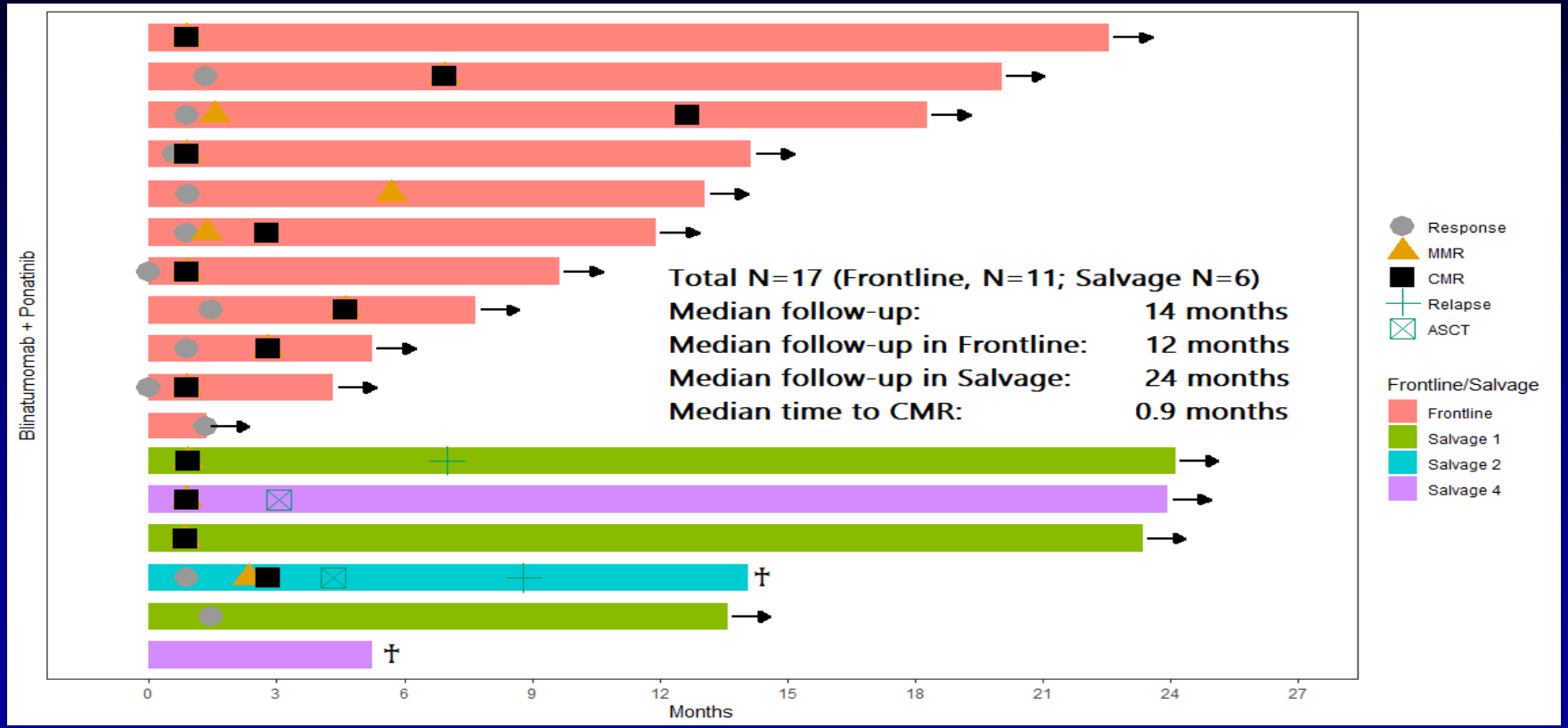


DFS



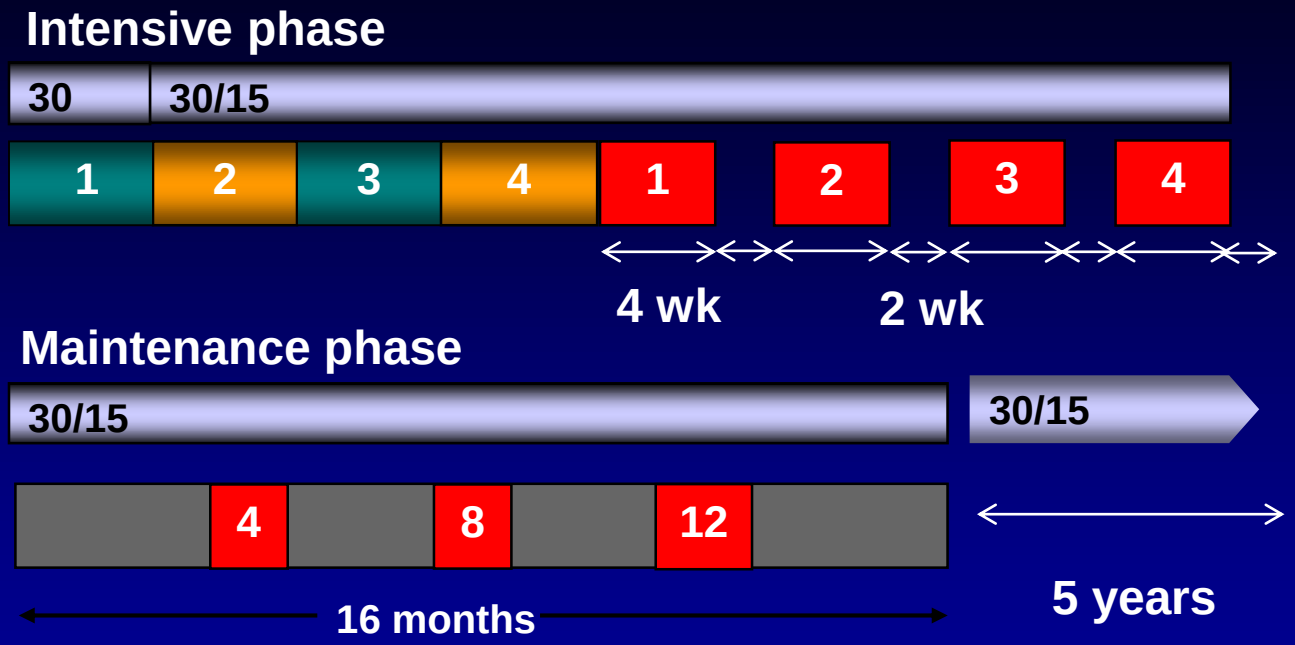
Chiaretti. *Blood.* 2019;134:abstract 615.

Blinatumomab + Ponatinib Swimmer Plot (N = 17)



Personal communication from Dr Jabbour.

HyperCVD + Ponatinib + Blinatumomab in Ph+ ALL



Risk-adapted intrathecal CNS prophylaxis (N = 12)

Mini-hyperCVD

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 Eduardo Rego

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Closing Remarks

Elias Jabbour and Eduardo Rego

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Emerging and Practical Concepts and Controversies in Leukemias

THANK YOU FOR YOUR PARTICIPATION!

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