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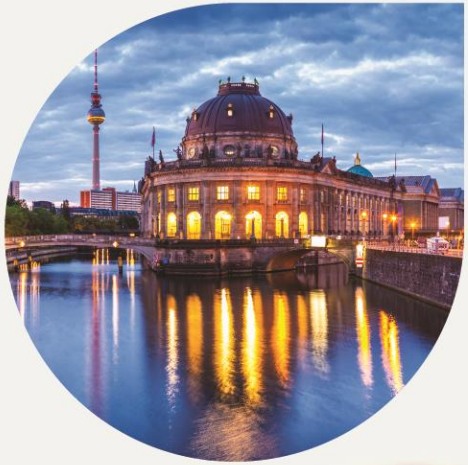

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

23–24 October 2020

APTITUDE HEALTH

Global Leukemia Academy

Welcome and meeting overview

Elias Jabbour and Franco Locatelli

APTITUDE HEALTH

Meeting co-chairs

Elias Jabbour, MD
University of Texas MD Anderson Cancer Center
Houston, TX, USA

Franco Locatelli, MD, PhD
University of Rome, IRCCS Ospedale Pediatrico
Bambino Gesù, Italy

Faculty

Rob Pieters, MD, PhD
Princess Máxima Center for Pediatric Oncology
University of Utrecht, The Netherlands

Josep Ribera, MD
Catalan Institute of Oncology
University Hospital Germans Triasi Pujol
Badalona, Spain

Philippe Rousselot, MD, PhD
University of Versailles
Saint-Quentin-en-Yvelines, France

Dieter Hoelzer, MD, PhD
University of Frankfurt, Germany

Patrick Brown, MD
Johns Hopkins University
Baltimore, MD, USA

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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
- Explore the impact of COVID-19 on current patient treatment

Virtual plenary sessions (Day 1)

Time CET	Title	Speaker/Moderator
16.00 – 16.10	**Welcome and meeting overview**	Elias Jabbour, Franco Locatelli
16.10 – 16.25	**Review of prognostic value of MRD in ALL**	Elias Jabbour
16.25 – 16.40	**How and when to check for MRD in ALL, including CR1 and CR2**	Josep-Maria Ribera
16.40 – 16.55	**Genetic variants in ALL – Ph+ and Ph-like**	Philippe Rousselot
16.55 – 17.15	**AYA ALL patients – what is the current treatment approach for this diverse patient population?**	*Moderator*: Franco Locatelli *Presenter*: Rob Pieters
17.15 – 17.40	**Bispecific T-cell engagers as post-reinduction therapy improves survival in pediatric and AYA B-ALL**	*Moderator:* Franco Locatelli *Presenter*: Patrick Brown
17.40 – 18.00	**Break**	
18.00 – 18.45	**Panel discussion on the role of HSCT** • Pros and cons of transplantation (10 min) • Role of transplant in MRD+ population (10 min) • Discussion and voting (25 min)	*Moderator*: Elias Jabbour *Presenters:* Patrick Brown Josep-Maria Ribera *All faculty*
18.45 – 19.25	**Debate on CD19-targeted approaches** • CAR T (10 min) • Bispecifics (10 min) • Discussion and voting (20 min)	*Moderator*: Franco Locatelli *Presenters:* Josep-Maria Ribera Elias Jabbour *All faculty*
19.25 – 19.55	**Emerging data and the management of ALL patients during COVID-19** • Presentation (10 min) • Panel discussion (20 min)	*Moderator*: Franco Locatelli *Presenter:* Elias Jabbour *All faculty*
19.55 – 20.00	**Session close**	Elias Jabbour, Franco Locatelli

Virtual breakout – adult ALL patients (Day 2)

Time CET	Title	Speaker
18.00 – 18.15	**Session open** • Educational ARS questions for the audience	Elias Jabbour
18.15 – 18.35	**Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens** • Presentation (15 min) • Q&A (5 min)	Elias Jabbour
18.35 – 18.55	**Current treatment options for relapsed ALL in adult and elderly patients** • Presentation (15 min) • Q&A (5 min)	Dieter Hoelzer
18.55 – 19.45	**Case-based panel discussion** • **Management of long- and short-term toxicities and treatment selection in adult and elderly patients** – Case 1 (15 min) – Case 2 (15 min) – Discussion (20 min)	*Case 1*: Philippe Rousselot *Case 2*: Josep-Maria Ribera *Faculty panel*: E. Jabbour, D. Hoelzer, J.M. Ribera, P. Rousselot
19.45 – 20.00	**Session close** • Educational ARS questions for the audience	Elias Jabbour

Virtual breakout – pediatric ALL patients (Day 2)

Time CET	Title	Speaker
18.00 – 18.15	**Session open** • Educational ARS questions for the audience	Franco Locatelli
18.15 – 18.45	**First-line treatment of pediatric ALL** • Presentation (15 min) • Q&A (15 min)	Rob Pieters
18.45 – 19.15	**Current treatment options for relapsed ALL in children, including HSCT and COVID-19 considerations** • Presentation (15 min) • Q&A (15 min)	Franco Locatelli
19.15 – 19.45	**Bispecific T-cell engagers for pediatric ALL** • Presentation (15 min) • Q&A (15 min)	Patrick Brown
19.45 – 20.15	**Case-based panel discussion** • **Management of long- and short-term toxicities and treatment selection in pediatric patients** – Overview of long-term toxicities (10 min) – Patient case presentation (10 min) – Discussion (10 min)	Rob Pieters Patrick Brown *Faculty panel:* R. Pieters, F. Locatelli, P. Brown
20.15 – 20.30	**Session close** • Educational ARS questions for the audience	Franco Locatelli

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Introduction to the voting system

Elias Jabbour

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Question 1

Which languages do you speak? (multiple-choice)

a) English
b) German
c) Spanish
d) French
e) Russian
f) Mandarin
g) Arabic

Question 2

How many patients with ALL are you currently following?

a) 0
b) 1–5
c) 6–15
d) 16–20
e) ≥21

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

APTITUDE HEALTH

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

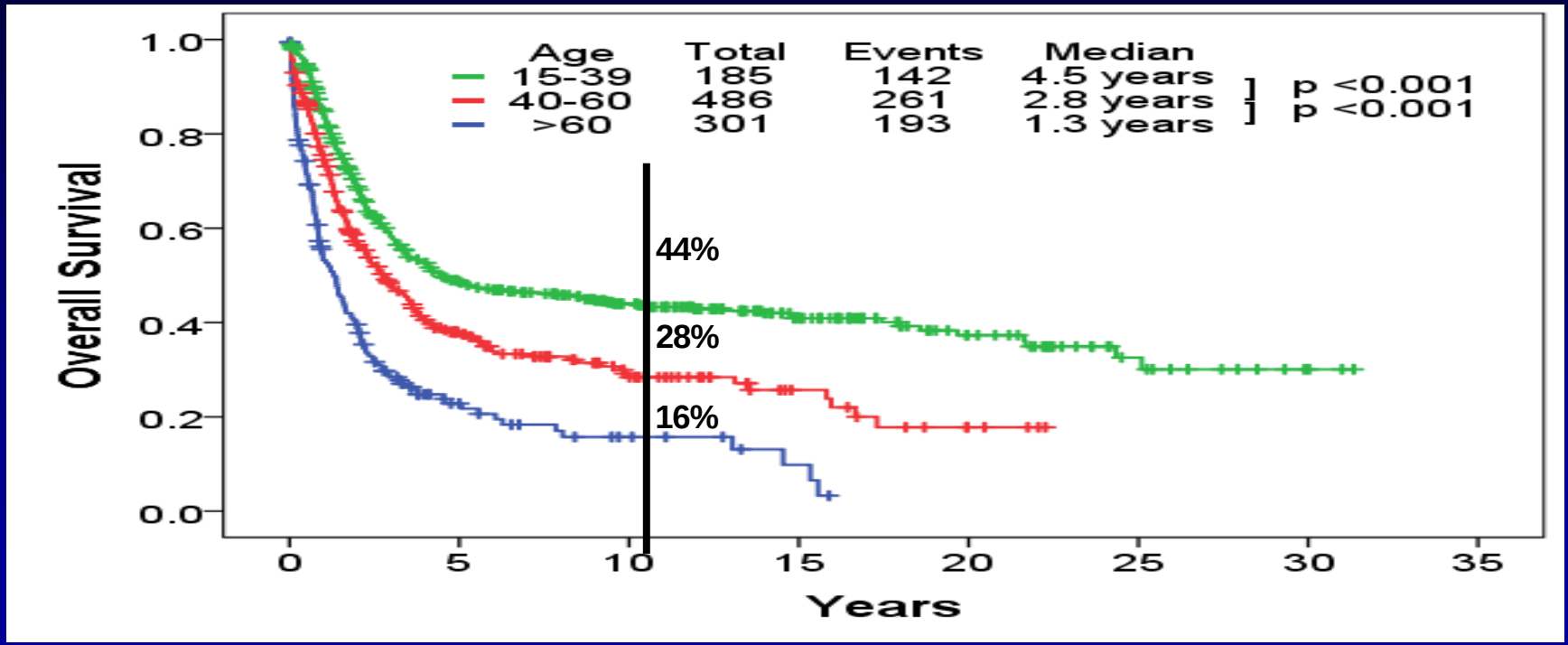
Autumn 2020

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

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

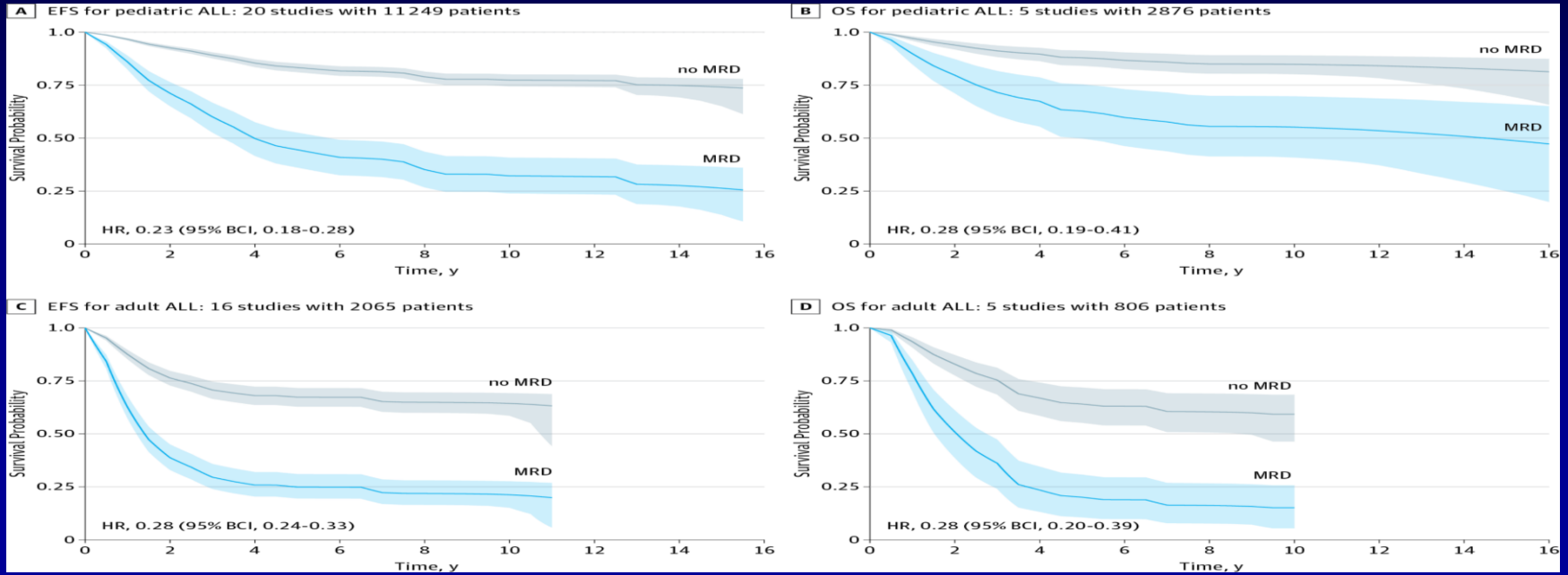
Treatment of ALL Before the MRD Era: High CR Rates but Relapse Is Common

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

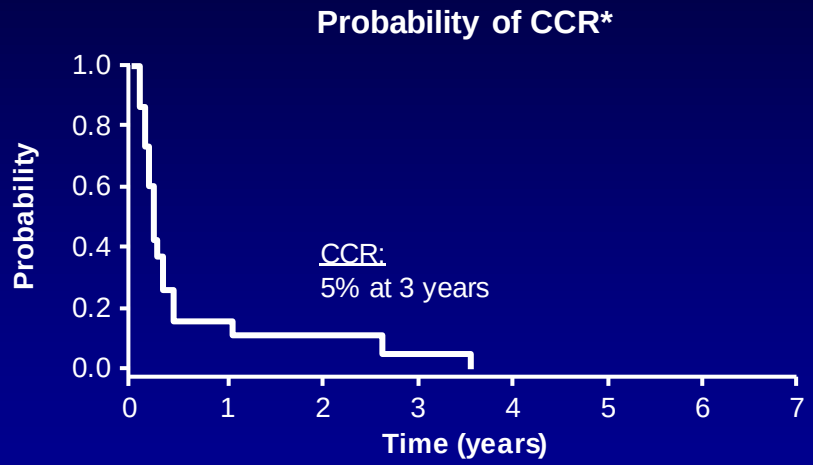
- Meta-analysis of 39 studies (pediatric and adult), including 13,637 patients with all subtypes
- Prognostic impact of MRD clearance consistent across therapies, MRD method, timing, level of cutoff, and subtypes

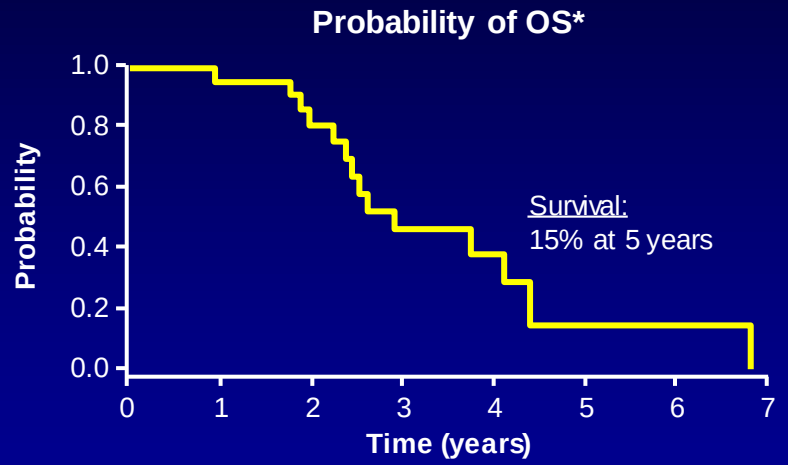


Berry DA. *JAMA Oncol.* 2017;3(7):e170580.

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.

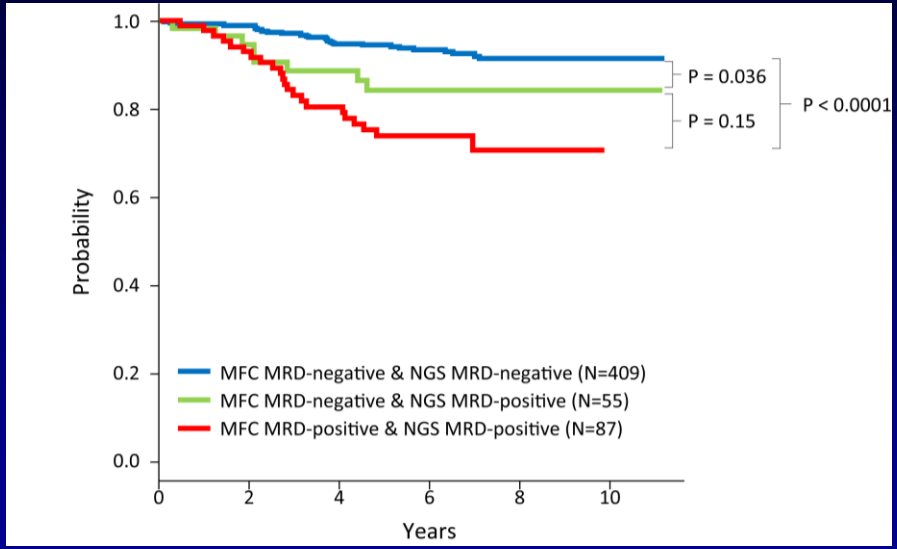
MRD Methods

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})



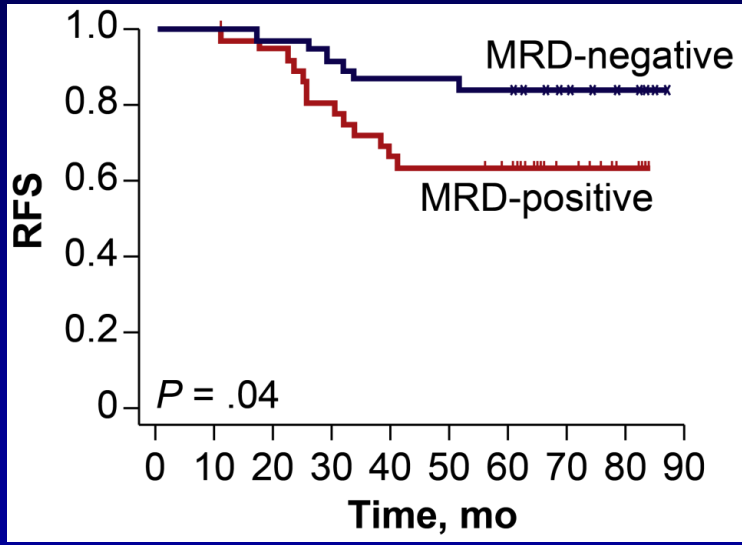
EFS was significantly worse in the NGS MRD+/flow cytometry MRD– group than patients who were MRD– by both methods (*P* = .036).
Six patients were identified as NGS MRD– and MFC MRD+.

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

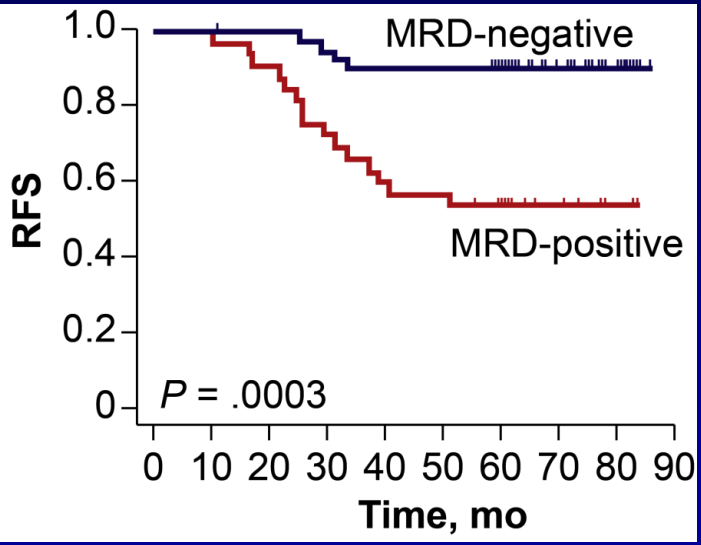
Comparison: NGS With RQ-PCR

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

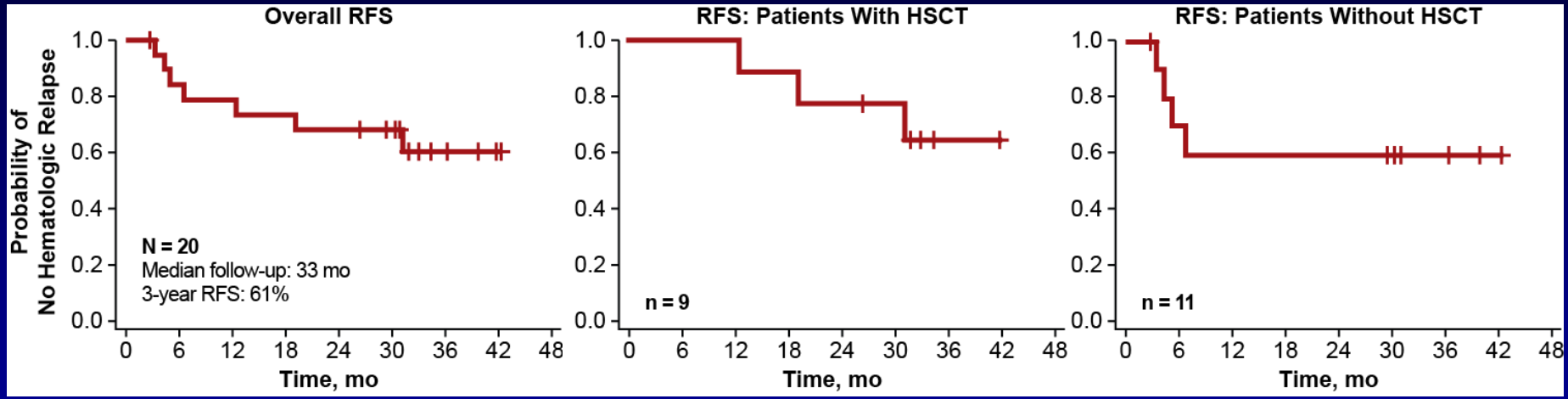
Postremission Rx of ALL According to FCM MRD

- 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.

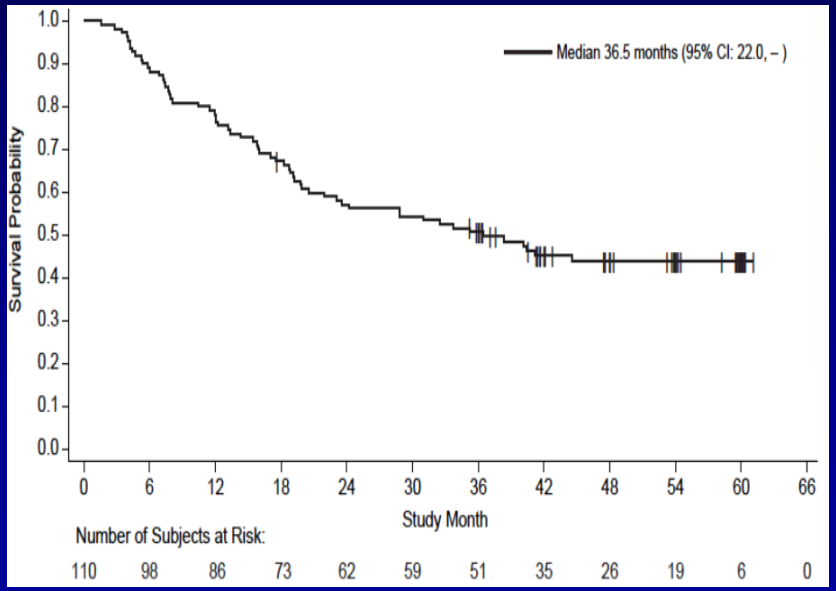
Blinatumomab in MRD+ BCP-ALL: MT103-202 Trial

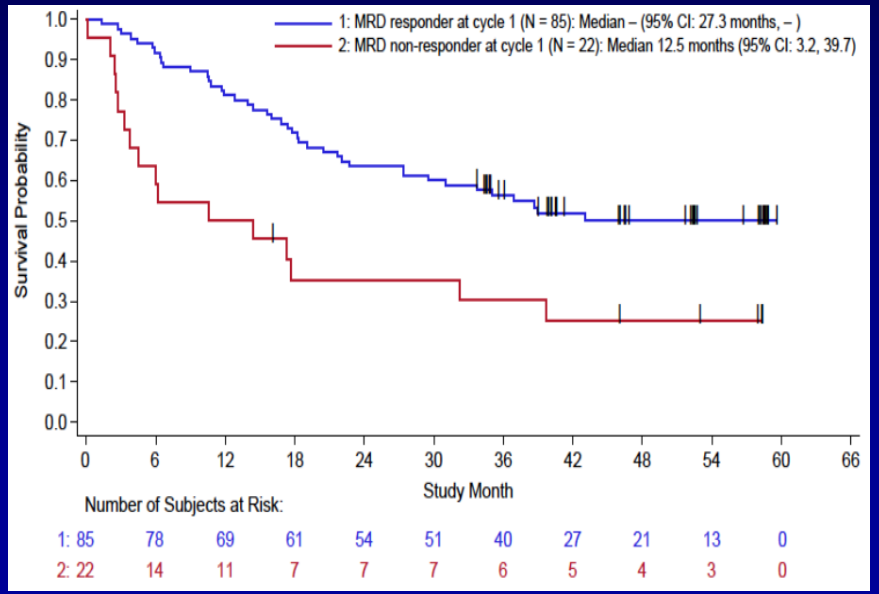


Topp MS, et al. *Blood*. 2012;120:5185-5187.

Blinatumomab for MRD+ ALL in CR1/CR2

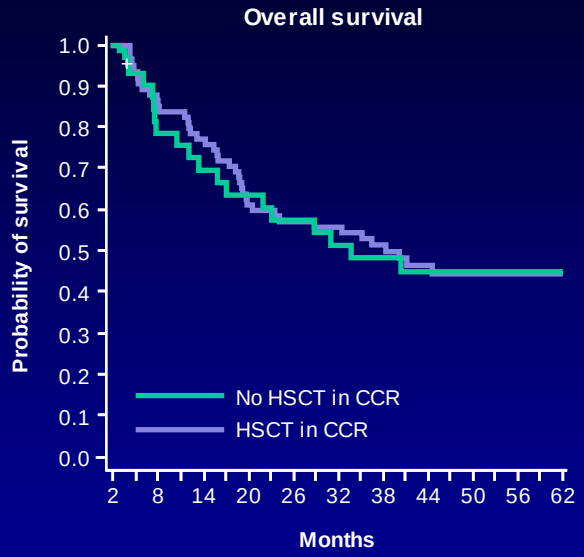
- 113 pts Rx. Post-blina **MRD– 88/113 = 78%**
- 110 evaluated (blasts <5%, MRD+); 74 received alloSCT. Median FU 53 mo
- Median OS 36.5 mo; **4-yr OS 45%; 4-yr OS if MRD– 52%**
- Continuous CR 30/74 post-alloSCT (40%); 12/36 without SCT (33%)

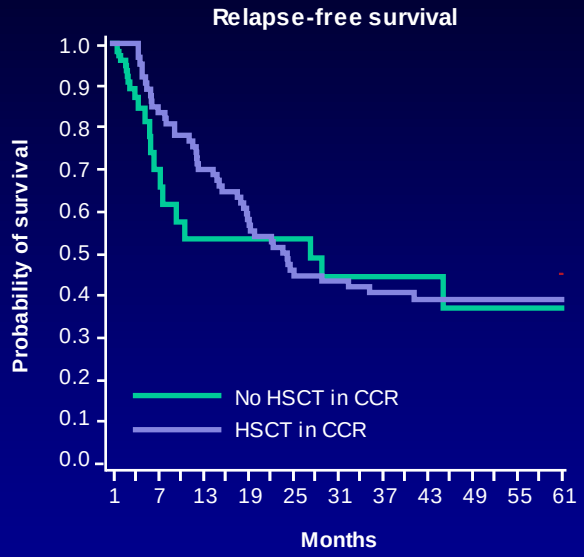


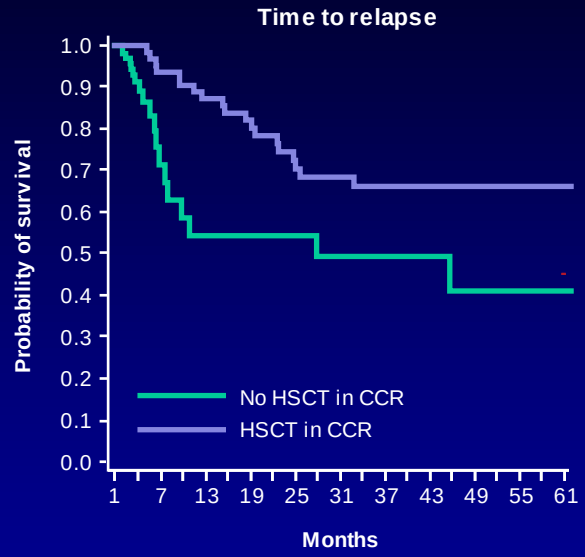


Goekbuget N, et al. *Blood.* 2018;132:abstract 554.

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

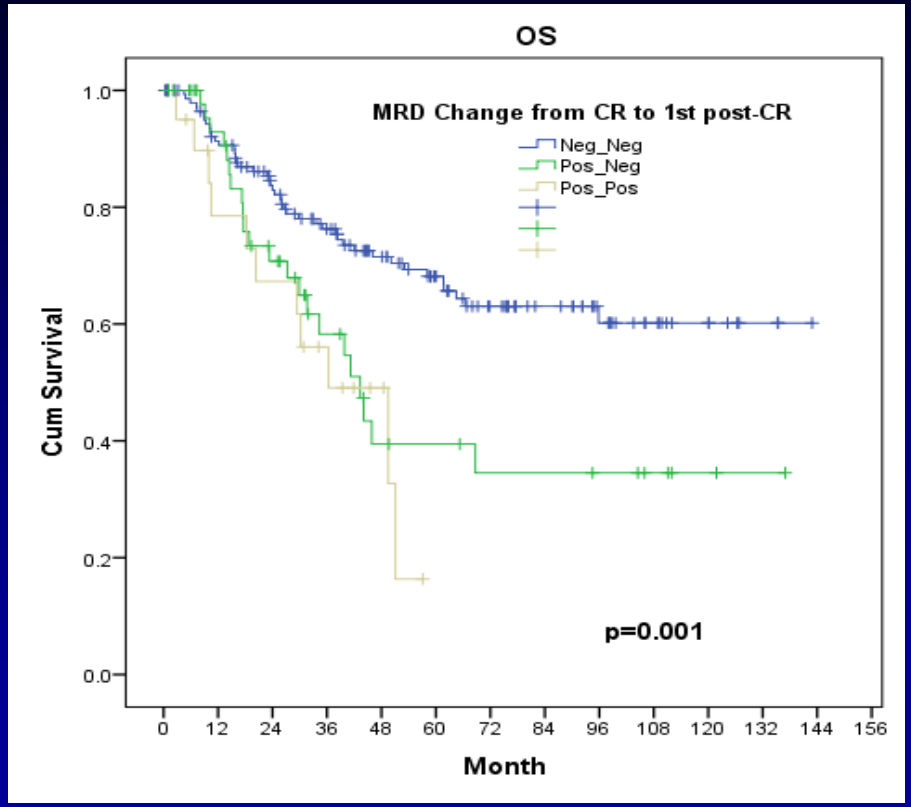
Non-HSCT	101	16	12	12	11	10	8	6	5	5	0
HSCT	2	61	53	42	34	33	25	19	14	7	0

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.

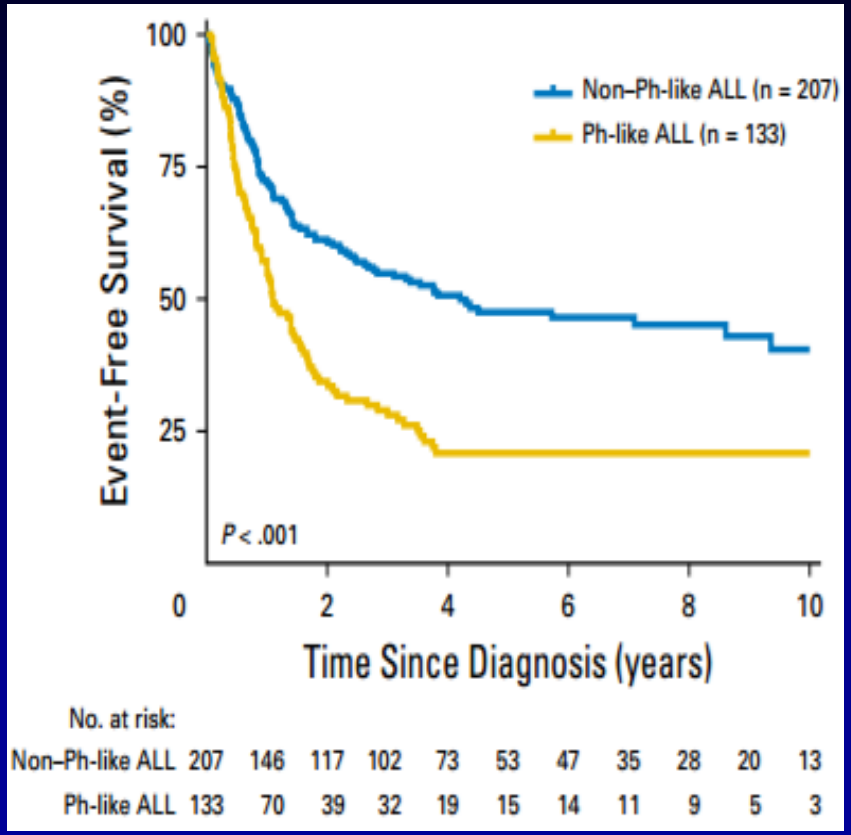
Dynamics of MRD: Outcome

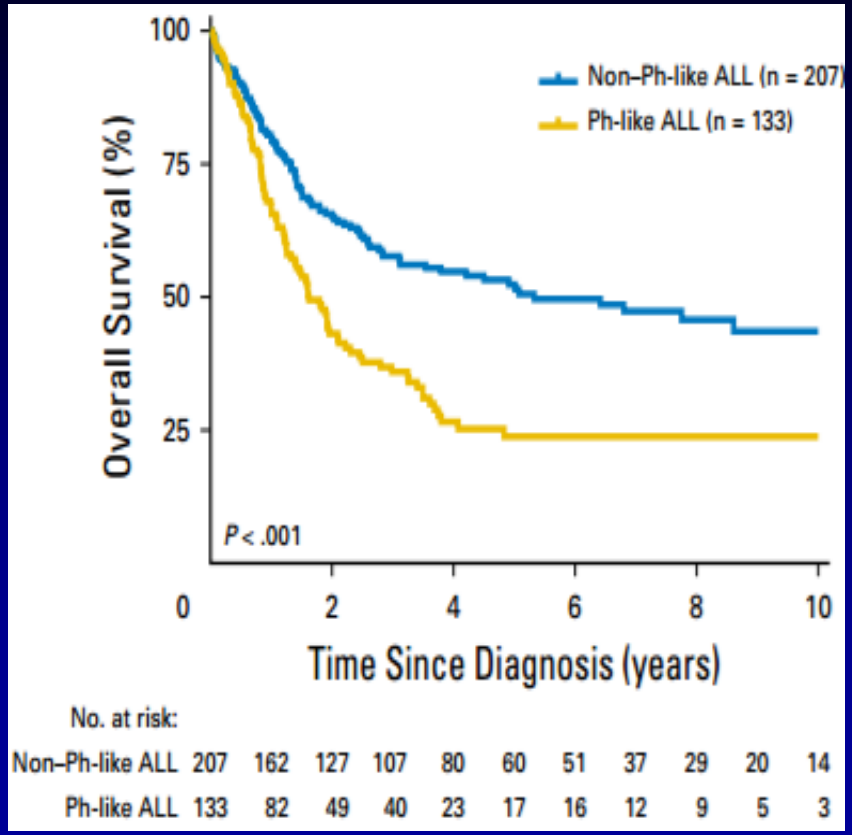
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA



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

Ph-Like ALL: Survival and EFS





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

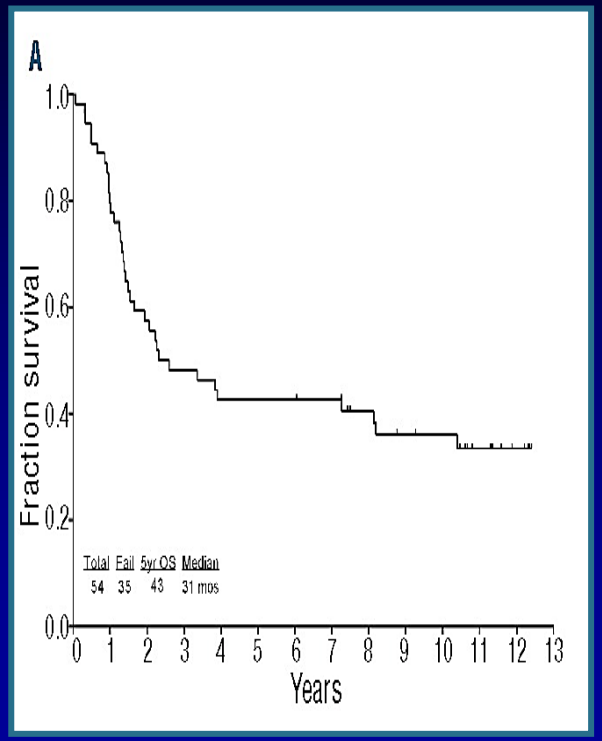
Ph-Like ALL: Higher MRD+ Rate

	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)	

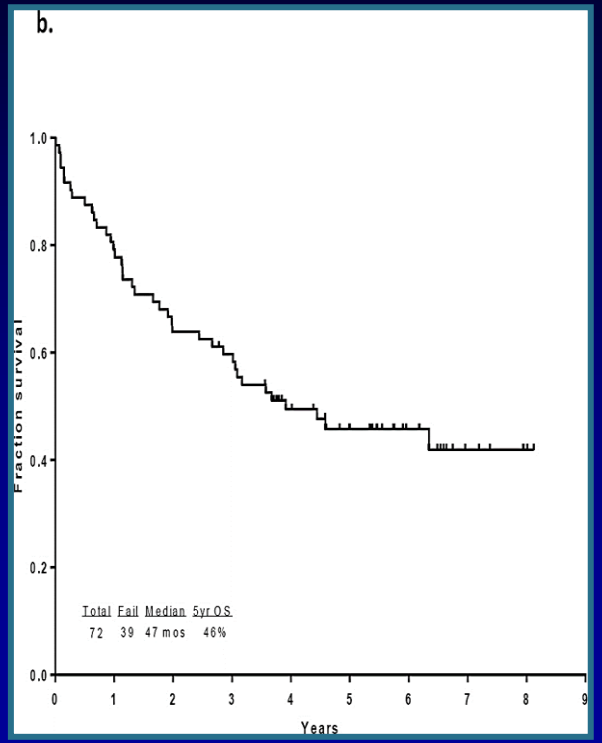
Jain. *Blood.* 2017;129:572-581.

TKI for Ph+ ALL

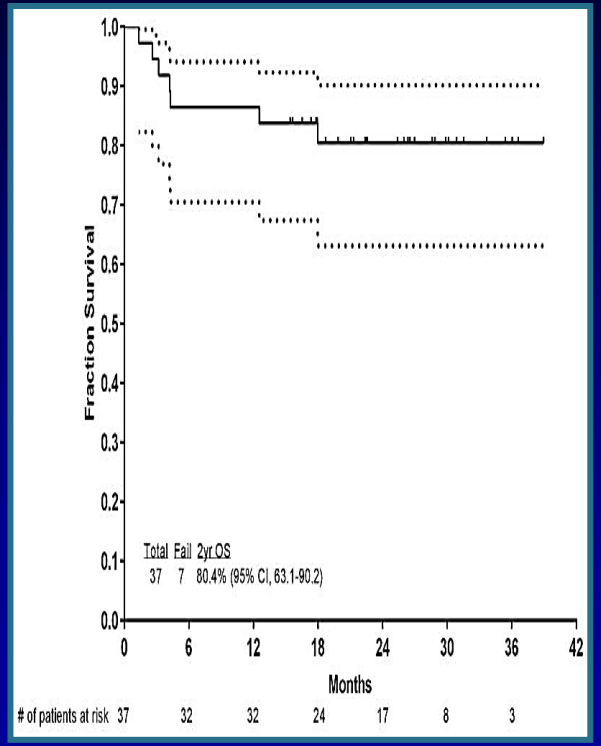
Imatinib: 5-yr OS = 43%



Dasatinib: 5-yr OS = 46%



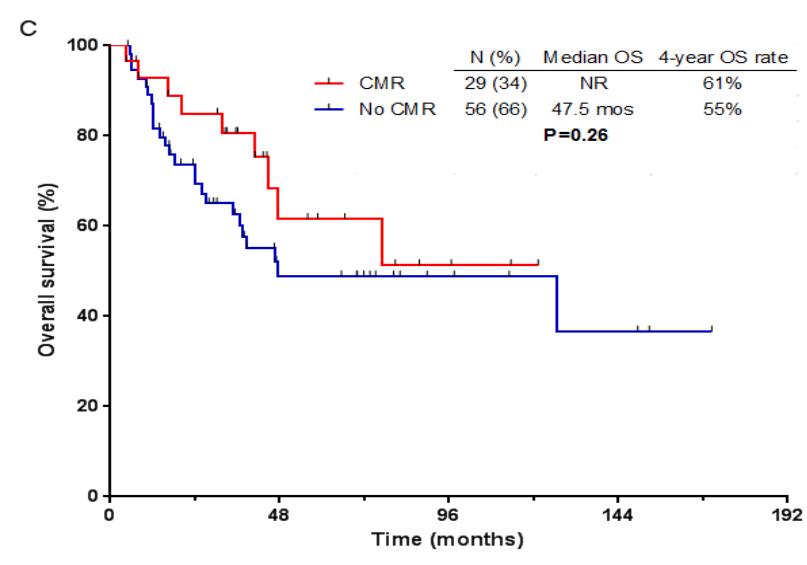
Ponatinib: 5-yr OS = 71%



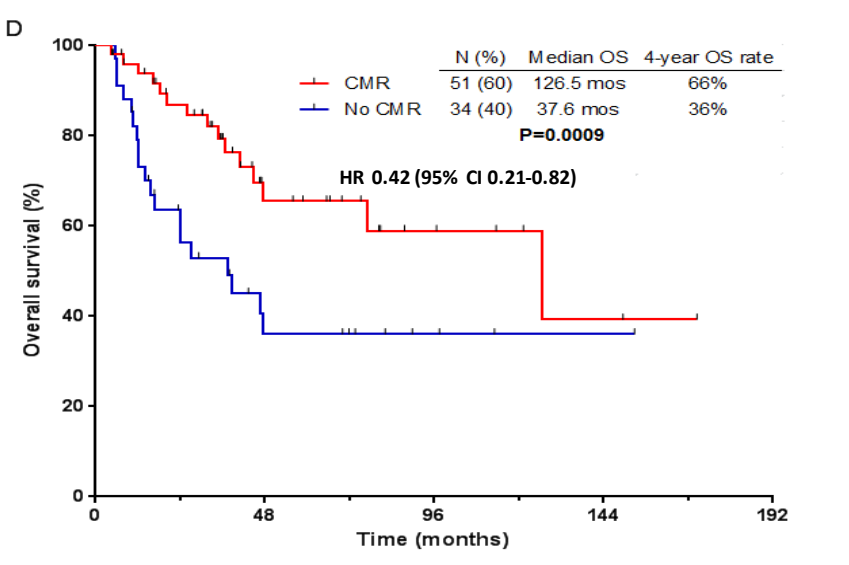
Daver. *Haematologica*. 2015; Ravandi. *Cancer*. 2015; Jabbour. *Lancet Oncol*. 2015; Jabbour. *Lancet Hematol*. 2018.

CMR in Ph+ ALL: OS for CMR vs Others

At CR



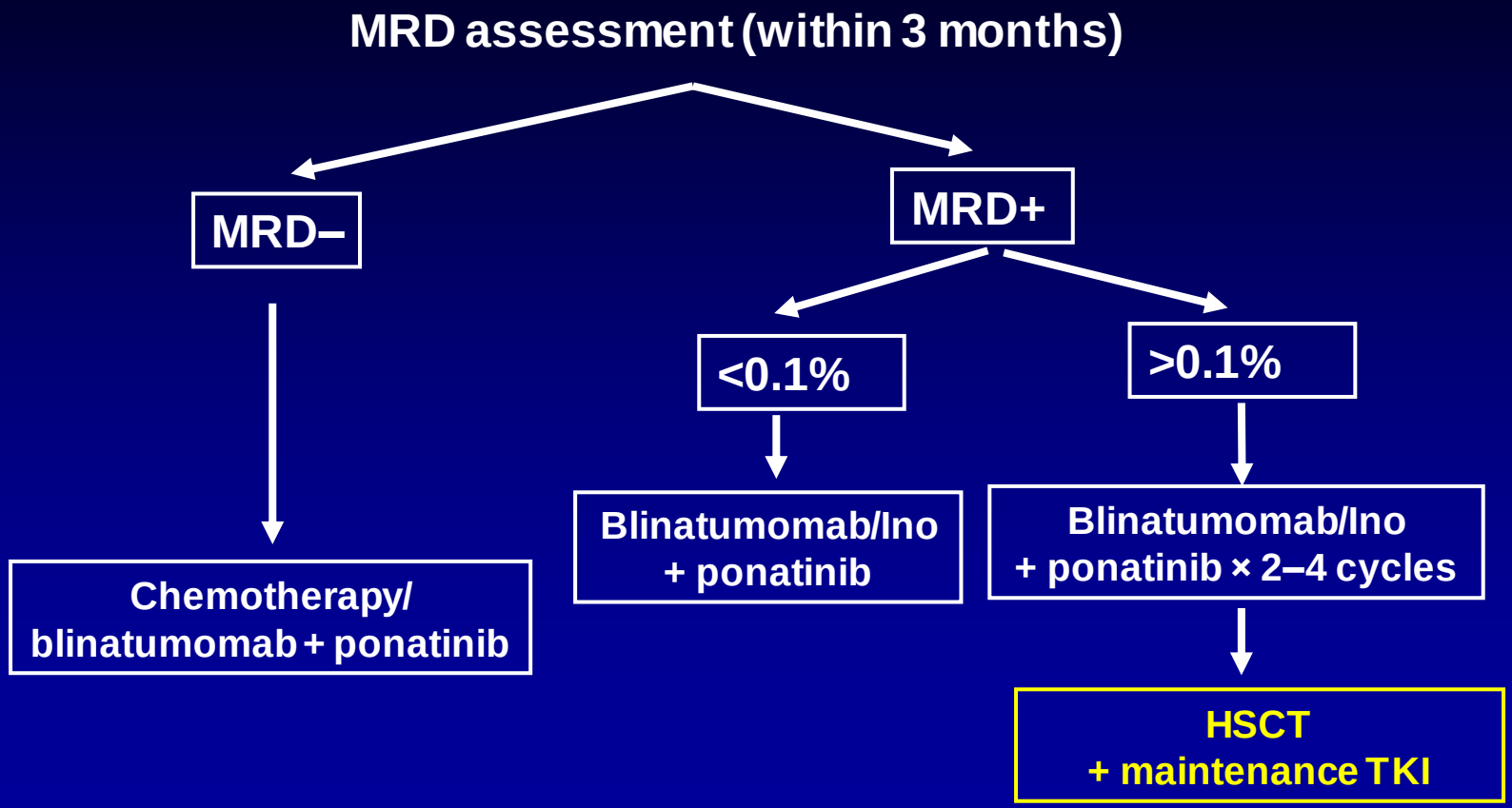
At 3 months



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

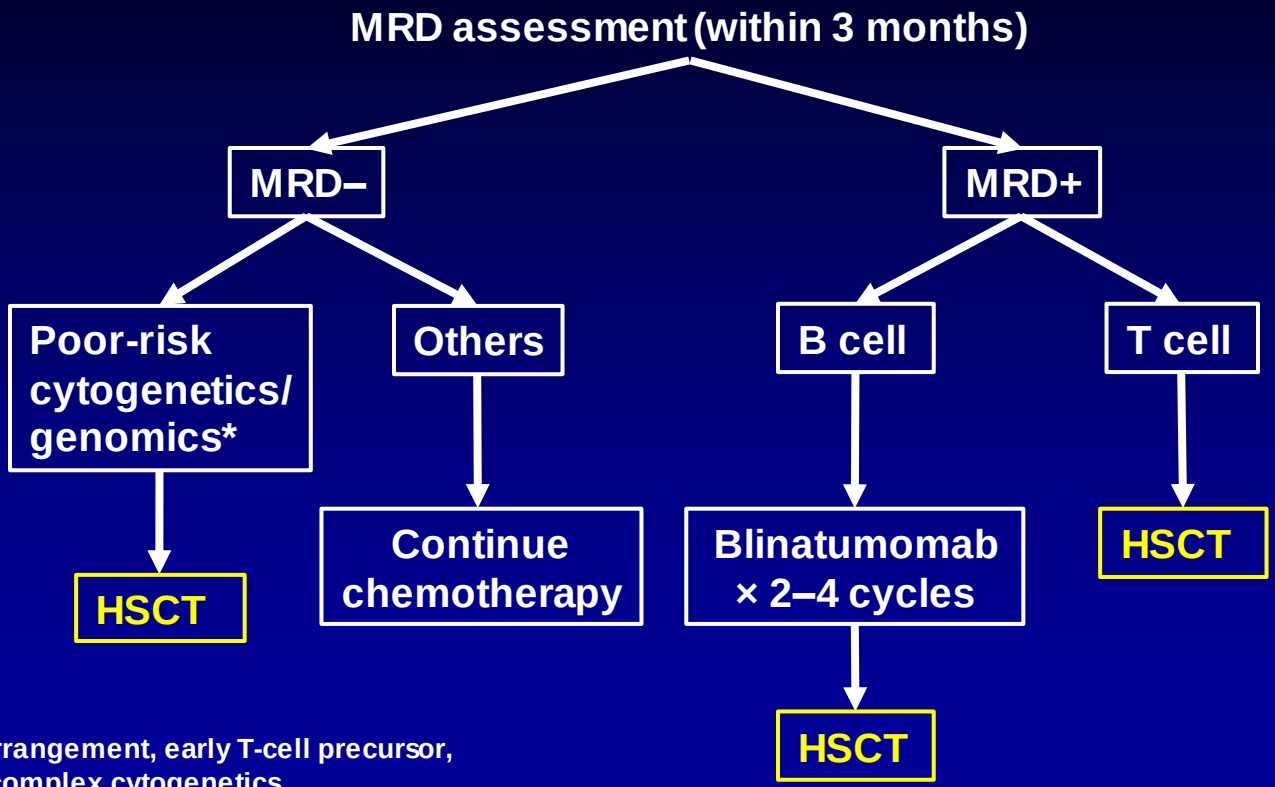
Short. *Blood.* 2016;128(4):504-507.

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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Q&A

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How and when to check for MRD in ALL, including CR1 and CR2

Josep-Maria Ribera

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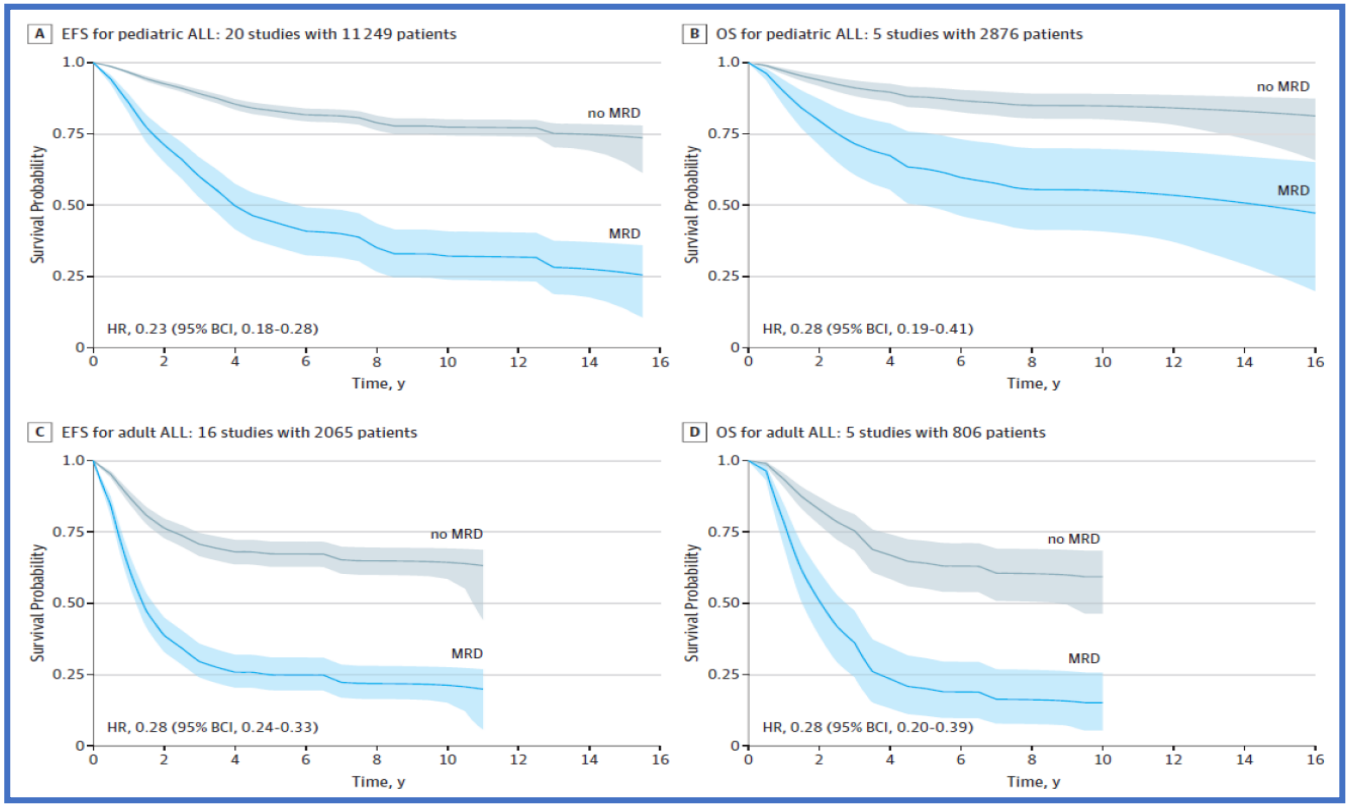
Disclosures

- Amgen: speaker and advisory boards honoraria, research support, clinical trials
- Pfizer: speaker and advisory boards honoraria, clinical trials
- Shire: speaker and advisory boards honoraria
- Ariad: speaker and advisory boards honoraria, clinical trials
- Takeda: speaker and advisory boards honoraria, clinical trials
- Novartis: speaker and advisory boards honoraria

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

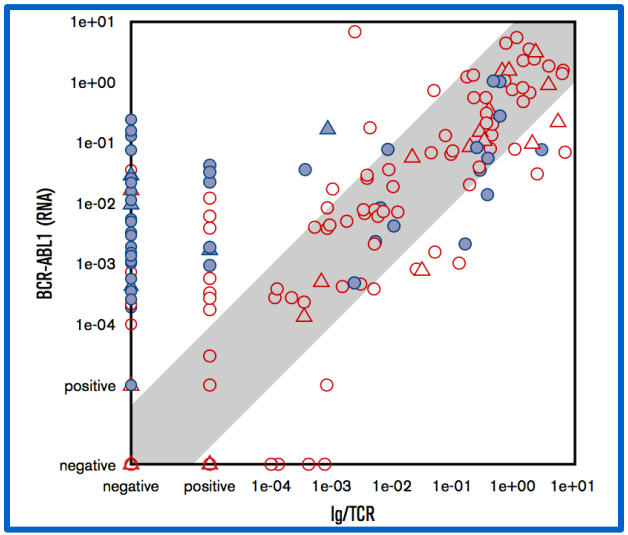


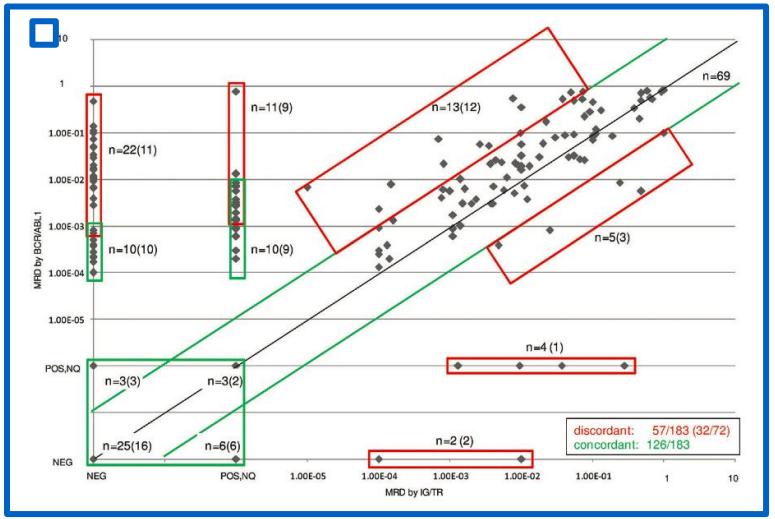
Meta-analysis of 20 pediatric ALL trials >11,000 patients

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

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

Discordance between MRD methods: The case of Ph+ ALL





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

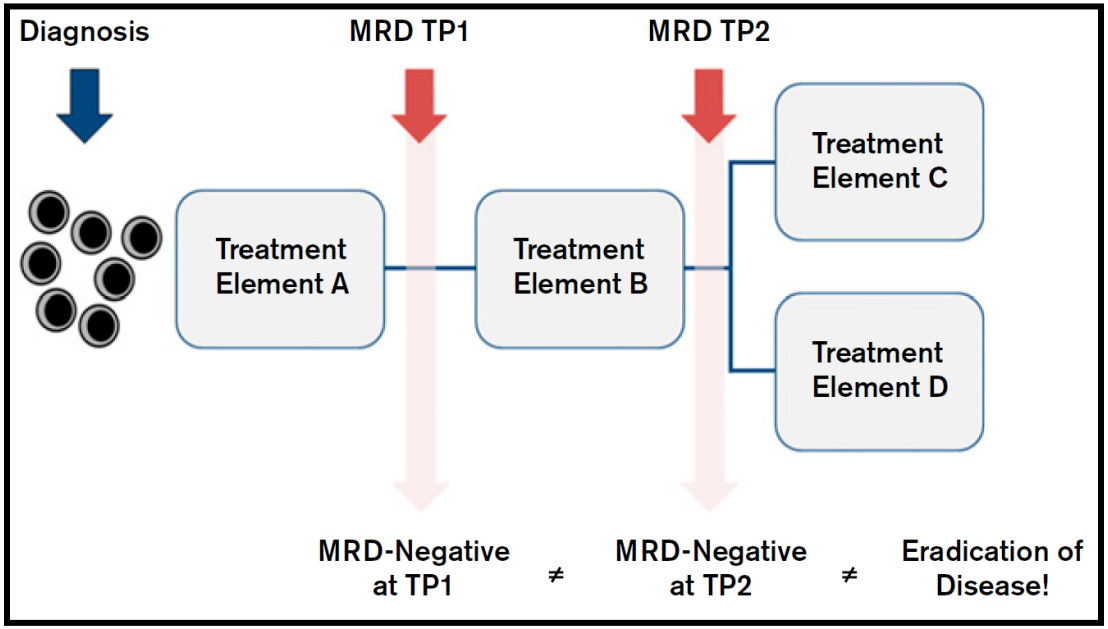
- Non-ALL B cells (15% to 83%)
- T cells (12% to 21%)
- Myeloid cells (15% to 80%)

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

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

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

Importance of time points in MRD assessment



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

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

What is known

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

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

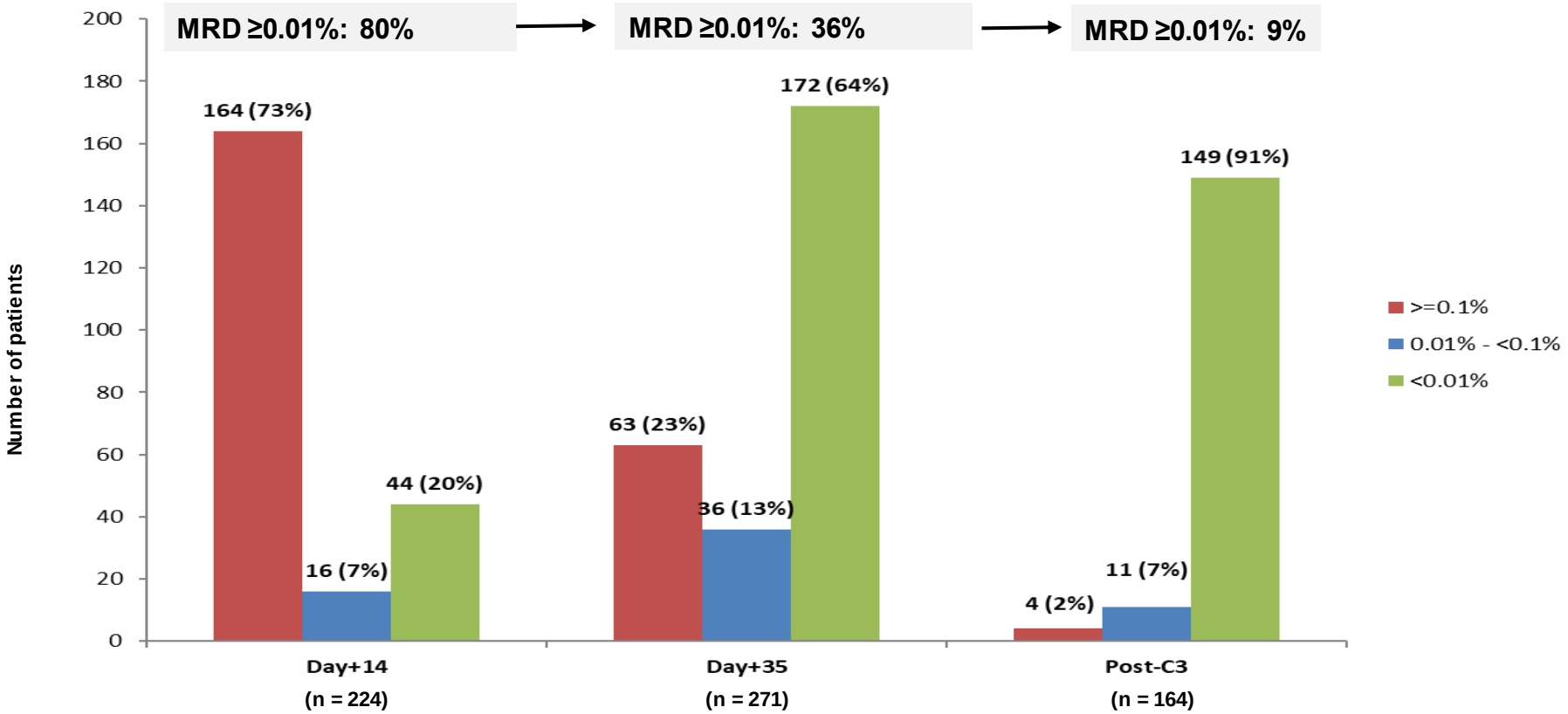
✓Adolescents and adults (15–60 yr) with **HR, Ph– ALL**

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

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

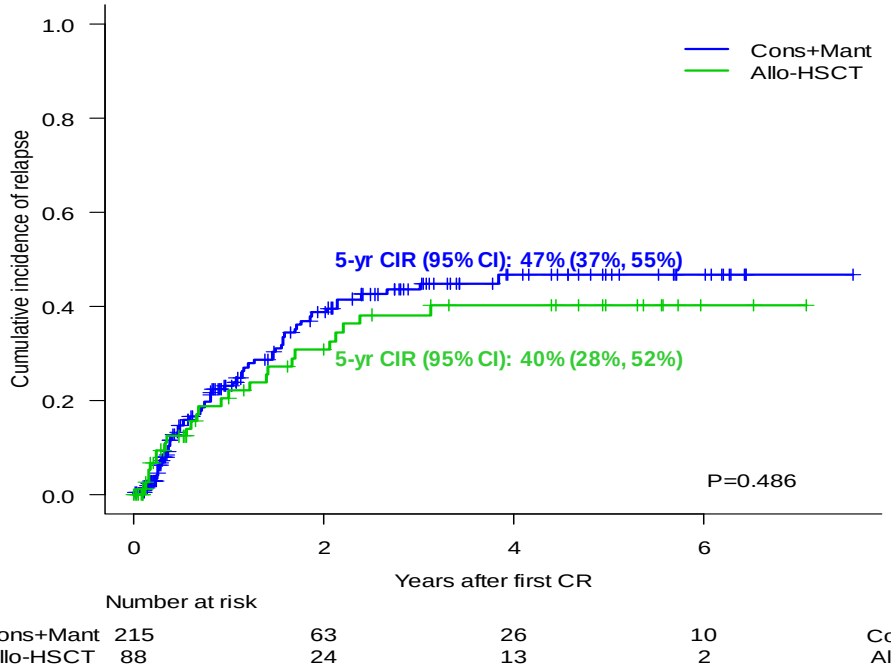
Trial	Risk groups	MRD assessment	Randomization assignment	References
NILG	SR and HR	PCR	No Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood.* 2009;113:4153-4162
PETHEMA HR03	HR	4-color flow	No AlloHSCT in poor early cytologic responders or MRD+ pts	Ribera JM. *J Clin Oncol.* 2014;32:1595-1604
NILG 10/07	SR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

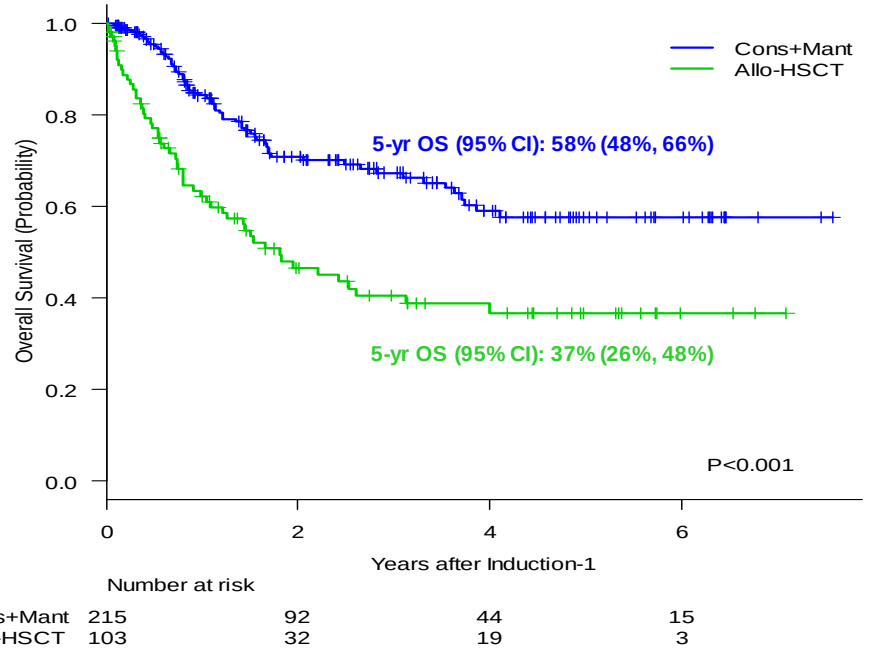
MRD level according to time points: ALL HR11 trial (high-risk patients only)



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

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

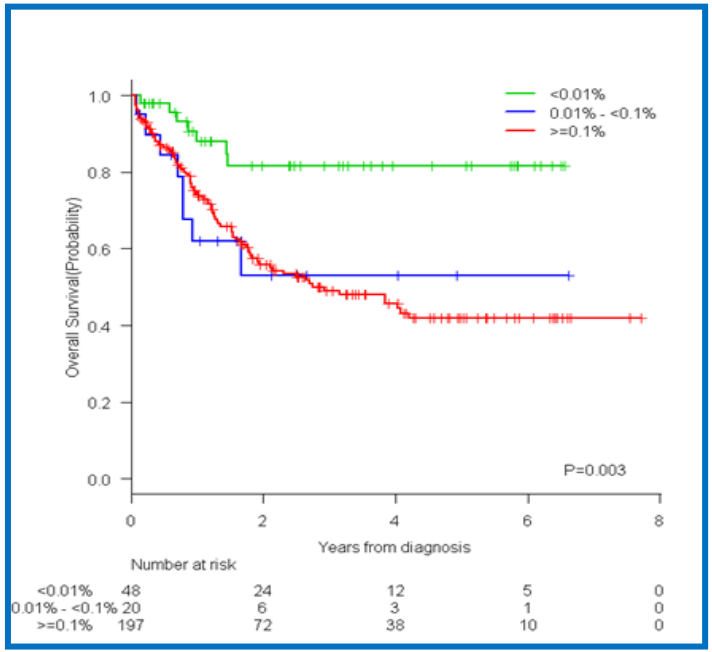




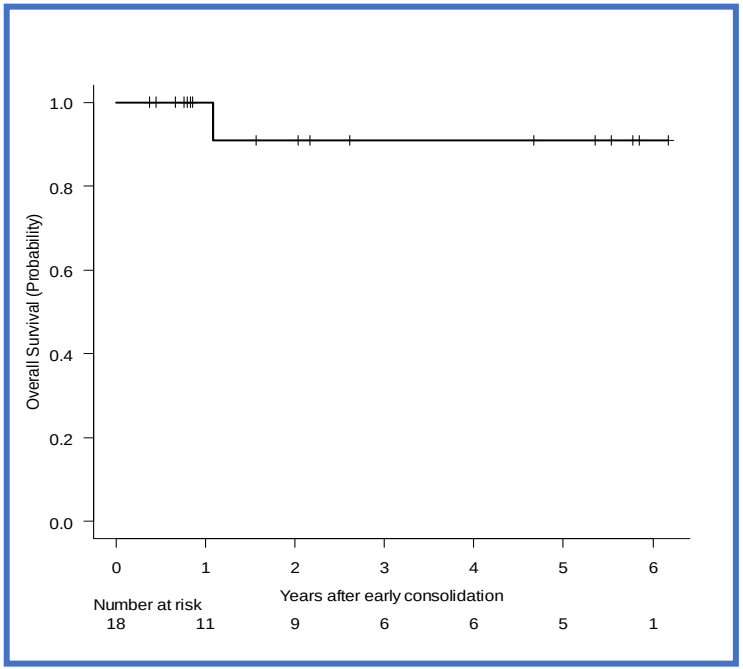
Ribera JM, et al. ASH 2019. Abstract 826 and manuscript submitted.

The importance of early MRD response

OS according to MRD on d14



OS according to MRD <0.01% on d14 and end-induction and end-consolidation



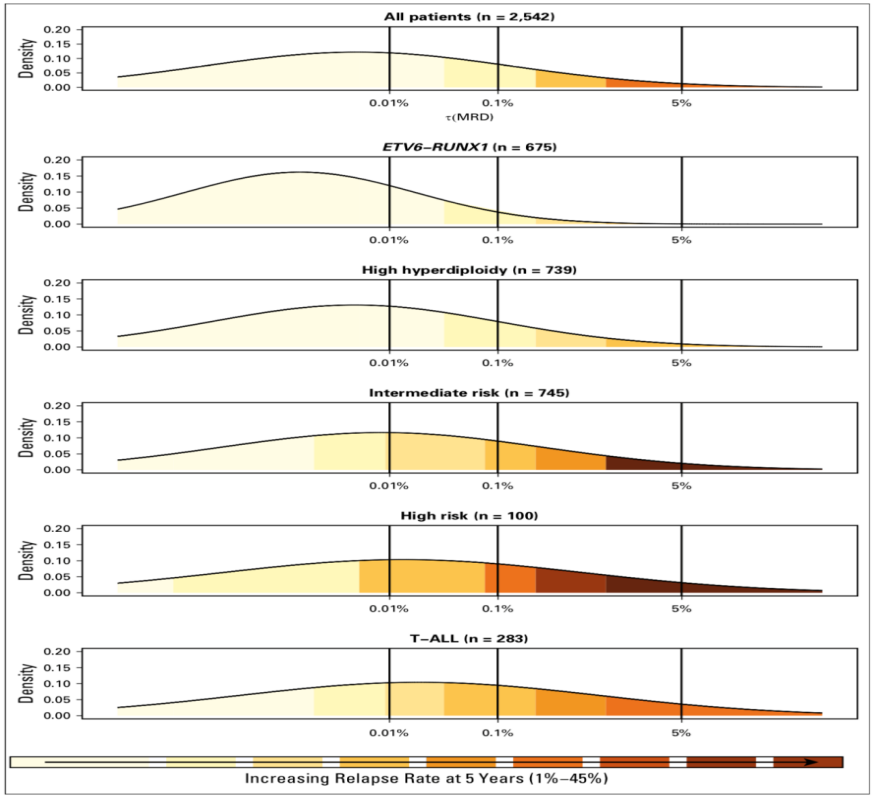
Ribera JM, et al. *Blood*. 2020 (manuscript submitted).

Value of MRD according to genetic subgroups

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

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

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

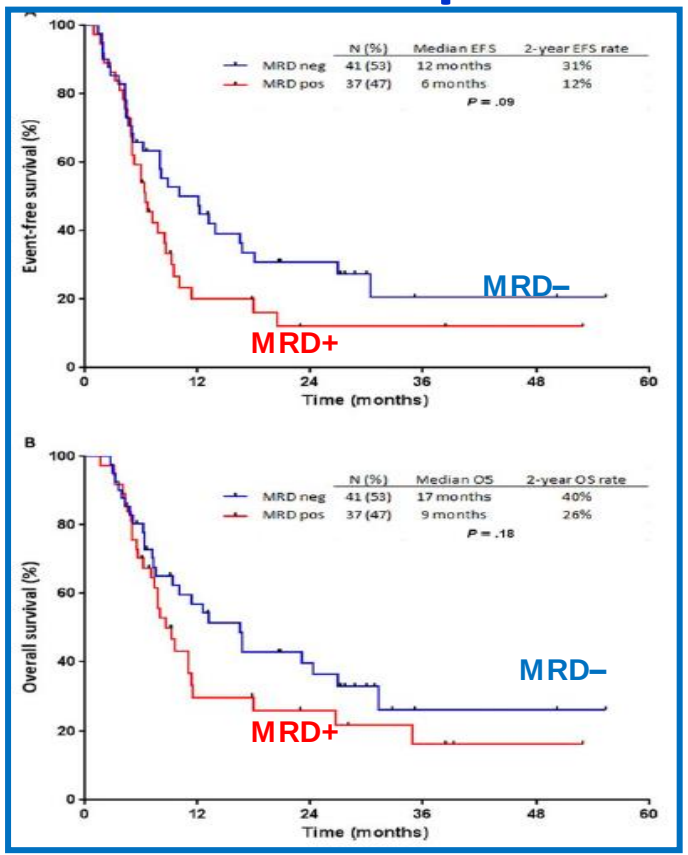


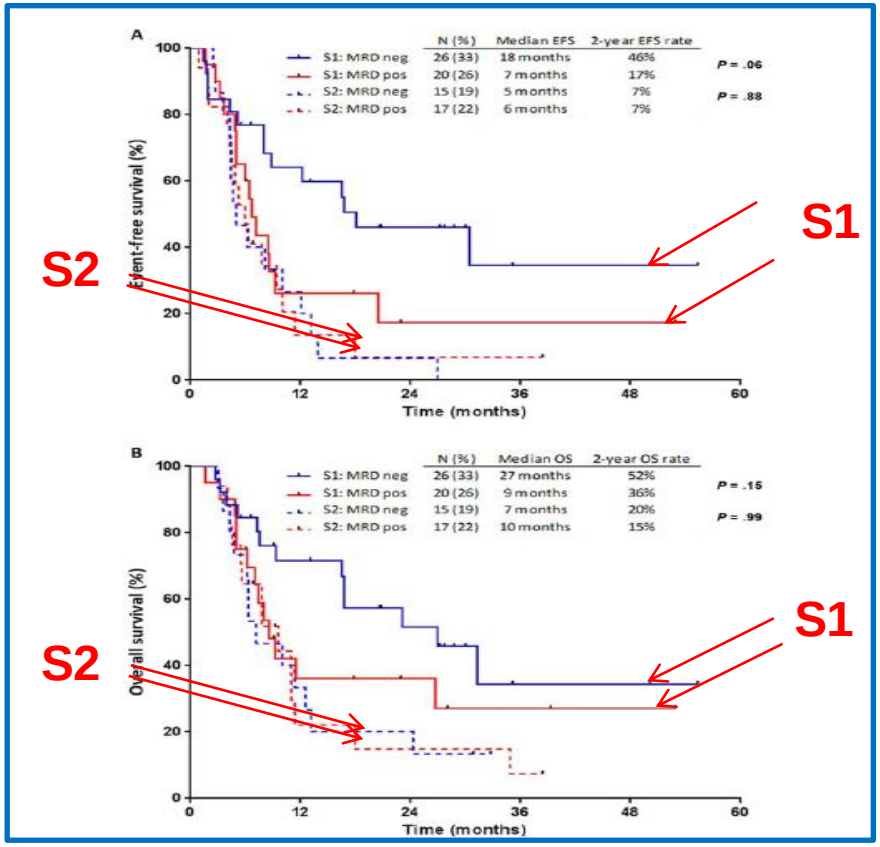
O'Connor D, et al. *J Clin Oncol.* 2018;36:34-43.

MRD in R/R ALL beyond CR1 under rescue CHT: Impact of salvage status

EFS

OS



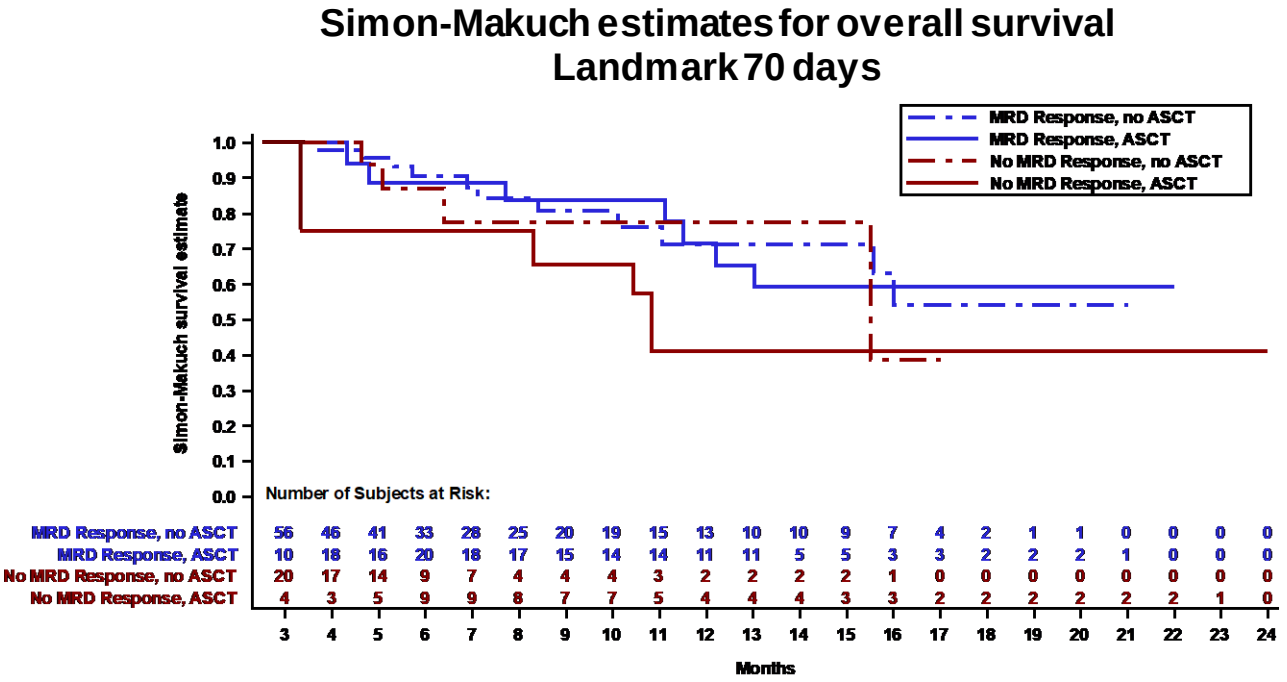


Jabbour E, et al. *Cancer.* 2017;123: 294-302.

MRD in R/R ALL under blinatumomab: OS by MRD response ± HSCT

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

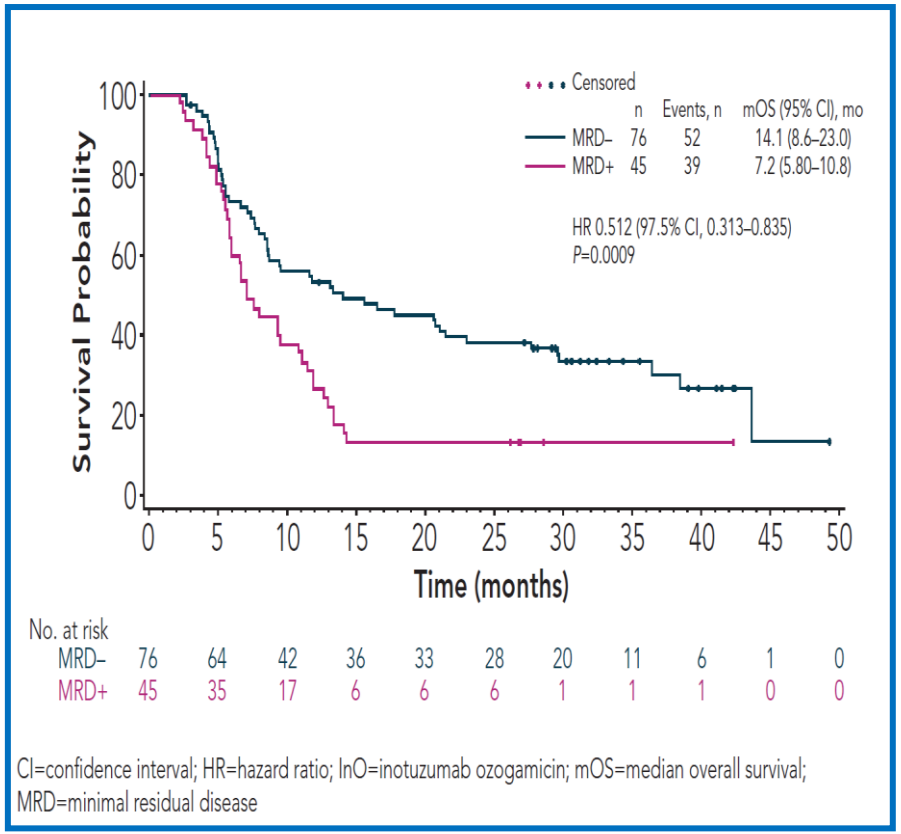
[a]Last response before landmark day 70.

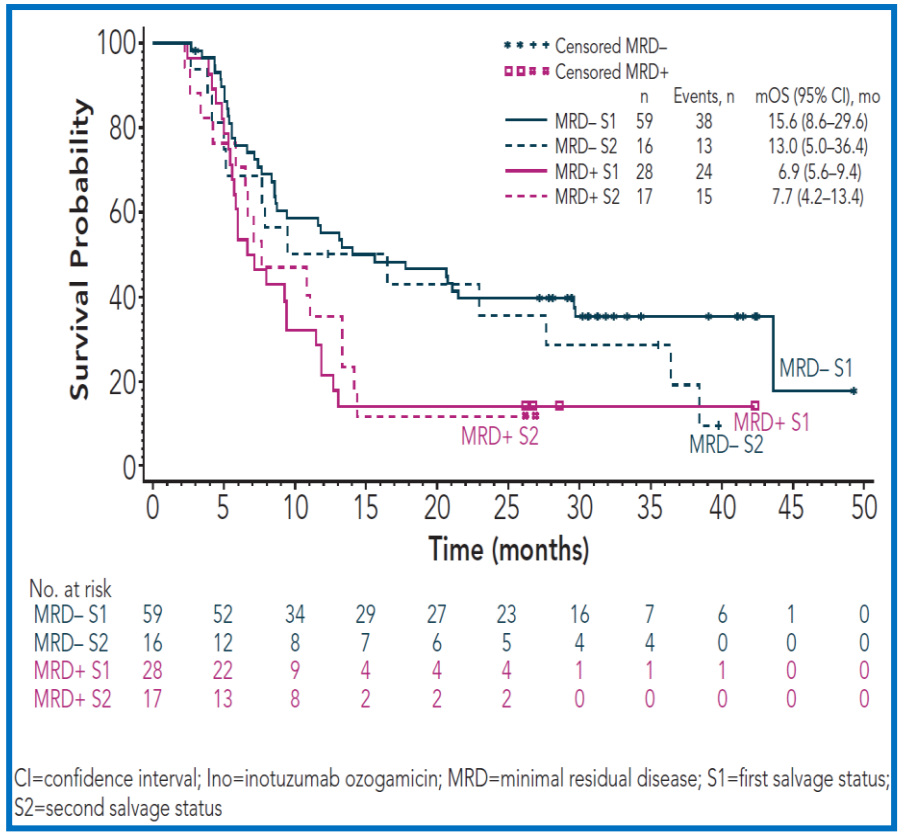


Landmark at day 70 was used to ensure adequate number of HSCT patients at the earlier time points. MRD status is also at day 70.

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

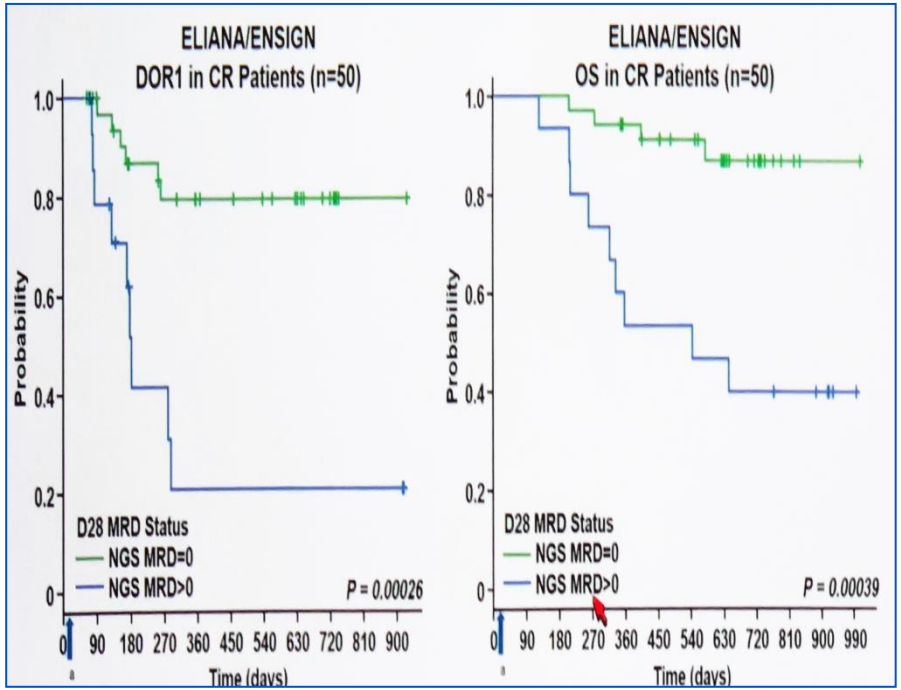
MRD in R/R ALL under InO: OS by MRD response ± HSCT

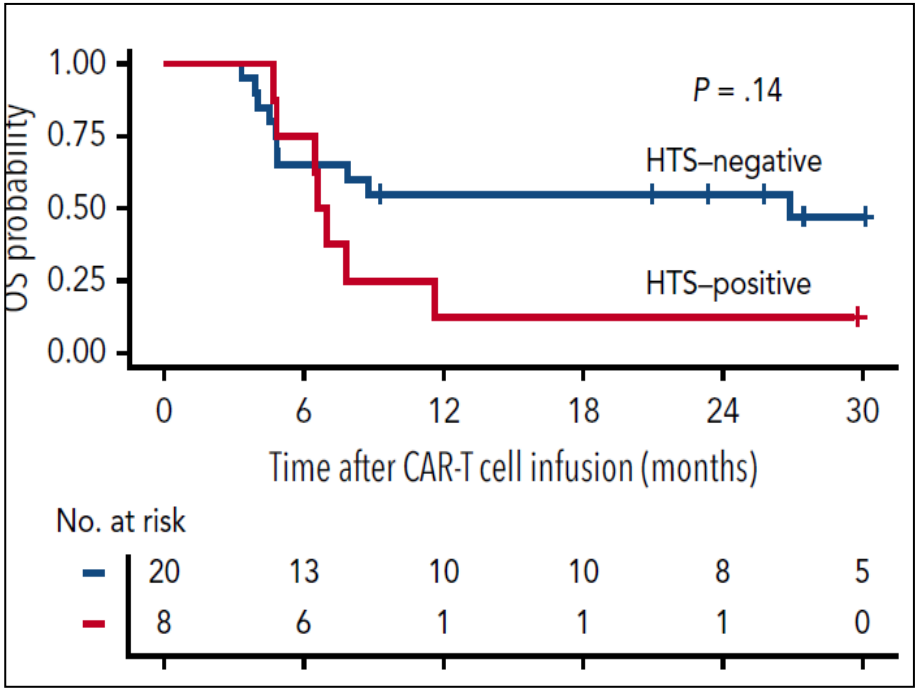




Jabbour E, et al. *Leuk Res.* 2020;88:106283.

Early MRD assessment after CAR T and 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.

Conclusions: MRD in CR1 and CR2

- **How to assess**
  - Each methodology has pros and cons
  - Select the methodology with more experience
  - Use MRD within specific trials
  - Do not exchange the method of MRD assessment within a trial
- **When to assess**
  - In CR1: After induction **and** after consolidation (or before HSCT) are the critical time points
  - In CR2: At the time of CR2 and before HSCT (if treated with Blin or InO) or after CR if treated with CAR T
- **And . . .**
  - Do not forget to study the genetic background of ALL in addition to MRD

Question 1

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

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

Question 2

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

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

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Q&A

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Genetic variants in ALL – Ph+ and Ph-like

Philippe Rousselot

APTITUDE HEALTH

Disclosures

- Research grants: Pfizer, Incyte
- Advisory boards: Amgen, Pfizer
- Travel grant: Pfizer

Initial therapy: similar high CR rates

Outcomes of newly diagnosed patients with Ph+ ALL: Chemotherapy and a TKI combination

Clinical Trial (year†)	N	Age, median [Range]	Chemotherapy	TKI, mg/day	CR,%
Imatinib					
Yanada (2006)[54]	80	48 [15-63]	JALSG ALL202	IM 600	96
Wassmann (2006)[8]	45	41 [19-63]	GMALL	IM 400	96
Fielding (2014)[9]	175	42 [16-64]	UKALLXII/ECOG2993	IM 400 - 600	92
Chalandon (2015)[12]	135	49 [18-59]	Low int. induction	IM 800	98
	133	45 [21-59]	High int. induction	IM 800	91
Bassan (2010)[55]	59	45 [20-66]	NILG	IM 600	92
Daver (2015)[10]	54	51 [17-84]	HyperCVAD	IM 400 - 800	93
De Labarthe (2007)[56]	45	45 [16-59]	GRAAPH 2003	IM 600 - 800	96
Lim (2015)[11]	87	41 [16-71]	Multiagent Chemo	IM 600	94
Nilotinib					
Kim (2015)[22]	90	47 [17-71]	Multiagent Chemo	NIL 800	91
Dasatinib					
Foa (2011)[29]	53	54 [24-76]	Prednisone	DAS 100-140	93
Ravandi (2015)[57]	72	55 [21-80]	HyperCVAD	DAS 100	96
Ravandi (2015)[58]	94	44 [20-60]	HyperCVAD	DAS 70-100	88
Ponatinib					
Jabbour (2015)[34,35]	64	48 [21-80]	HyperCVAD	PON 30-45	100

Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor; N, number of patients; m, month; mg, milligram; CR, complete remission;CMR, complete molecular response rate at CR or approximately 3-month of therapy; n/a, not available; SCT in CR1, stem cell transplant in first CR; OS, overall survival; IM, imatinib; Int., intensity; DAS, dasatinib; NIL, nilotinib; PON, ponatinib; JALSG, Japan Adult Leukemia Study Group; GMALL, German Multicenter Study Group for ALL; UKALLXII, United Kingdom ALL XII; Hyper-CVAD, hyperfarctionated cyclophosphamide, vincristine, dexamethasone, and daunorubicin alternating with cytarabine and methotrexate; NILG, Northern Italy Leukemia Group; GRAAPH, Group for Research in Adult Philadelphia chromosome-positive ALL

† publication year

Imatinib: 94% CR

Nilotinib: 91% CR

Dasatinib: 92% CR

Ponatinib: 100% CR

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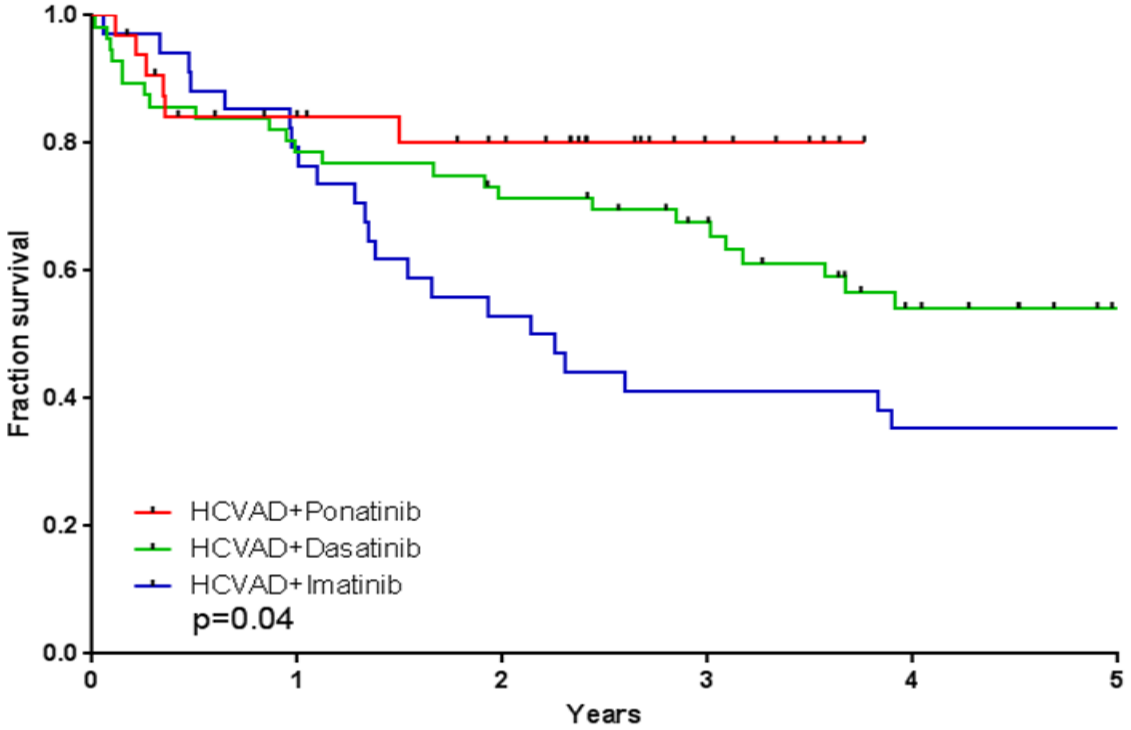
Courtesy of M Yilmaz.

Yilmaz M, et al. *Clin Adv Hematol Oncol*. 2018;16(3):216-223.

Relapse-free survival and OS Summary from MDACC: HCVAD + TKIs

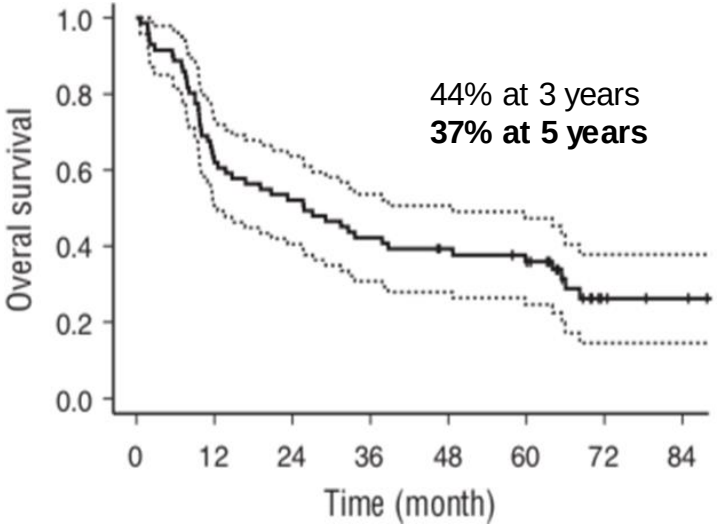


Courtesy of E Jabbour.

EWALL studies in aged patients (>55 y)
EWALL backbone

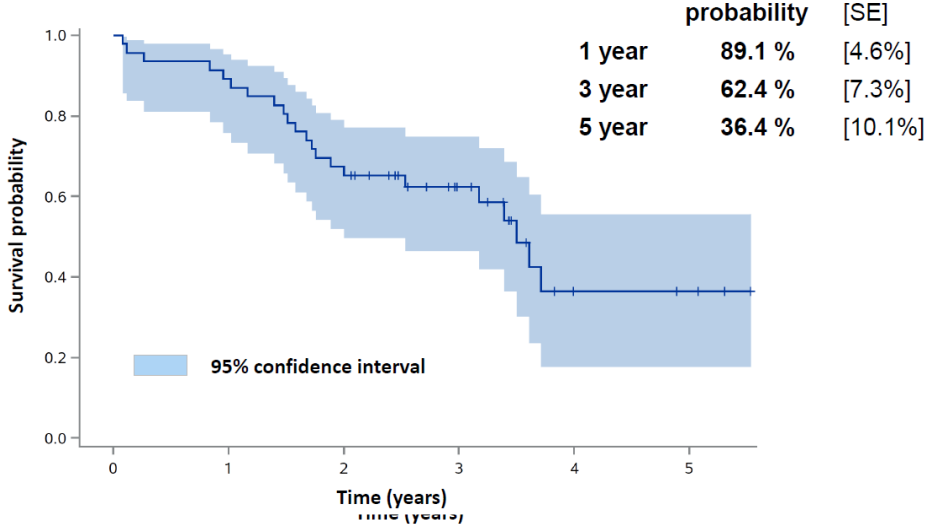
EWALL-01

- **Dasatinib 140 mg/d then 100 mg/d**
- **CR: 67/71 = 94%**
- **MRD2: 60% MR4 and 20% de MR5**
- **Transplant rate: 10%**



EWALL-02

- **Nilotinib 800 mg/d**
- **CR: 68/72 = 94%**
- **MRD1: 79% MR4 and 38% de MR5**
- **Transplant rate: 39%**



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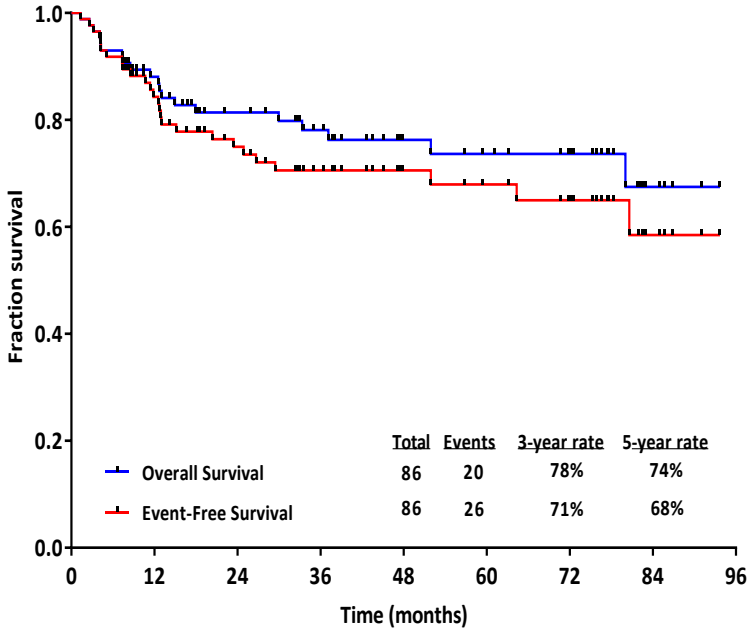
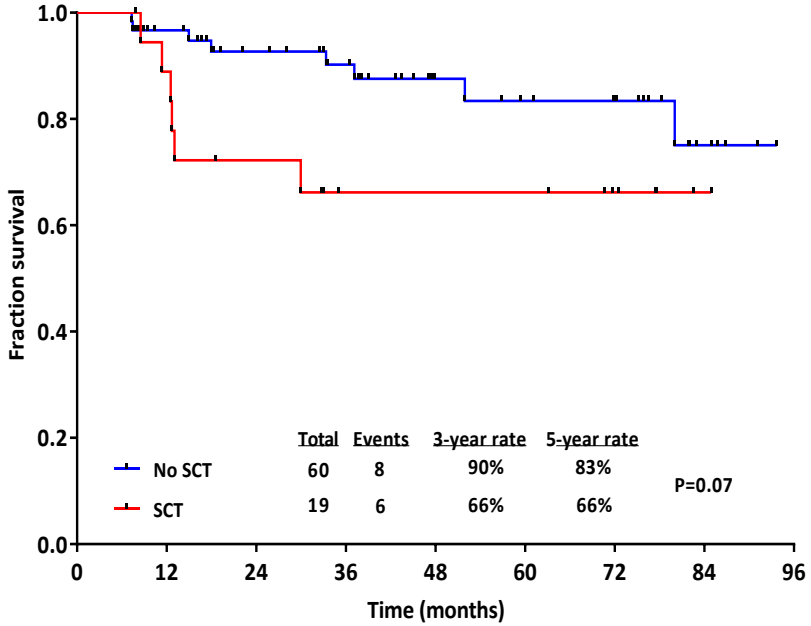
Rousselot P, et al. *Blood.* 2016;128(6):774-782; Ottmann OG, et al. *Blood.* 2018;132:abstract 31.

Hyper-CVAD + ponatinib in Ph+ ALL: Outcome

EFS and OS



Impact of allo-SCT: 6-mo landmark



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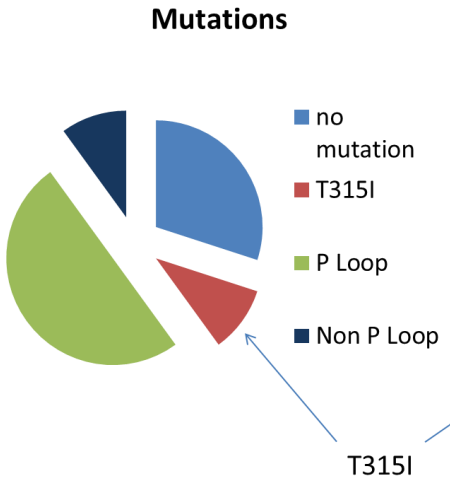
Short NJ, et al. *Blood*. 2019;134:abstract 283.

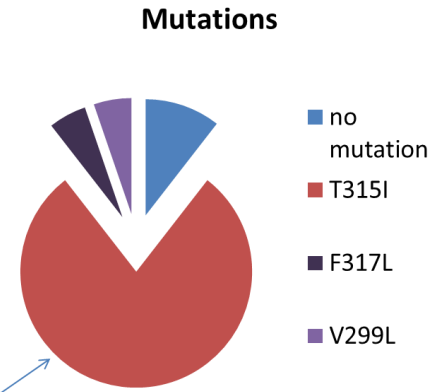
Best TKI for BCR-ABL tk domain mutations

Mutations analysis in relapse

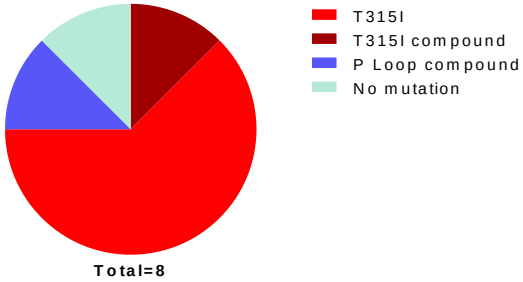
AFR07 : IMATINIB



EWALL-PH-01 : DASATINIB



GRAAPH 2014 : NILOTINIB



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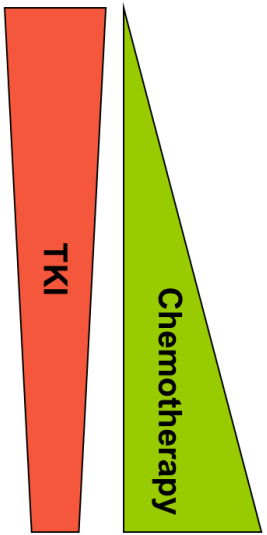
Rousselot P, et al. *Blood*. 2016;128(6):774-782.

What is the best chemotherapy schedule for initial therapy?

- GIMEMA
  - Prednisone + TKI
- EWALL
  - Low Chemo
  - TKI
- MD Anderson
  - HyperC VAD + TKI



Minimum

Maximum

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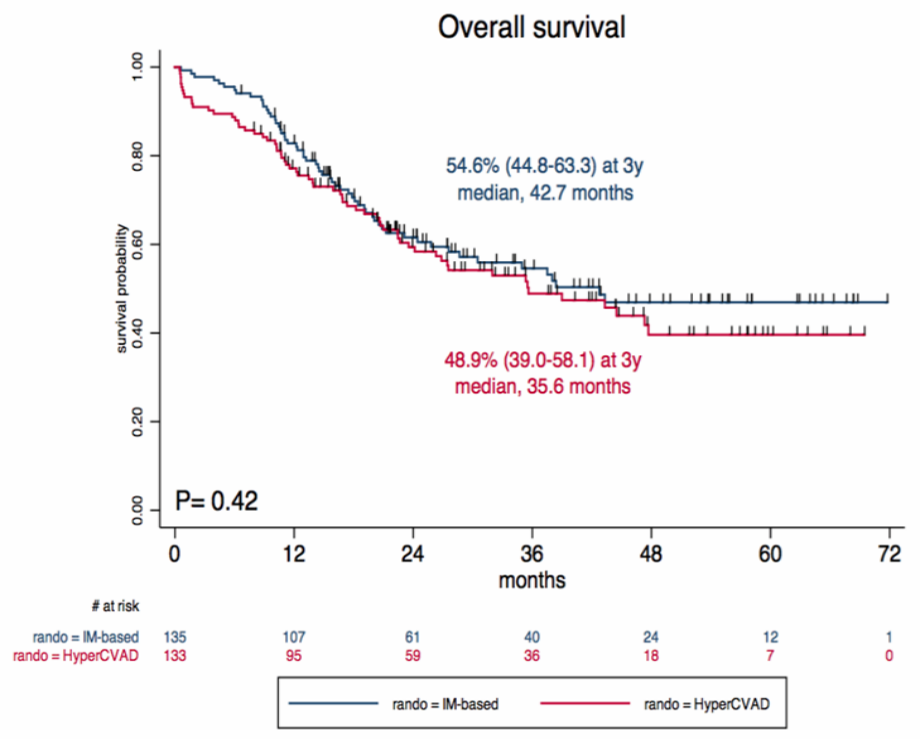
Personal communication from Dr Rousselot.

High-intensity vs low-intensity chemotherapy for induction – GRAAPH 2005



	IM-based (n= 135)	IM-HyperCVAD (n=133)	p	Total (n=268)
CR	**133 (98.5%)**	**121 (91.7%)**	**0.006**	**254 (94.8%)**
Courses to CR				
one	132 (97.8%)	118 (88.7%)	0.003	250 (93.2%)
two	1 (0.7%)	3 (2.2%)	-	4 (1.5%)
Resistance after 2 cycles	1 (0.7%)	3 (2.2%)	0.35	3 (1%)
D60 mortality	**1 (0.7%)**	**9 (6.7%)**	**0.01**	**10 (3.7%)**

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Chalandon Y, et al. *Blood.* 2015;125:3711.

Two evolving strategies to treat Ph+ ALL

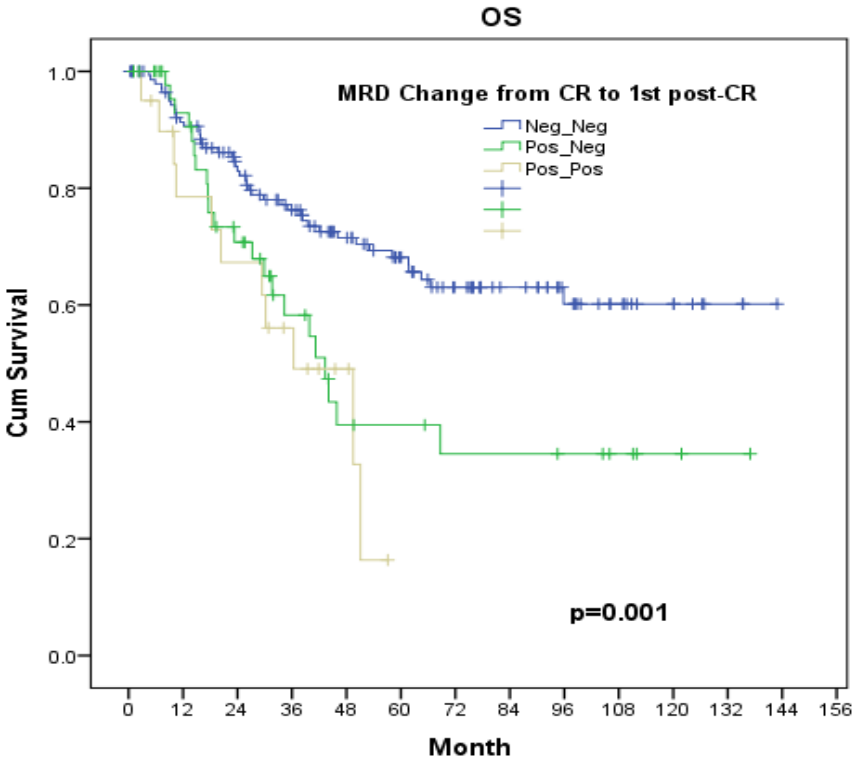
Parameter	Hyper-CVAD + Ponatinib	TKIs With Minimal ChemoRx
% CR	90-100	90-100
% CMR	80	20
Allo-SCT required	Only if no CMR	In all
Outcome p190 vs p210	Same	P190 better
% 3-yr survival/DFS	70-80	40-50

A third strategy? Minimal chemo first followed by intensive consolidations

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

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



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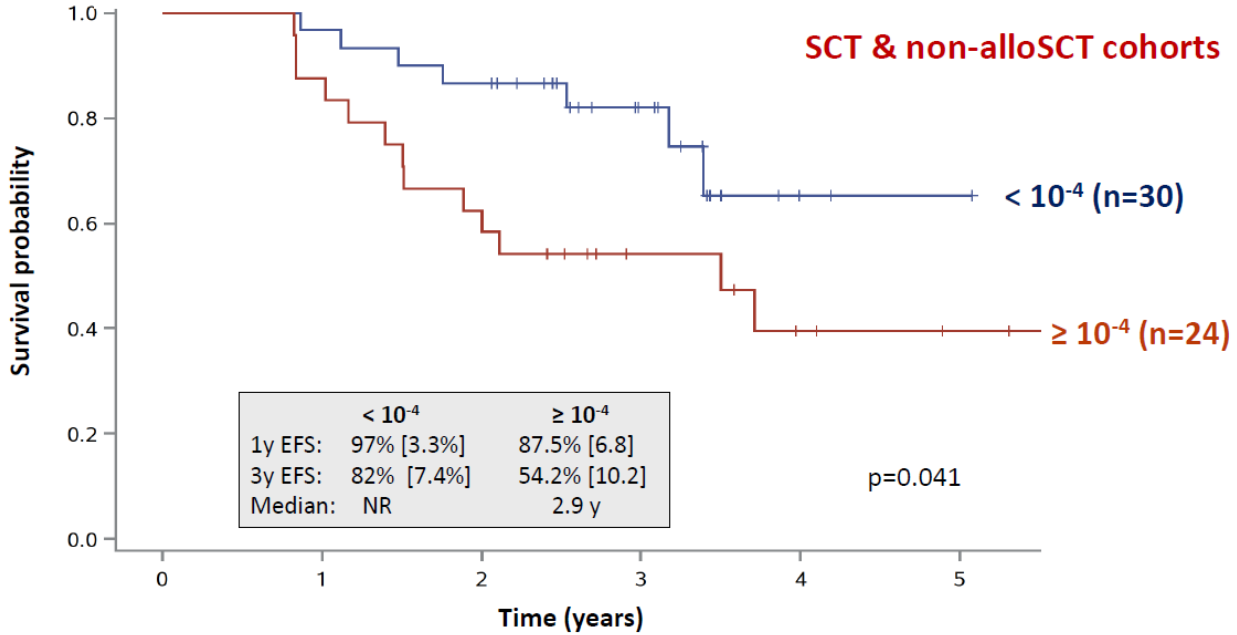
Yilmaz M, et al. *Blood.* 2019;134:abstract 1297.

EWALL-02: Low intensity chemo and nilotinib

OS by MRD Response after CONS1/2

(B/A ratio < 10^{-4} *vs.* ≥ 10^{-4})



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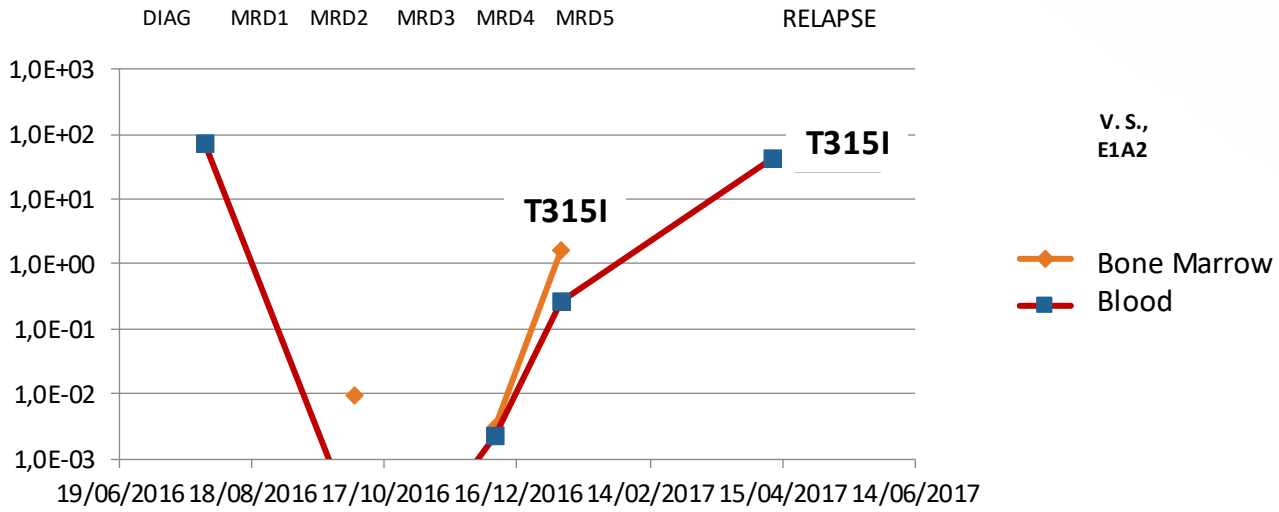
Ottmann OG, et al. *Blood*. 2018;132:abstract 31.

GRAAPH2014 004-1016-V-S (nilotinib)



- T315I 25% at MRD5
- Relapse 3 months later with T315I at 100%
- No mutation detected at diagnosis

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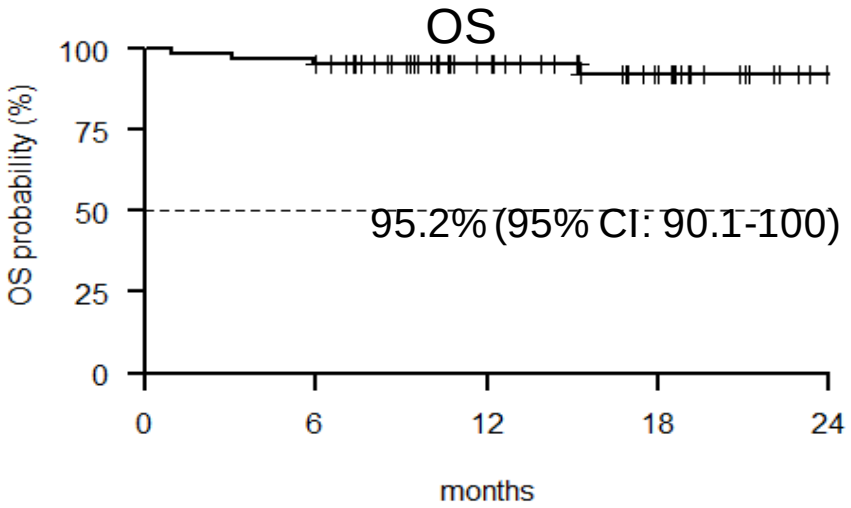
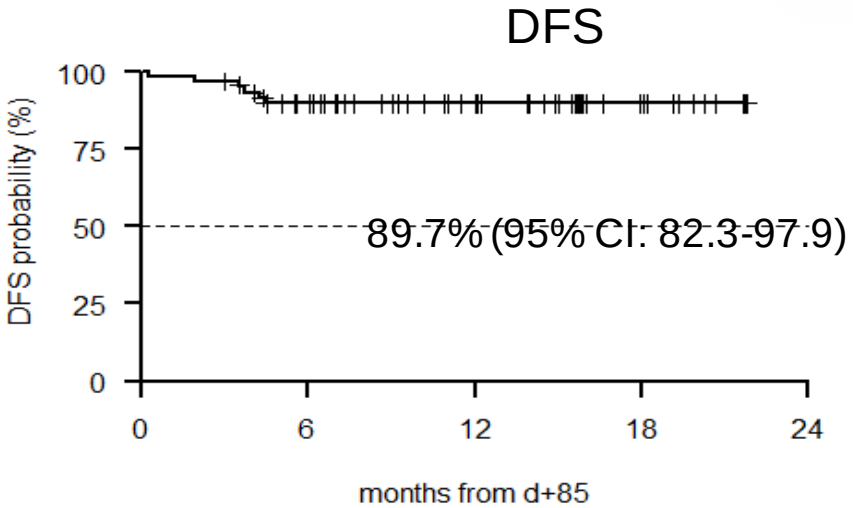
Courtesy of JM Cayuela.

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%





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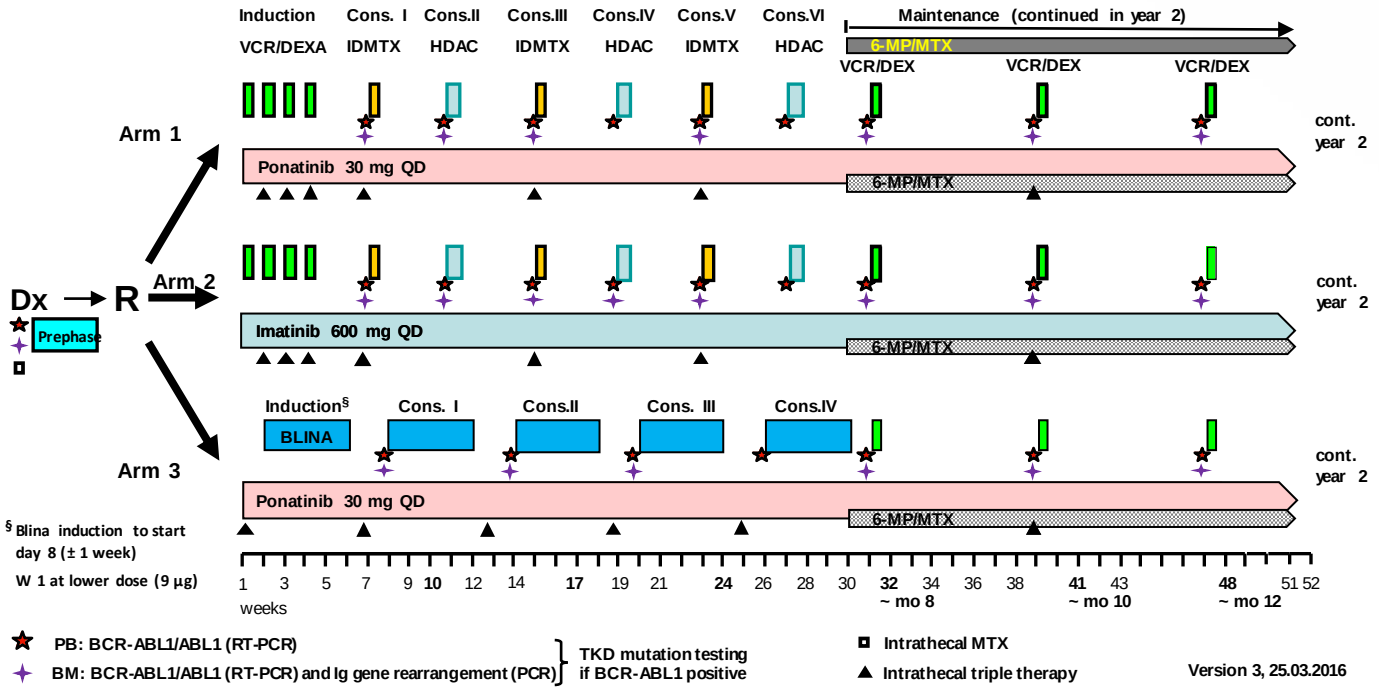
Chiaretti S, et al. *Blood.* 2019;134:abstract 615.

EWALL PH03: Study design

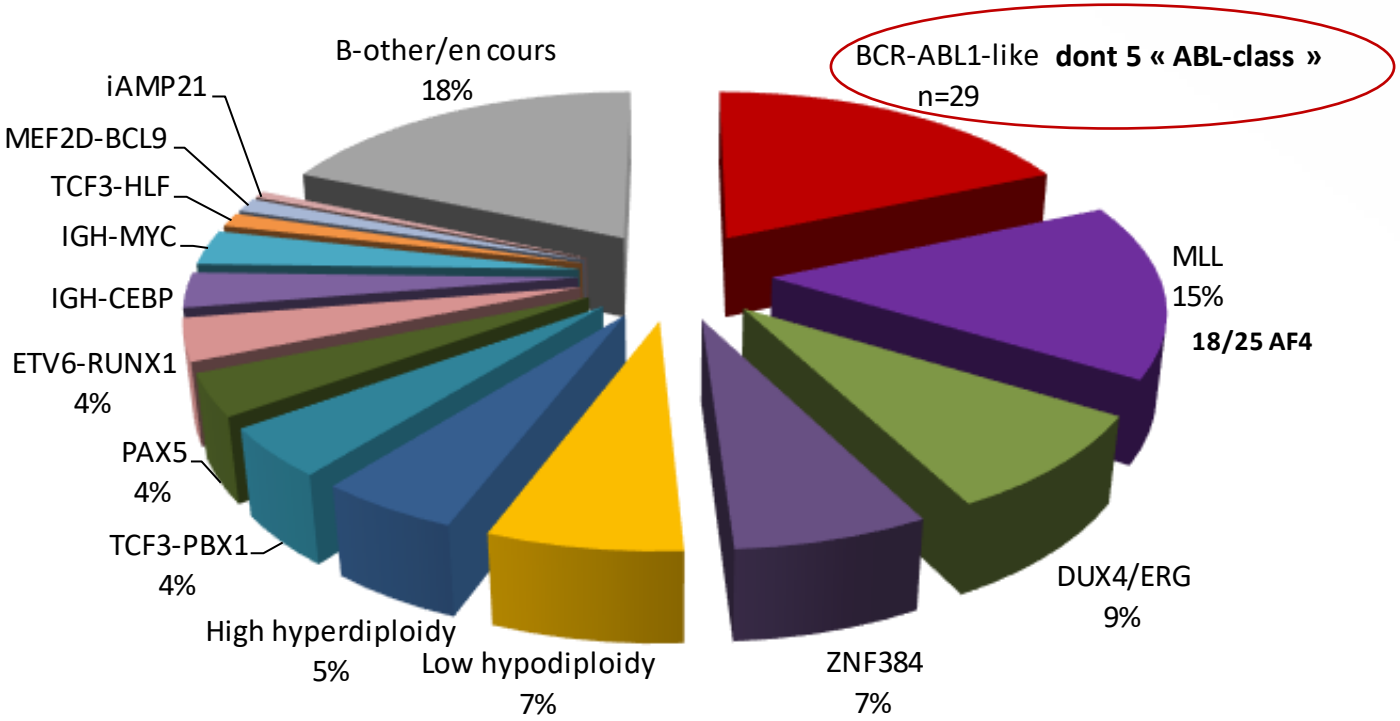
Patients aged 55y or older



https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-003350-25/GB

BCR-ABL+ like ALL

GRAALL-2014 BCP-ALL: Oncogenetics (N = 188)



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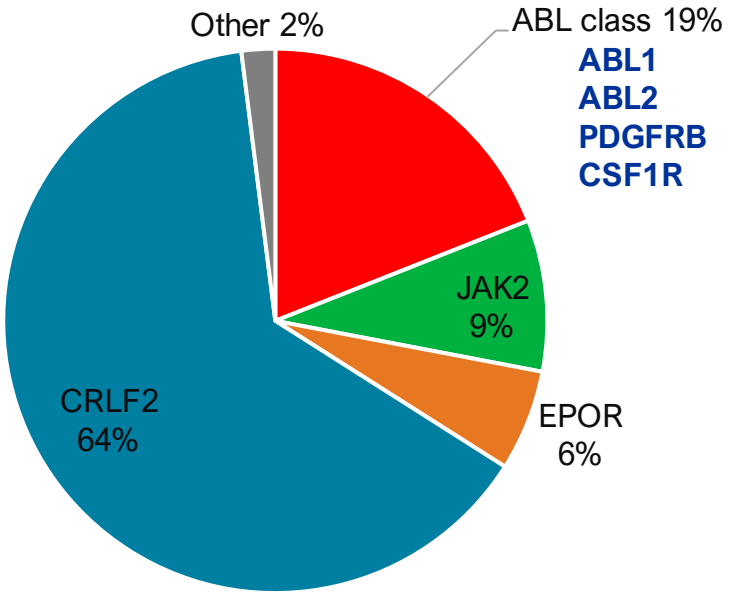
Courtesy of E Clappier.

Ph-like BCP-ALL

Relative frequency of Ph-like ALL alterations in children, adolescents, and adults



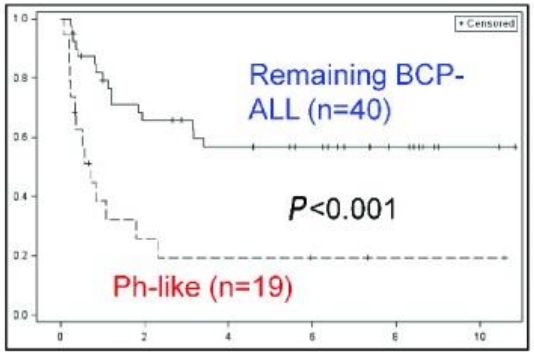
Summary data from 5 recent clinical studies (n = 2506 cases) depict the most common ABL class and CRLF2/JAK pathway-associated translocations occurring in children and adults with Ph-like ALL.

Adapted from Harvey RC and Tasian SK. *Blood Adv.* 2020.
Hunger SP, Mullighan CG. *Blood.* 2015;125(26):3977-3987; Harvey RC, Tasian SK. *Blood Adv.* 2020;4(1):218-228.

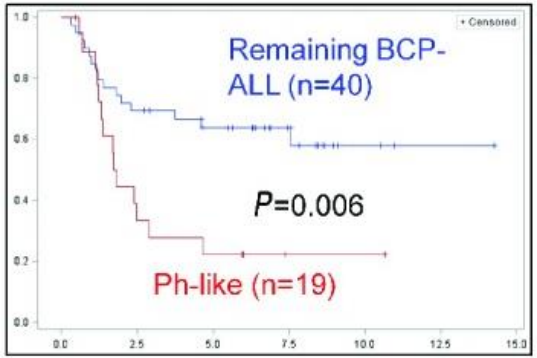
Ph-like ALL outcome in adults

GMALL: 06/99 & 07/03[1]

DFS

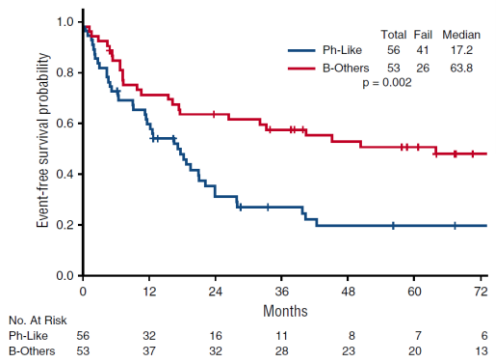


OS



MDACC: HyperCVAD/A-BFM[2]

EFS



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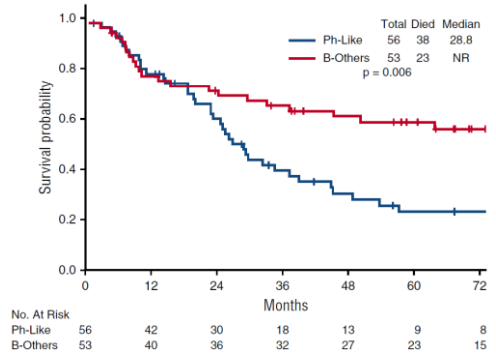

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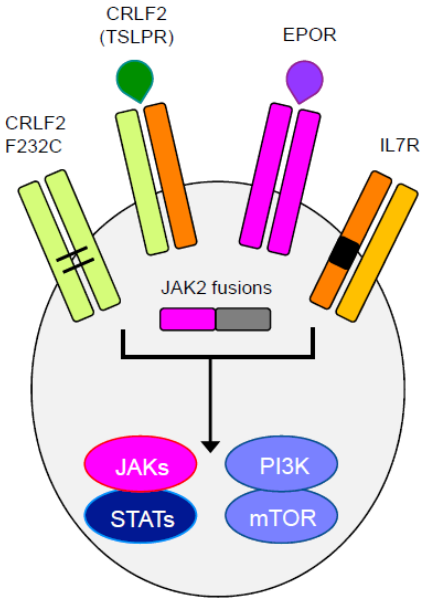
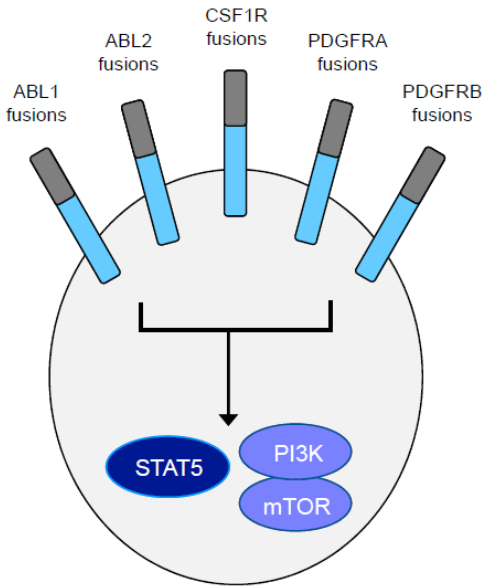
1. Herold T, et al. *Haematologica*. 2017;102:130-138; 2. Jain N, et al. *Blood.* 2017;129:572-581.

CRLF2 / EPO-R / JAK-STAT



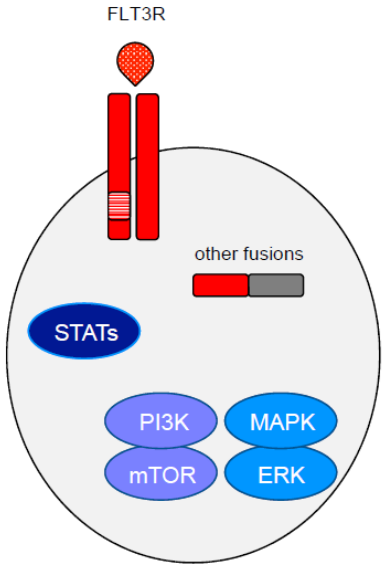
JAK inhibitors
PI3K pathway inhibitors
HDAC inhibitors
anti-TSLPR antibodies & CAR T cells

ABL-class fusion



ABL inhibitors
PI3K pathway inhibitors

Other



FLT3 inhibitors
TRK inhibitors
FAK inhibitors
PI3K pathway inhibitors
MEK inhibitors

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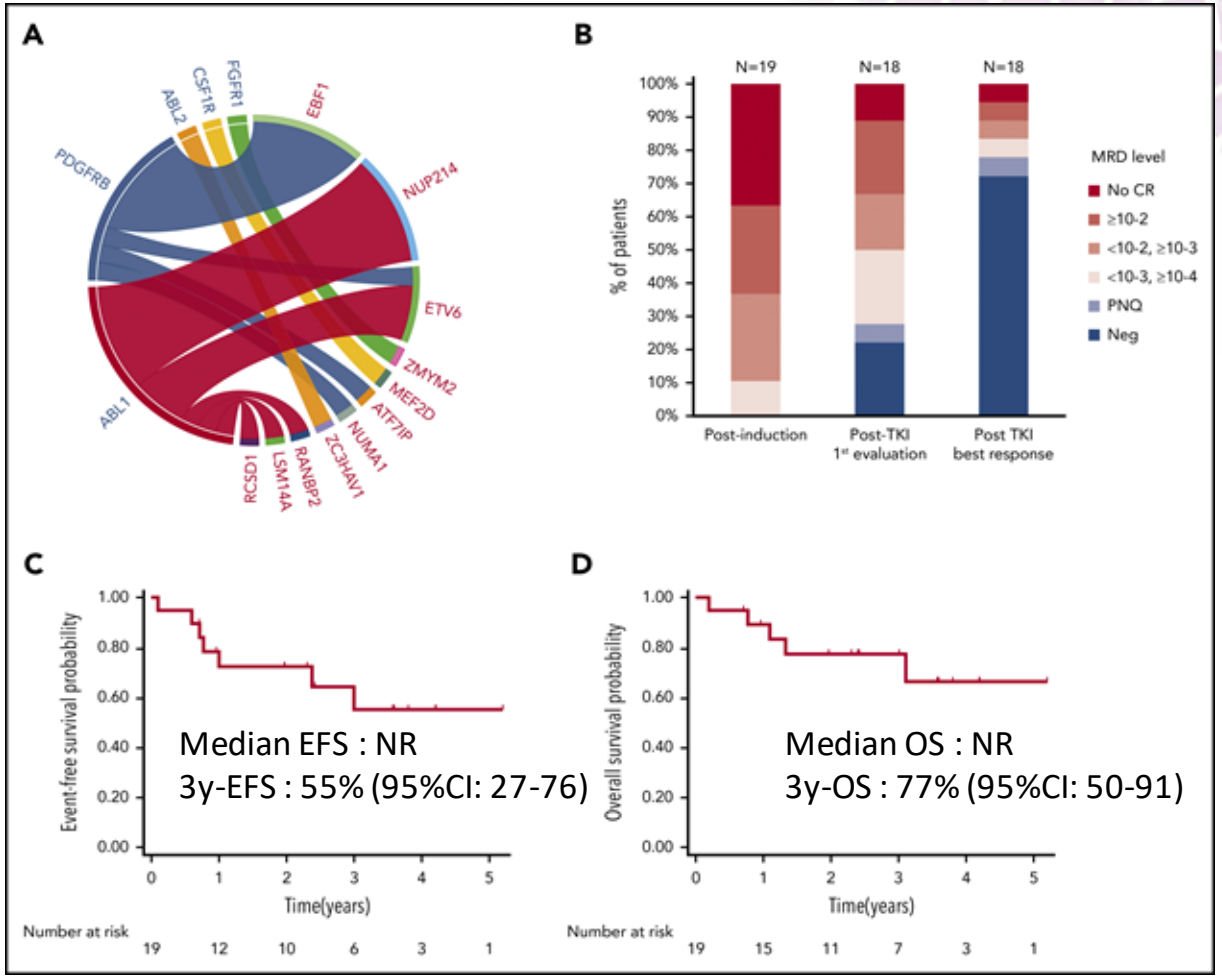
Tasian SK, et al. *Blood.* 2017;130(19):2064-2072.

Ph-like ALL with targetable ABL-family gene

French TKI experience



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Tanasi I, et al. *Blood.* 2019;134(16):1351-1355.

Conclusions

- Best TKI for induction: all equivalent
- Best TKI for overall survival: a trend for 2G TKIs and ponatinib
- Best chemo regimen: room for a decrease in intensity, at least during induction
- MRD monitoring
  - BCR-ABL and Ig/TCR
  - MRD negativity of better prognostic
  - MRD discrepancy: unknown significance
- Relapses: new treatment modalities but median OS = 6 months
- Future
  - Chemo-free regimens
- BCR-ABL–like
  - Not so few patients
  - Personalized therapy?

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  - JM Cayuela, S Hayette, MM Coudé
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ELN European LeukemiaNet

GRAALL LALA GOELAMS SAKK

UVSQ université PARIS-SACLAY UFR Simone Veil - Santé CAMPUS DE SAINT-QUENTIN-EN-YVELINES

CHV

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Q&A

APTITUDE HEALTH

Global Leukemia Academy

AYA ALL patients – what is the current treatment approach for this diverse patient population?

Rob Pieters

APTITUDE HEALTH

Treatment of adolescents/young adults (AYA) with ALL

Rob Pieters
Chief Medical Officer

Disclosures

No conflict of interest

Question 1

Which assertion is NOT correct for AYA ALL patients?

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

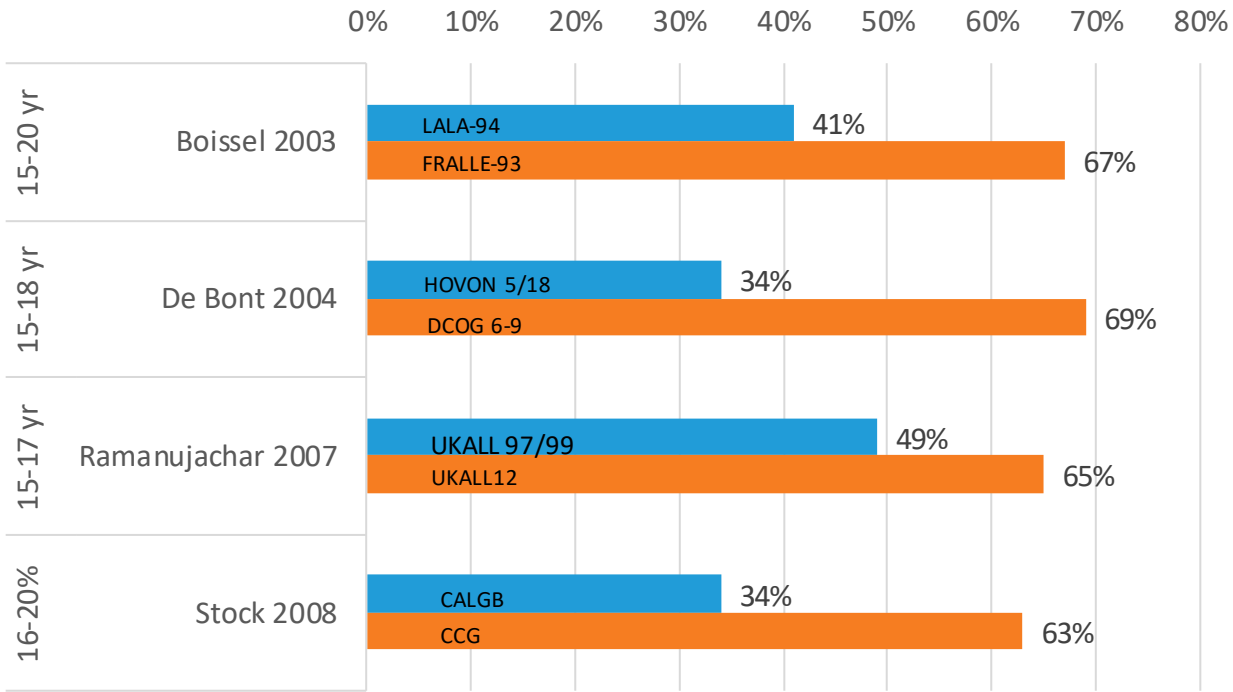
Inferior outcome for AYA patients; why?

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

Pediatric vs adult treatment protocols

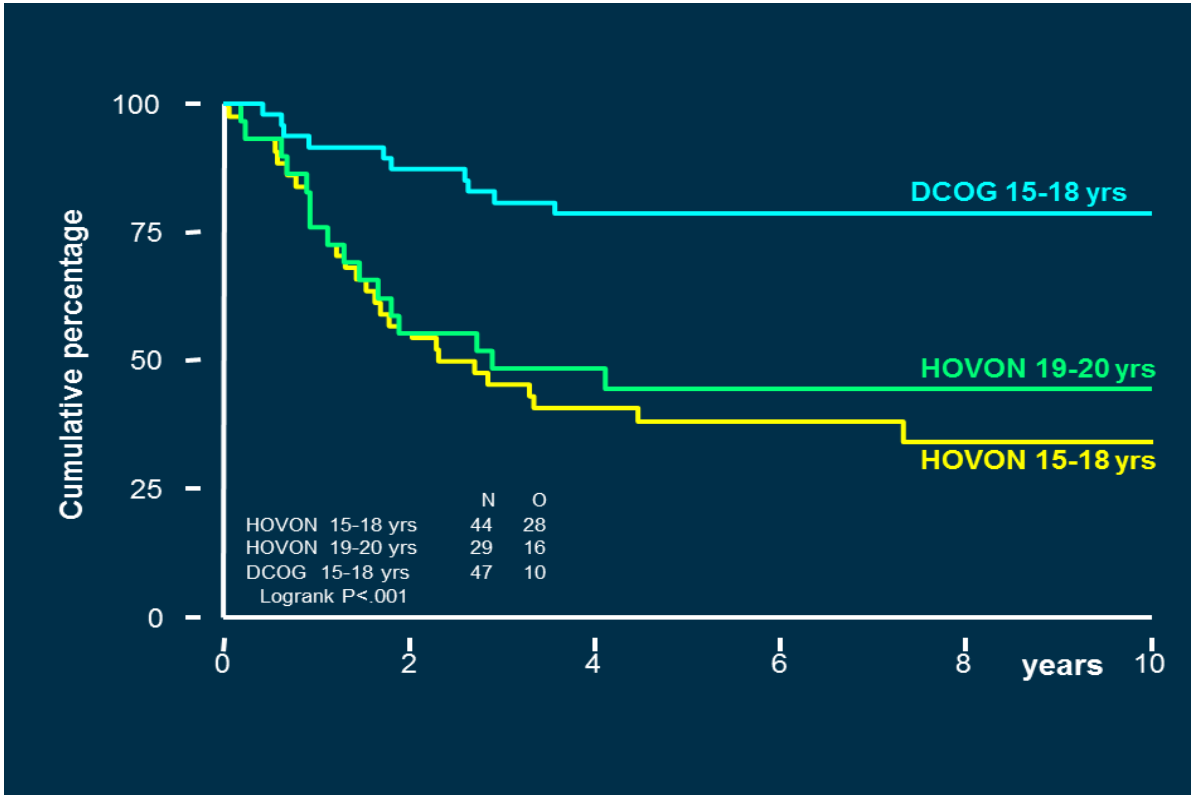
- More intensive use of
  - Glucocorticoids
  - Vincristine
  - Asparaginase
  - Methotrexate
  - 6-mercaptopurine
- Less intensive use of
  - Anthracyclines
  - Cyclophosphamide
- Less frequent use of alloSCT
- Prolonged maintenance, delayed intensification, CNS-directed therapy

Retrospective comparison of 5-yr EFS in AYA patients treated on pediatric and adult protocols



Boissel N, et al. *J Clin Oncol*. 2003;21(5):774-780; De Bont JM, et al. *Leukemia*. 2004;18(12):2032-2035; Ramanujachar R, et al. *Pediatr Blood Cancer*. 2007;48(3):254-261; Stock W, et al. *Blood*. 2008;112(5):1646-1654.

Adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands



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

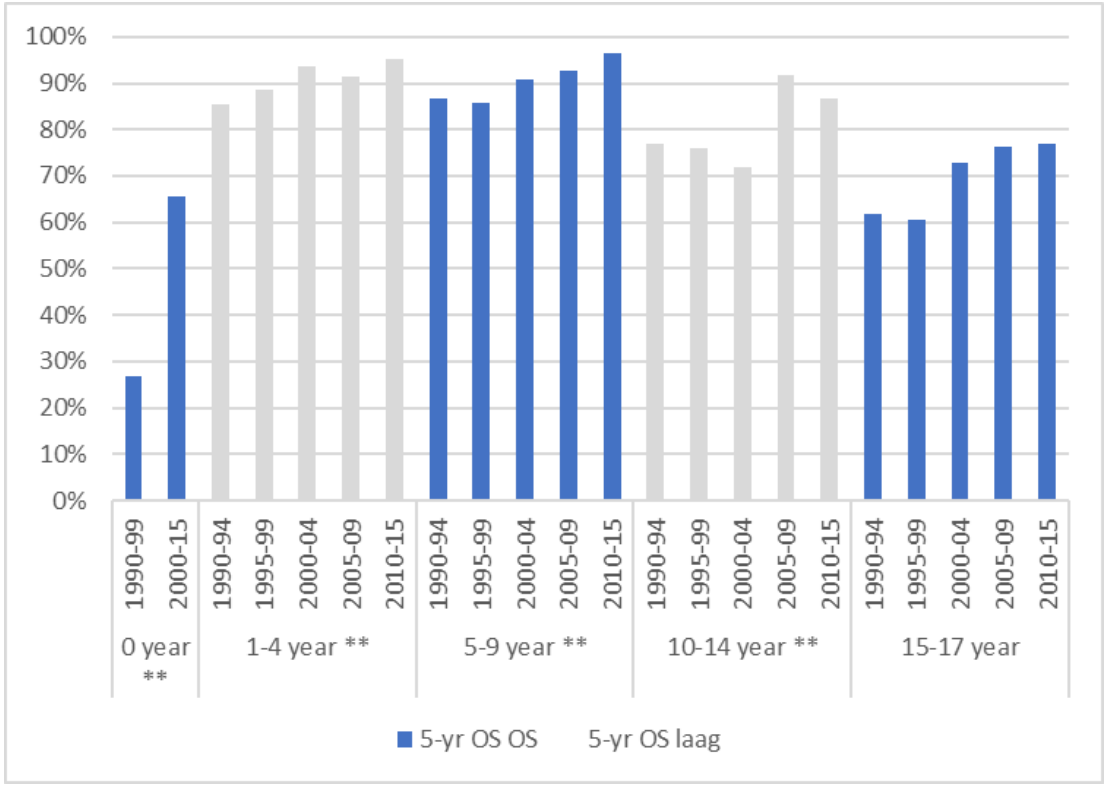
Adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands

5 yrs actuarial probabilities

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

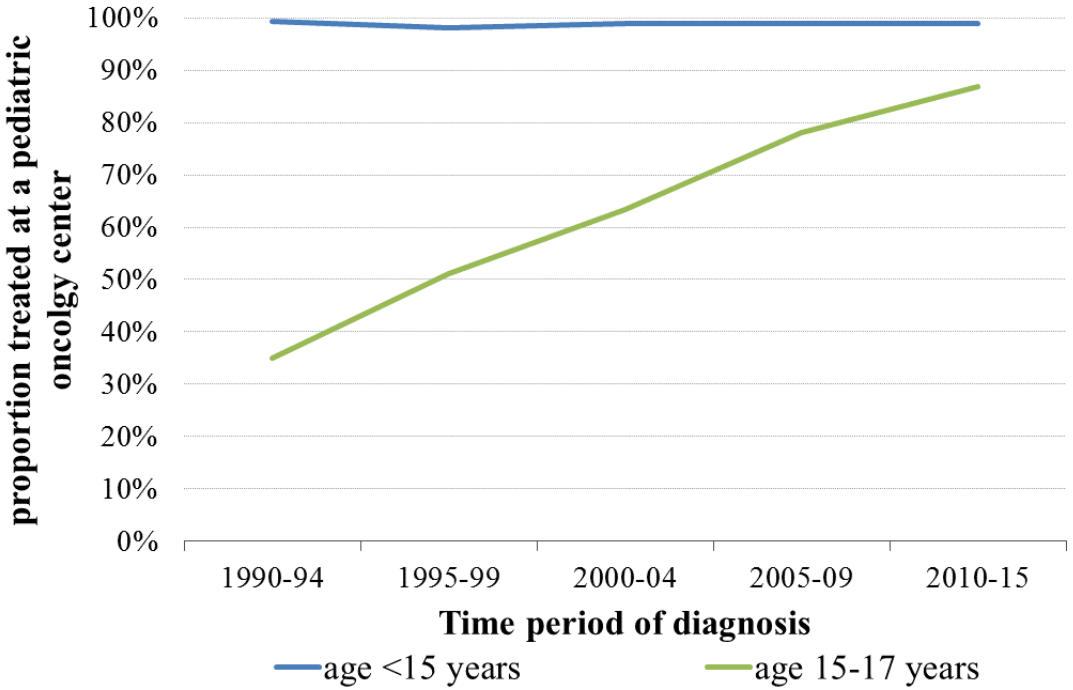
De Bont JM, et al. *Leukemia*. 2004;18(12):2032-2035.

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



Reedijk AMJ, et al. *Leukemia.* 2020. doi: 10.1038/s41375-020-01024-0. Online ahead of print.

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



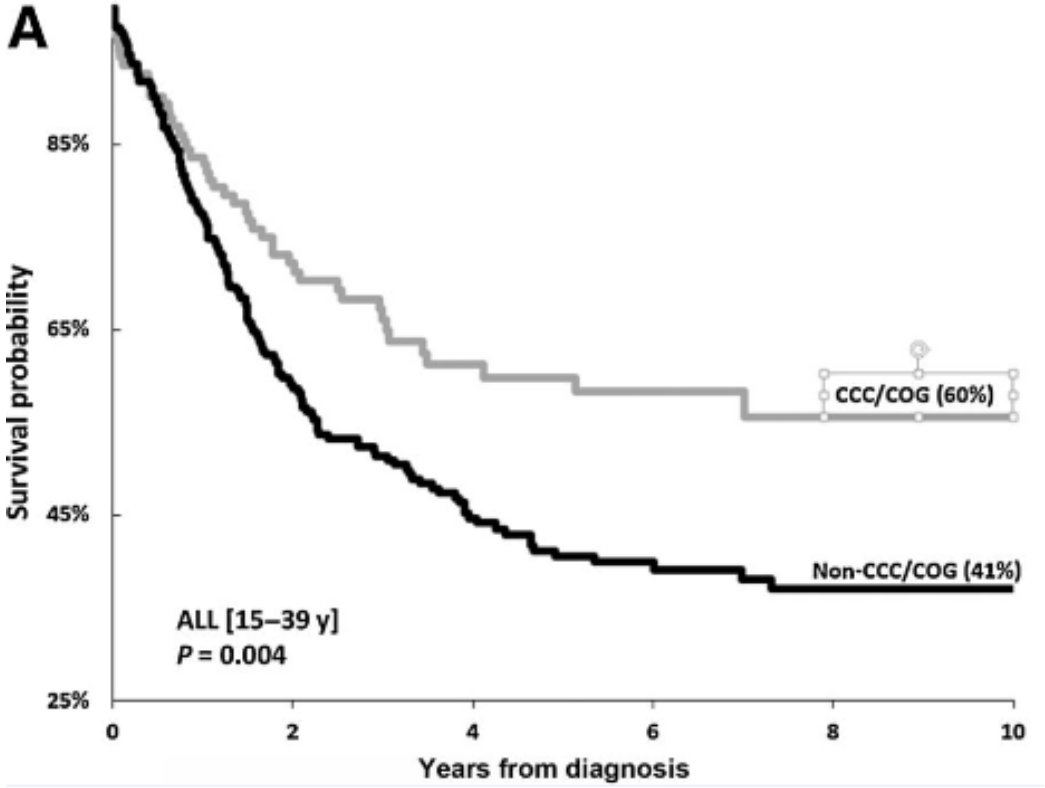
Reedijk AMJ, et al. *Leukemia.* 2020. doi: 10.1038/s41375-020-01024-0. Online ahead of print.

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

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

Reedijk AMJ, et al. Leukemia. 2020. doi: 10.1038/s41375-020-01024-0. Online ahead of print.

Survival in patients 15-39 years with ALL by treatment site in North-America



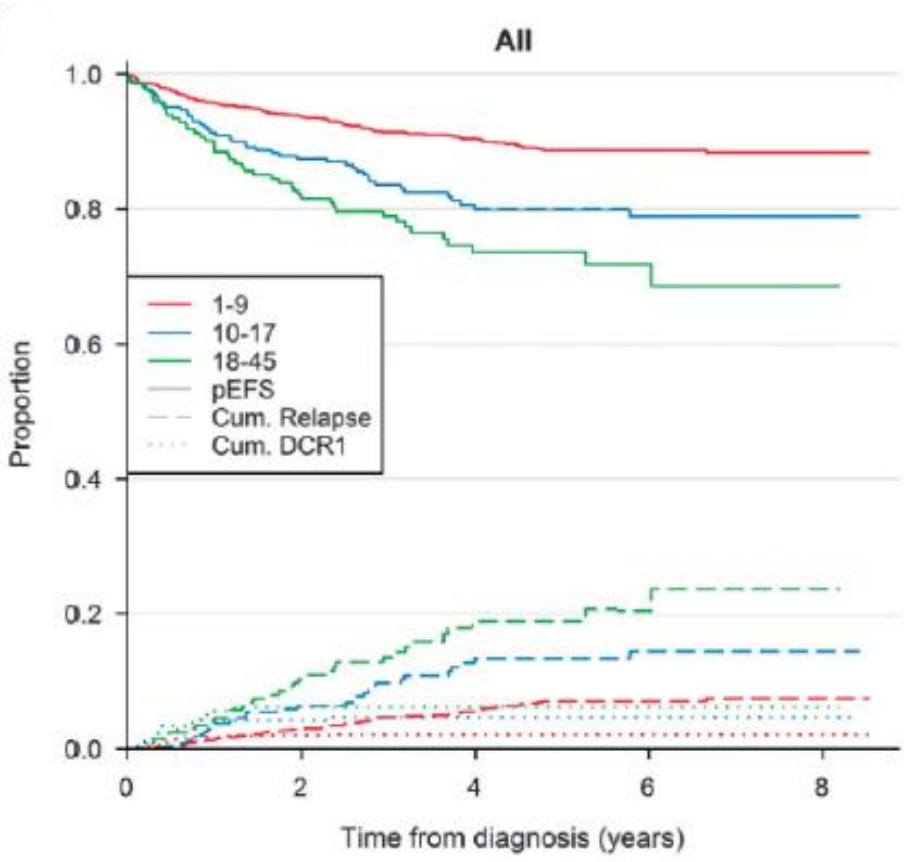
Wolfson J, et al. *Cancer Epidemiol Biomarkers Prev.* 2017;26(3):312-320.

Outcomes in older adolescents treated in recent pediatric trials

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

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

EFS, relapse and death in first remission by age



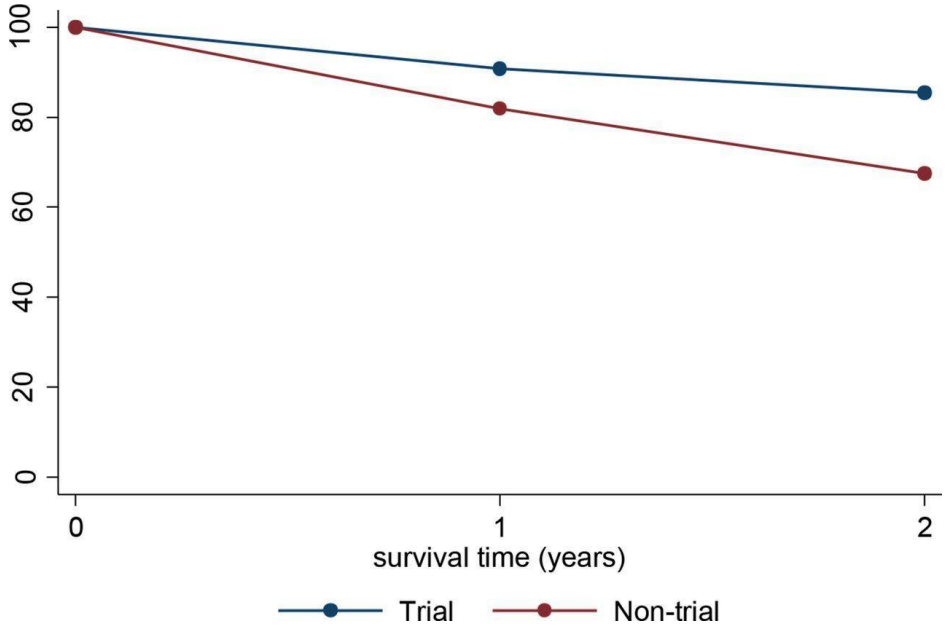
Toft N, et al. *Leukemia.* 2018;32(3):606-615.

Toxicity by age

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

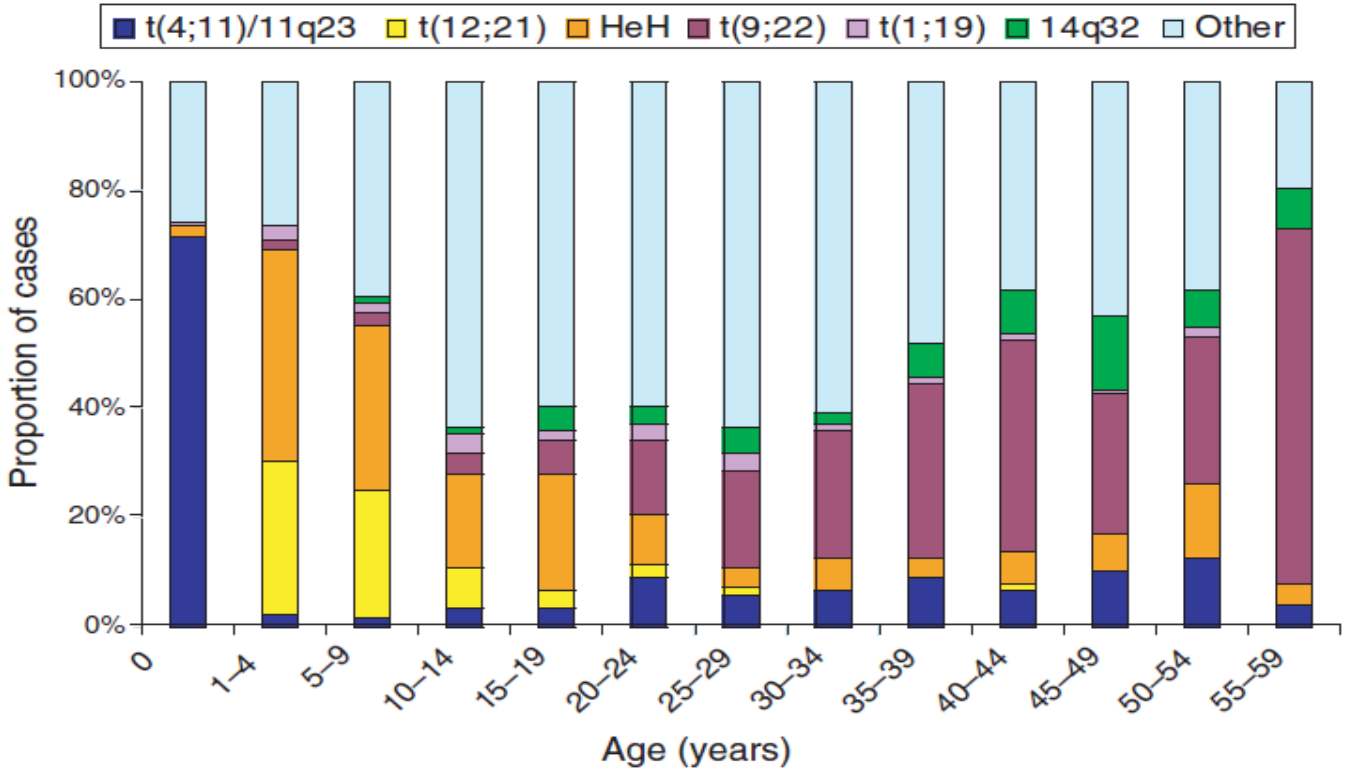
Toft N, et al. *Leukemia*. 2018;32(3):606-615.

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



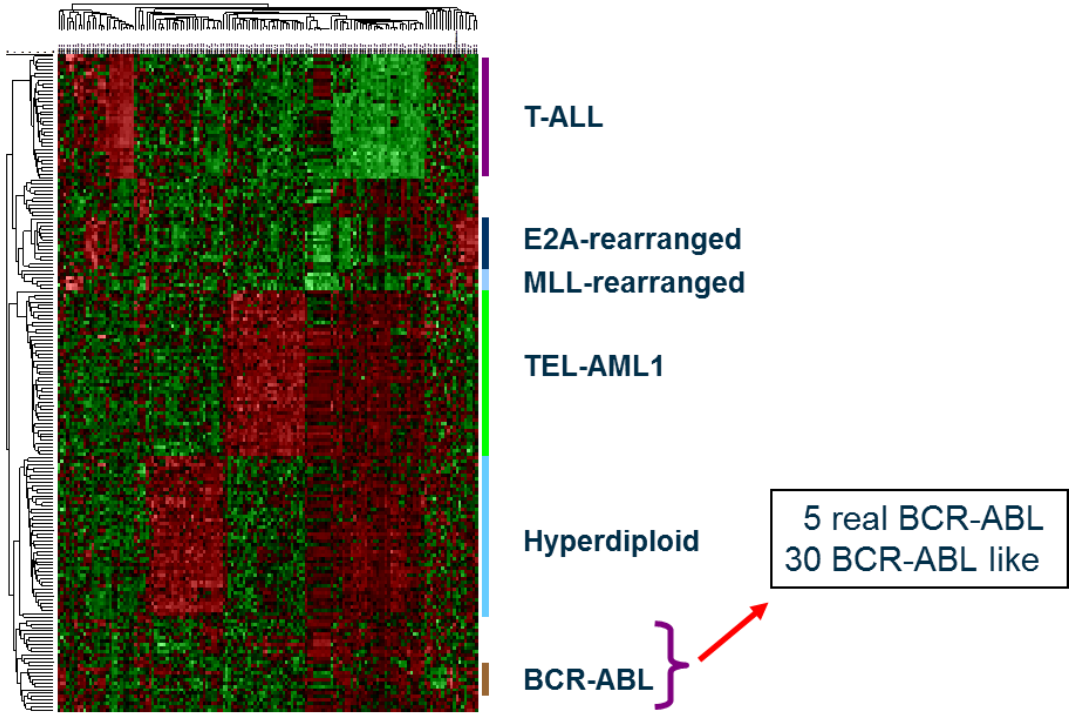
Hough R, et al. *BMJ Open.* 2017;7(10):e017052.

Distribution of cytogenetic subtypes of ALL by age



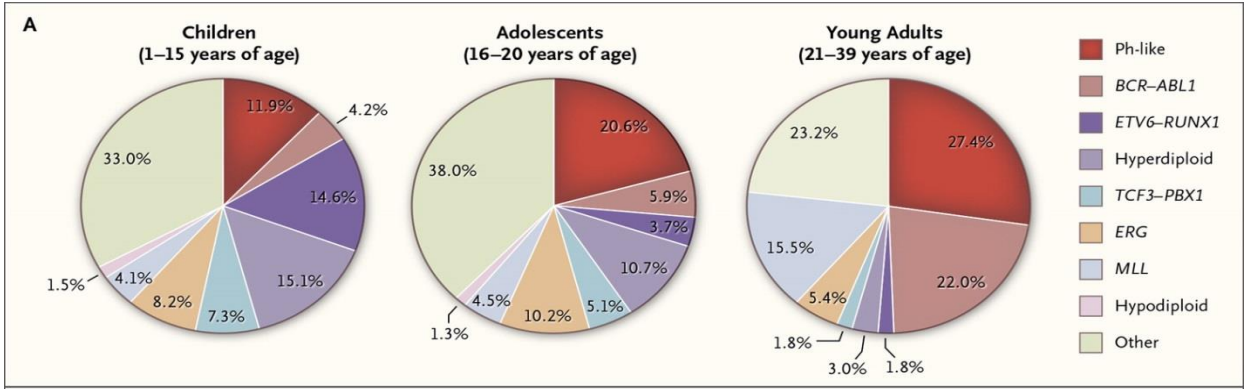
Harrison CJ. *Br J Haematol*. 2009;144(2):147-56.

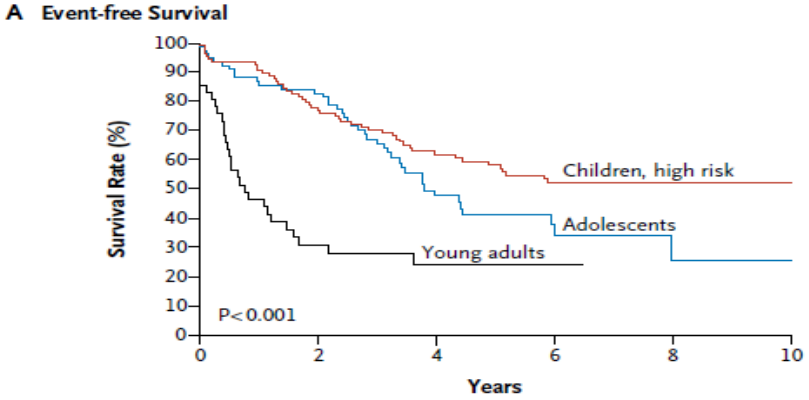
Discovery of BCR-ABL-like ALL within B-other group

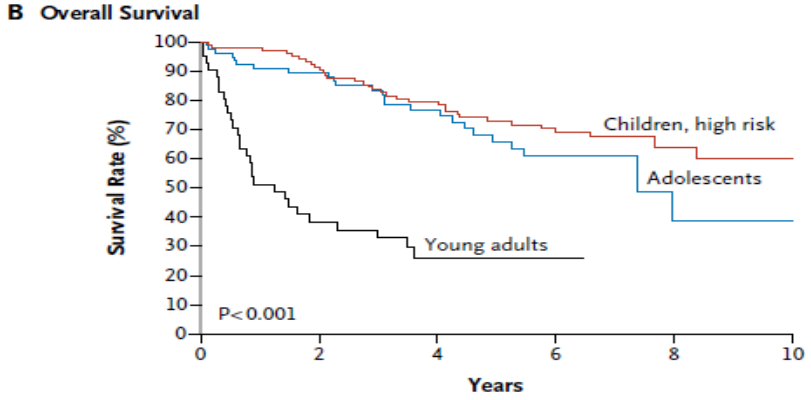


Den Boer ML, et al. *Lancet Oncol*. 2009;10(2):125-34.

Ph-like ALL: Prevalence and outcomes







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

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

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

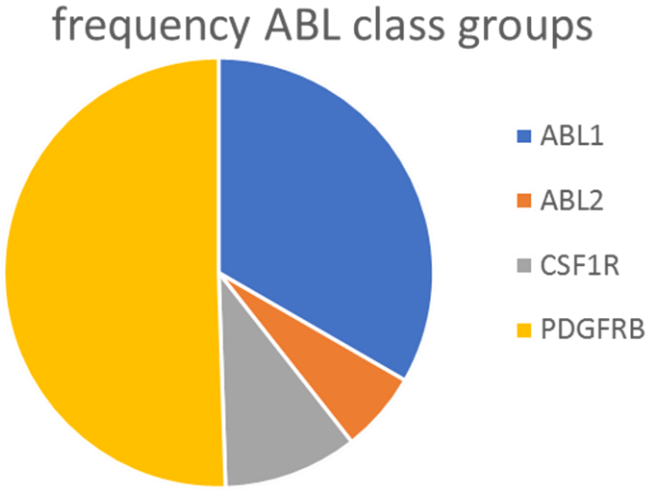
12% with ***ABL-1* class** fusions
Targetable with TKI e.g. imatinib/dasatinib

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

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

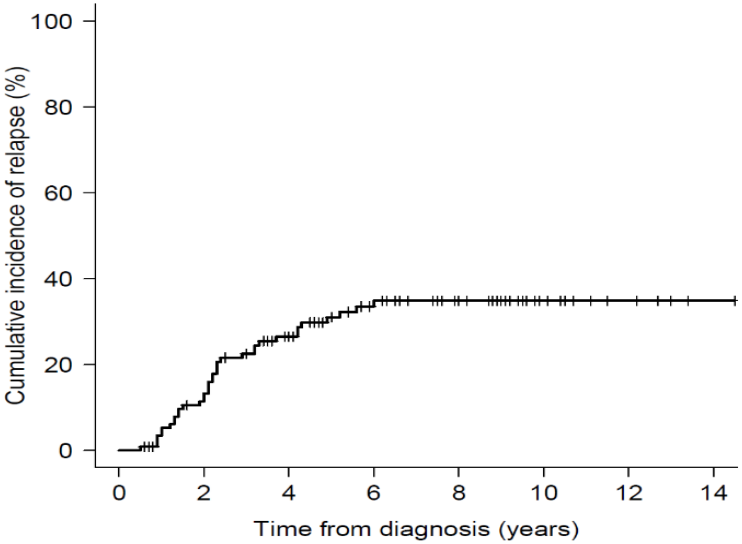
Outcome of ABL-class ALL treated without tyrosine kinase inhibitors (TKI): a Ponte di Legno group analysis

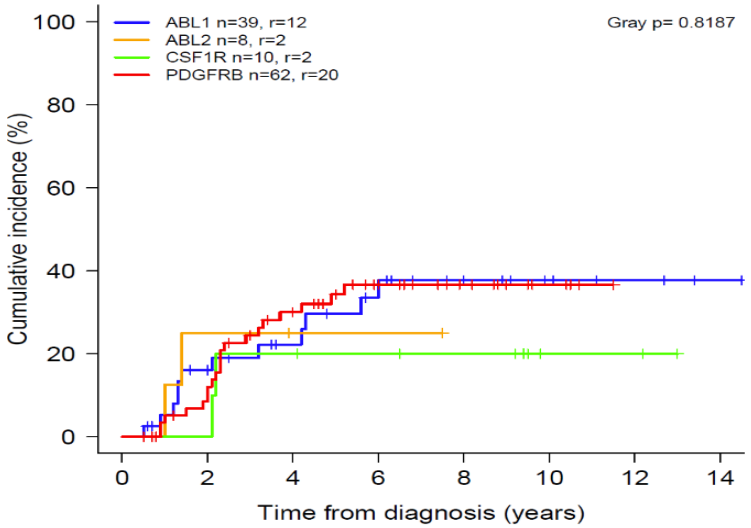
- 122 cases
  - PDGFRB (52%)
  - ABL1 (33%)
  - CSF1R (8%)
  - ABL2 (7%)
- Recent protocols (2000-2018)
- Not treated with TKI
- 10 study groups
  - Europe: DCOG/AIEOP/BFM/UK-ALL/COALL
  - Asia: JACLS/Ma-Spore/ANZCHOG/TCCSG
  - North-America: SJCRH/COG



Den Boer ML, *Lancet Haematol.* 2020.

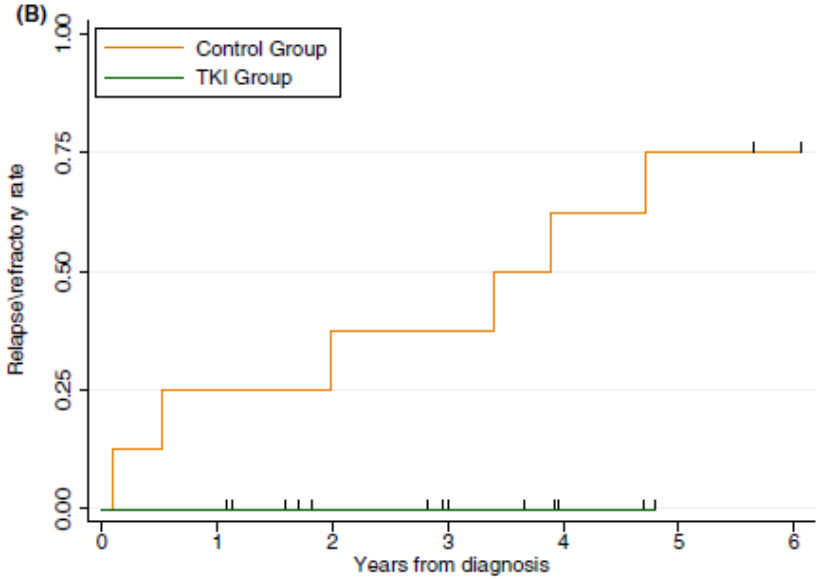
Cumulative incidence of relapse in ABL-class patients

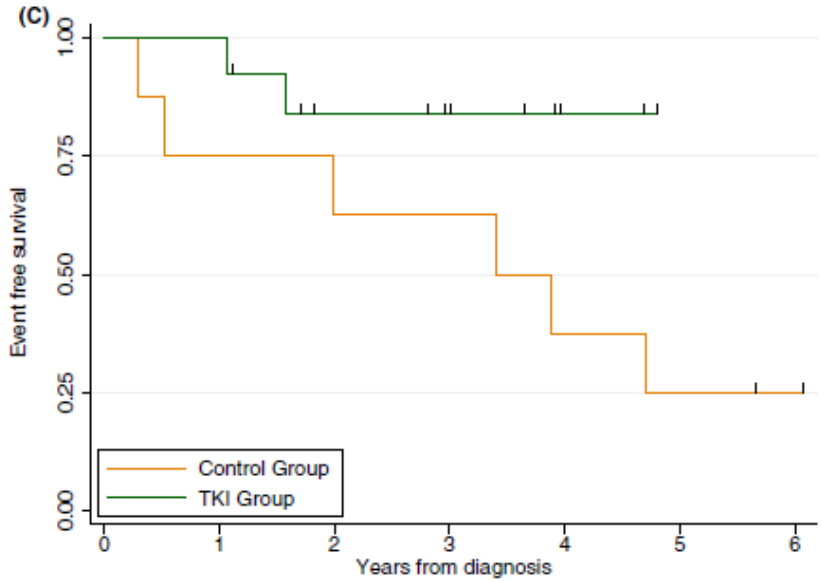




Den Boer ML, *Lancet Haematol.* 2020.

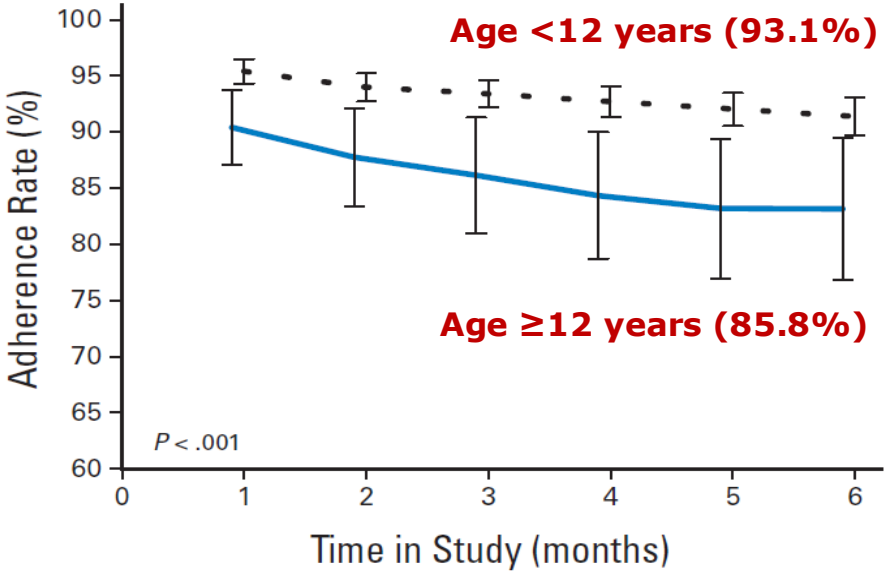
Outcome of ABL-class ALL treated with or without imatinib

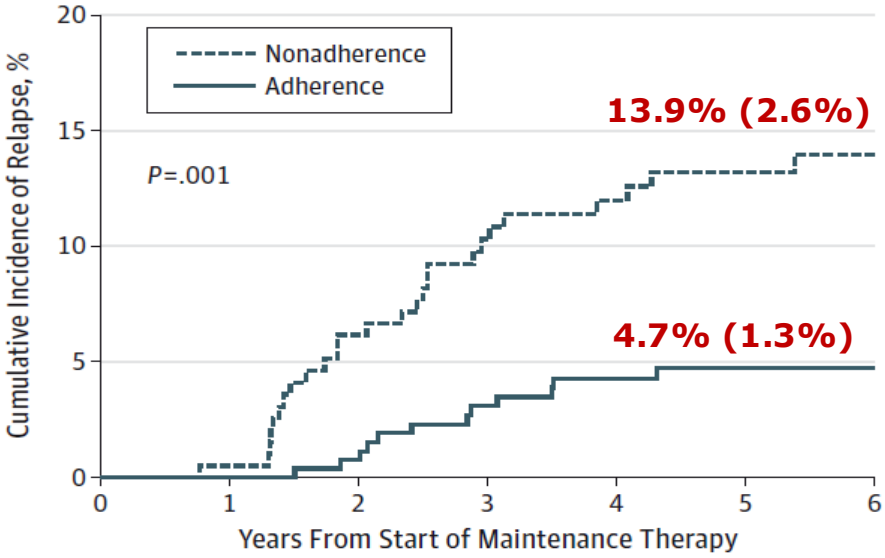




Moorman AV, et al. *Br J Haematol*. 2020; doi: 10.1111/bjh.17093. Online ahead of print.

Low adherence to oral 6MP significantly increases relapse risk





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

AYA conclusions

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

Question 1

After listening to the presentation, which assertion is NOT correct for AYA ALL patients?

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

Thank you

princess máxima center
pediatric oncology

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Q&A

APTITUDE HEALTH

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Bispecific T-cell engagers as post-reinduction therapy improves survival in pediatric and AYA B-ALL

Patrick Brown

APTITUDE HEALTH

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

A Report from Children's Oncology Group Study AALL1331

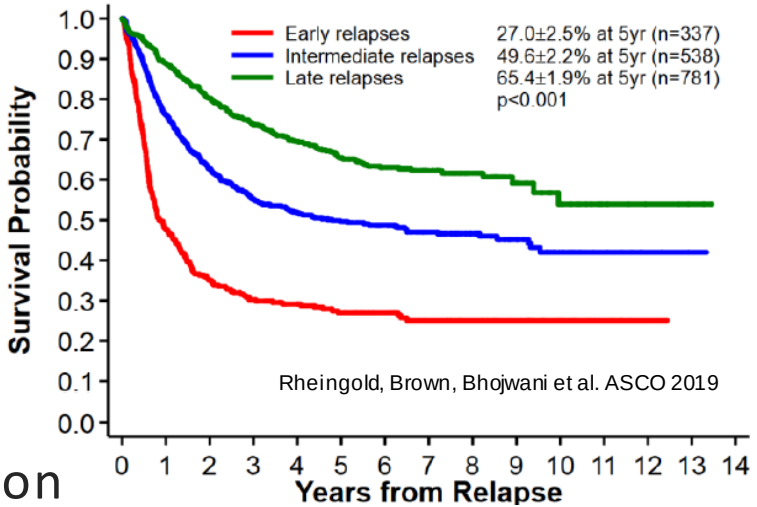
Patrick A. Brown, Lingyun Ji, Xinxin Xu, Meenakshi Devidas, Laura Hogan, Michael J. Borowitz, Elizabeth A. Raetz, Gerhard Zugmaier, Elad Sharon, Lia Gore, James A. Whitlock, Michael A. Pulsipher, Stephen P. Hunger, Mignon L. Loh

CHILDREN'S ONCOLOGY GROUP

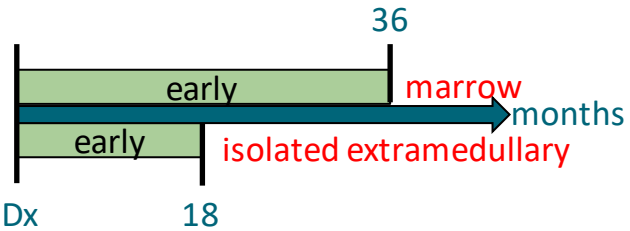
Brown PA, et al. *Blood*. 2019;134(suppl_2):LBA-1.

Background

- Poor survival for first relapse B-ALL in children, adolescents and young adults (AYA), especially early relapses



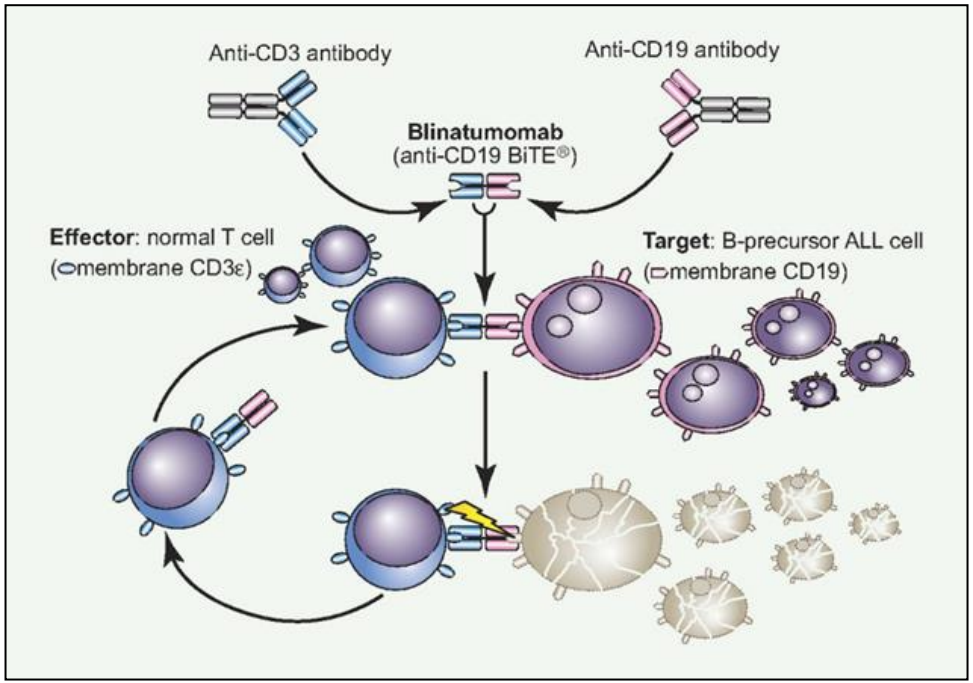
- Standard treatment approach
  - Reinduction chemotherapy -> 2nd remission
  - Consolidation
    - Early relapse: Intensive chemo -> HSCT
      - Goal: MRD-negativity prior to HSCT
    - Late relapse
      - "MRD high": same as early
      - "MRD low": Intensive chemo -> maintenance therapy



CHILDREN'S ONCOLOGY GROUP

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

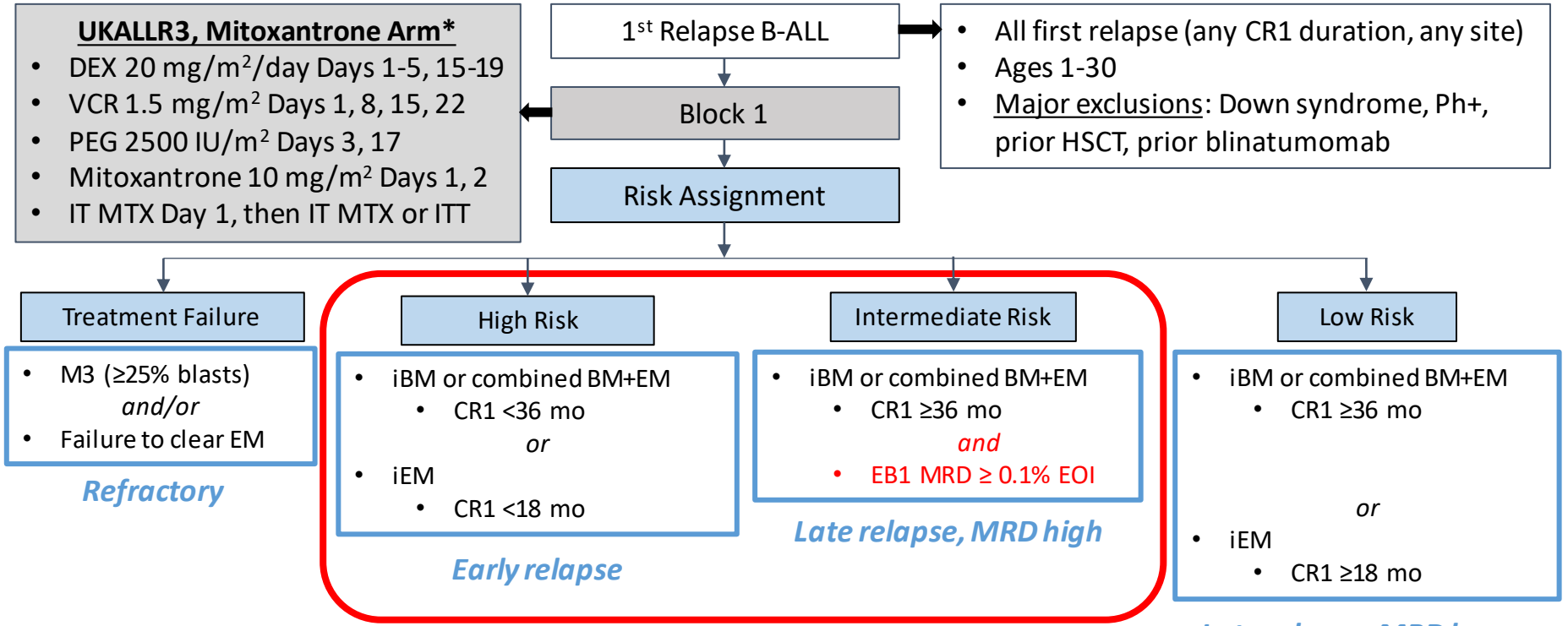
- In MRD+ setting (adults)
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

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

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

CHILDREN'S ONCOLOGY GROUP

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

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

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

Stratifications

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

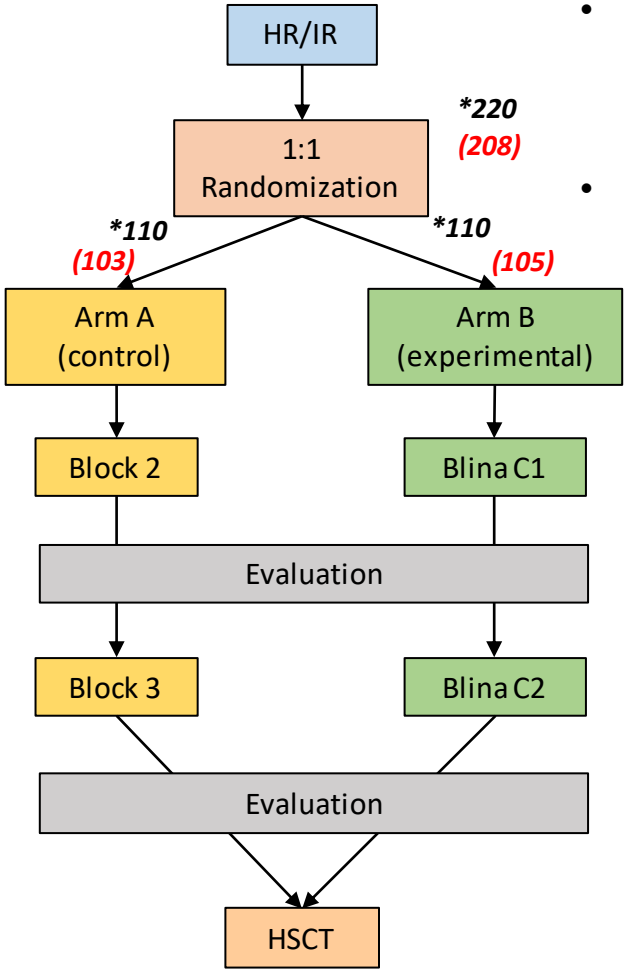
UKALLR3, Block 2*

- 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 $\mu g/m^2$/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 cut-off 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 cross-over to experimental Arm B for patients still receiving therapy
- DSMC recommendation based on
  - The difference in **DFS and OS** between arms
  - The profound difference in **toxicity** between arms
  - The highly significant difference in **MRD** clearance rates between arms

CHILDREN'S ONCOLOGY GROUP

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

Baseline Characteristics

16% AYA →

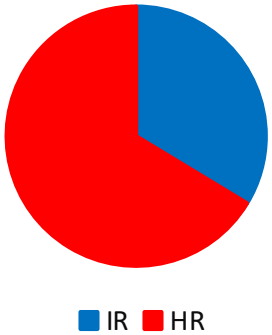
	Arm A (n=103)	Arm B (n=105)
Age at enrollment (years)		
Median (range)	*9 (1-27)*	*9 (1-25)*
1-9	55 (53%)	55 (52%)
10-17	30 (29%)	35 (33%)
18-30	18 (18%)	15 (14%)
Sex		
Female	49 (48%)	48 (46%)
Male	54 (52%)	57 (54%)
NCI Risk Group at Diagnosis		
High Risk	60 (58%)	59 (56%)
Standard Risk	43 (42%)	46 (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

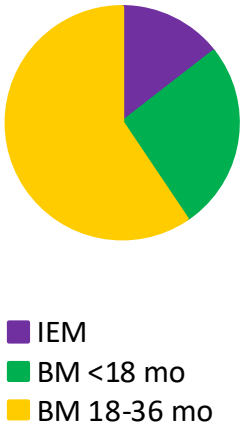
CHILDREN'S ONCOLOGY GROUP

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 BM 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%)

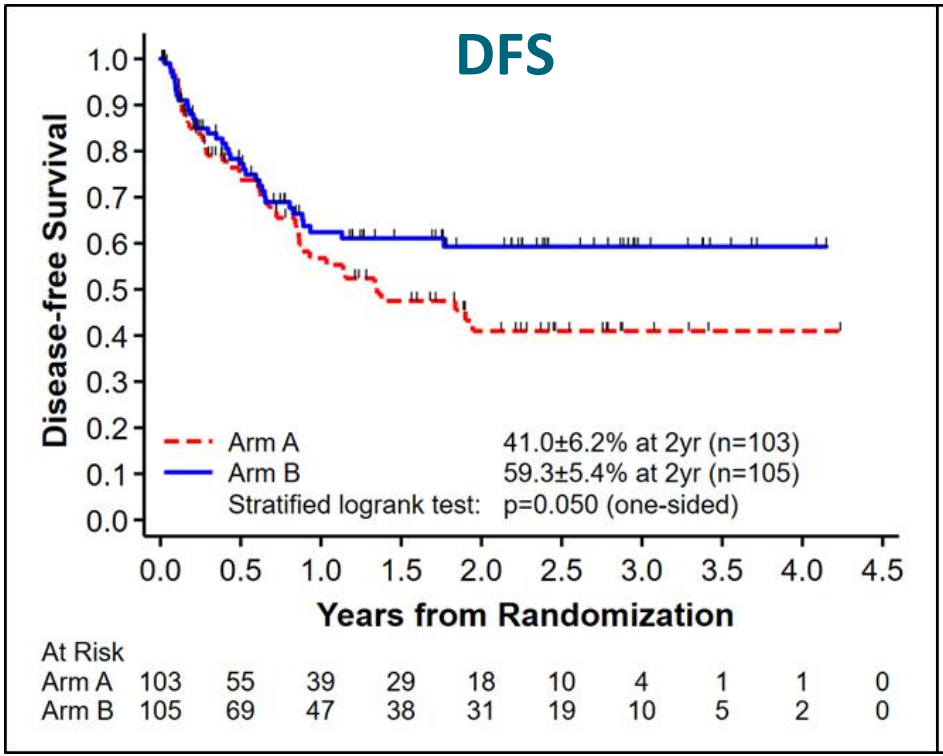


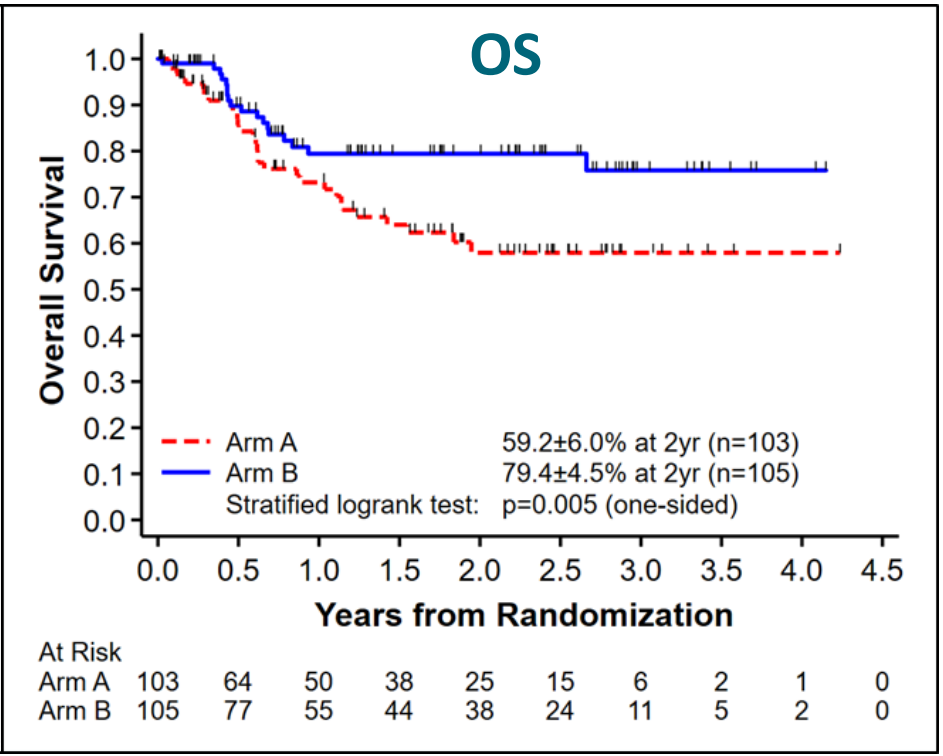


CHILDREN'S ONCOLOGY GROUP

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

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



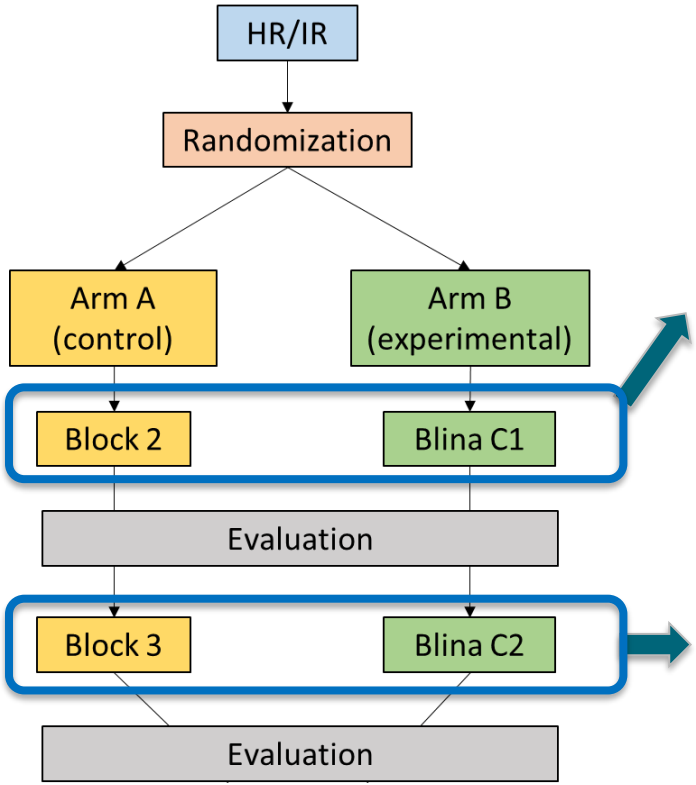


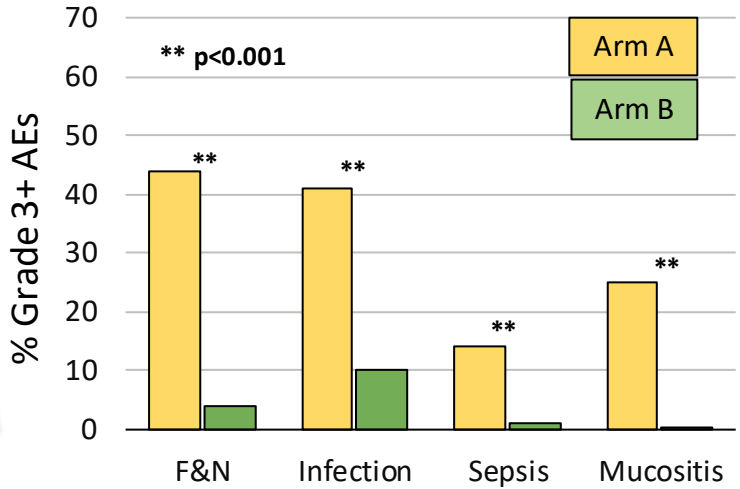
CHILDREN'S ONCOLOGY GROUP

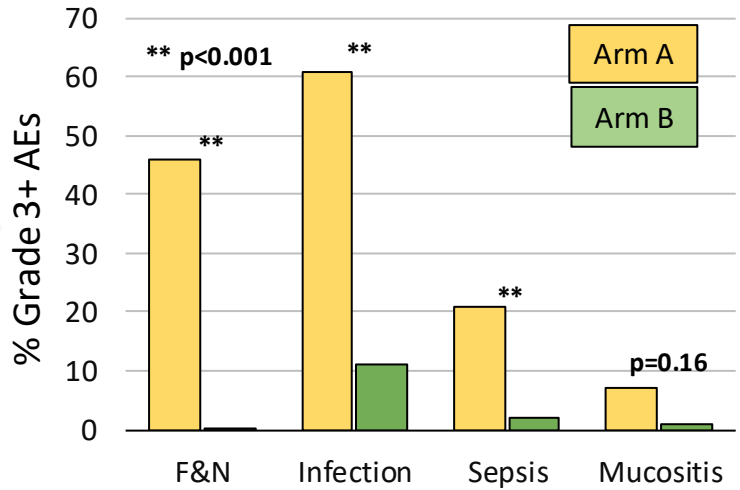
Median follow up 1.4 years

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

Adverse Events







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

CHILDREN'S ONCOLOGY GROUP

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

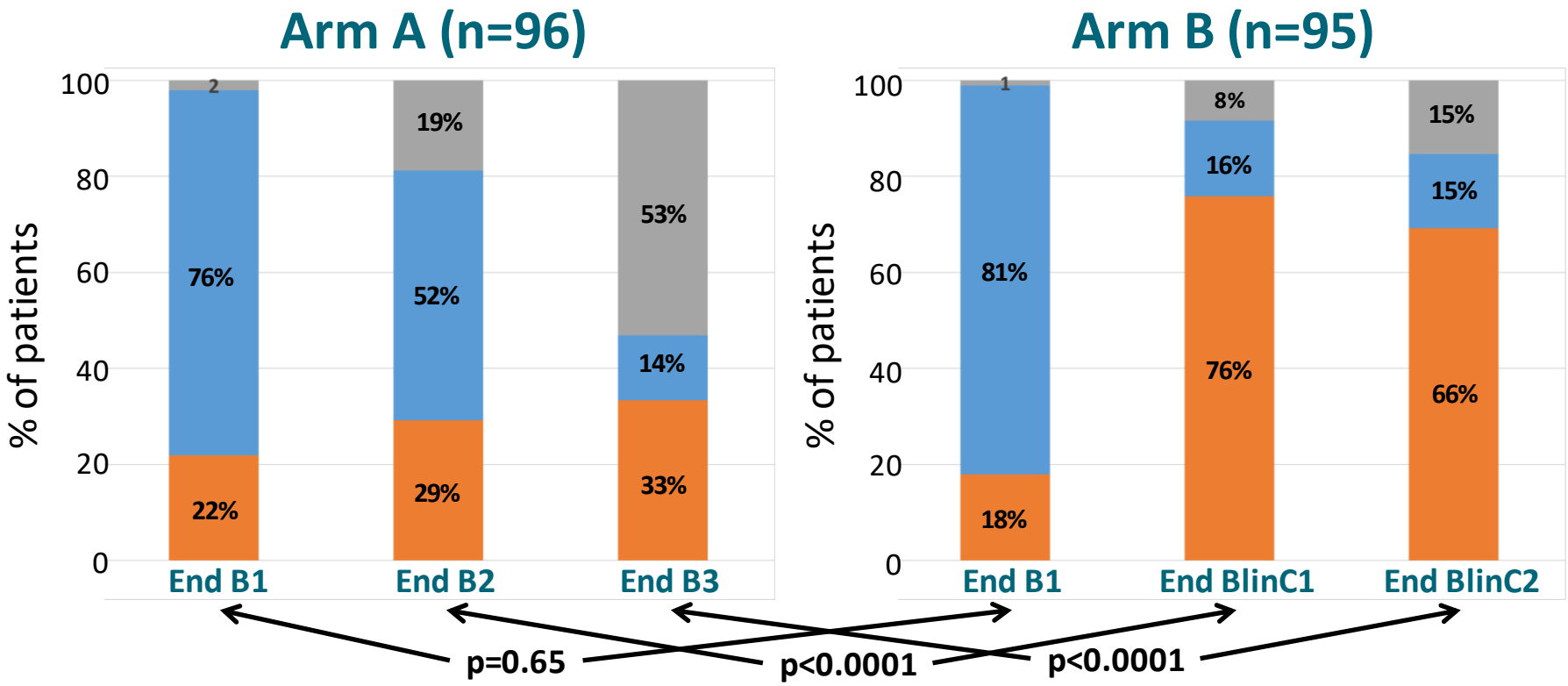
Blinatumomab-Related AEs on Arm B

	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.

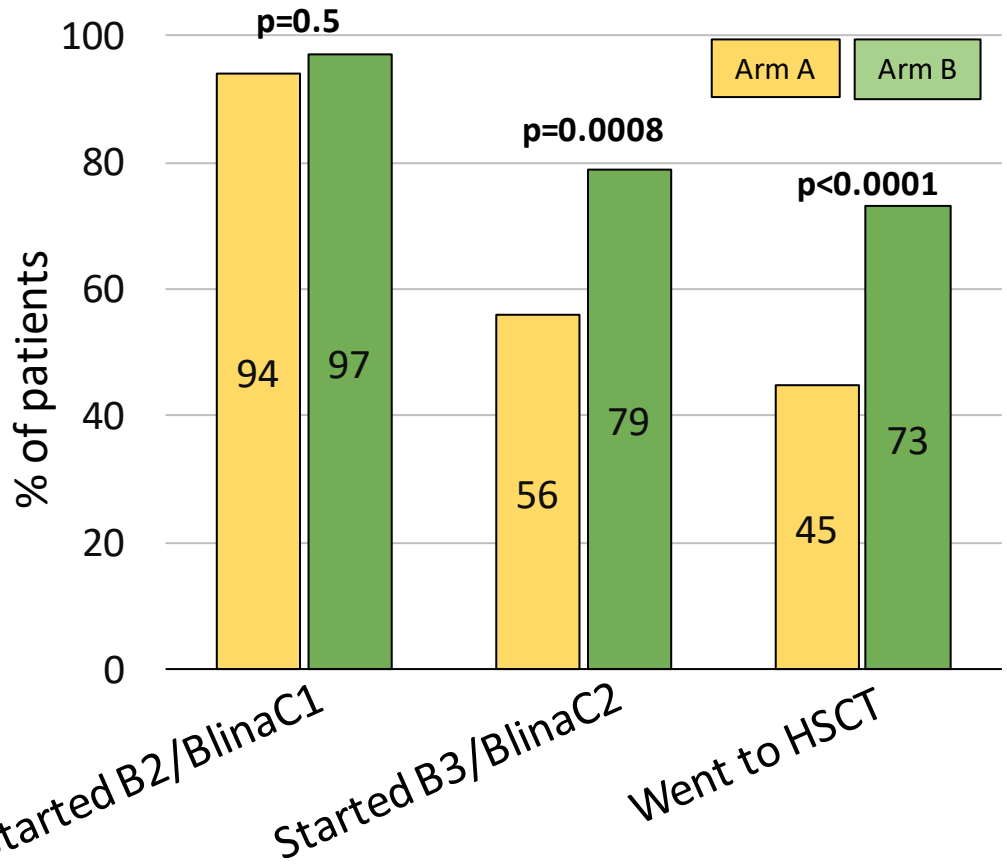
MRD Clearance (for iBM and BM+EM)



CHILDREN'S ONCOLOGY GROUP

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

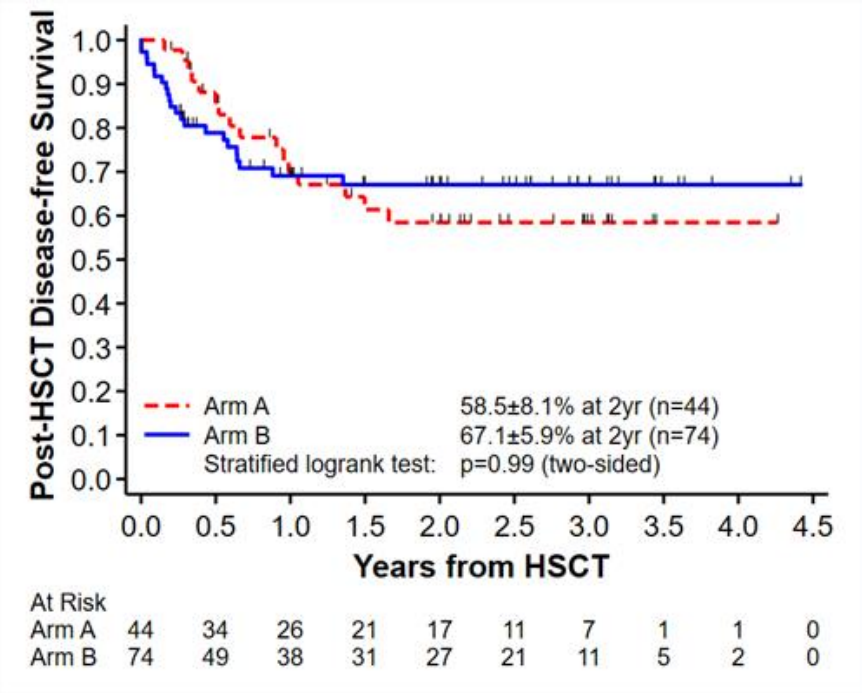
Drop Out/HSCT Rates: Arm A vs Arm B

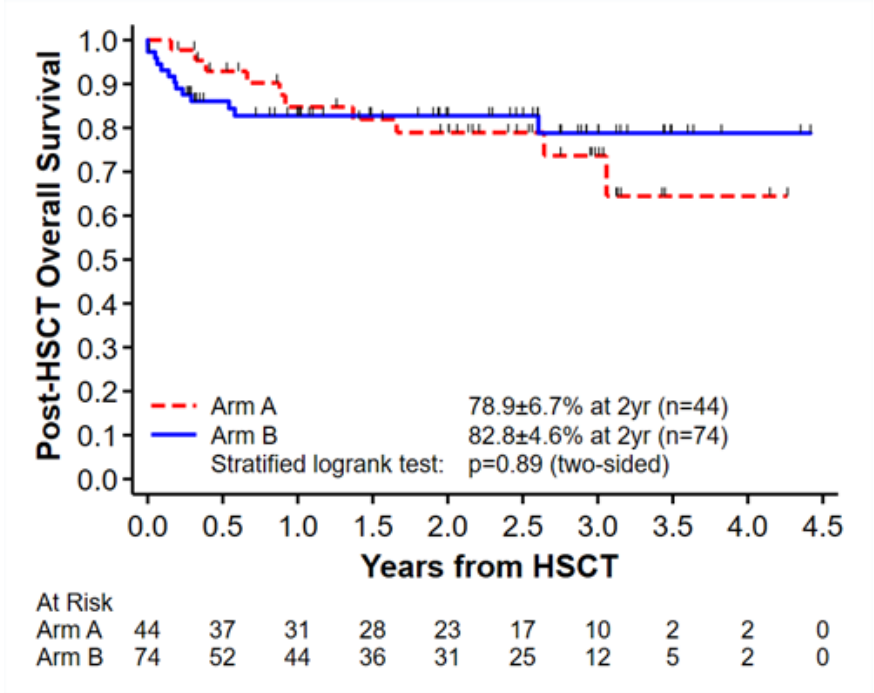


A significant contributor to the improved outcomes for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may be the **ability of blinatumomab to successfully bridge to HSCT**

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

Post-HSCT Survival





CHILDREN'S ONCOLOGY GROUP

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

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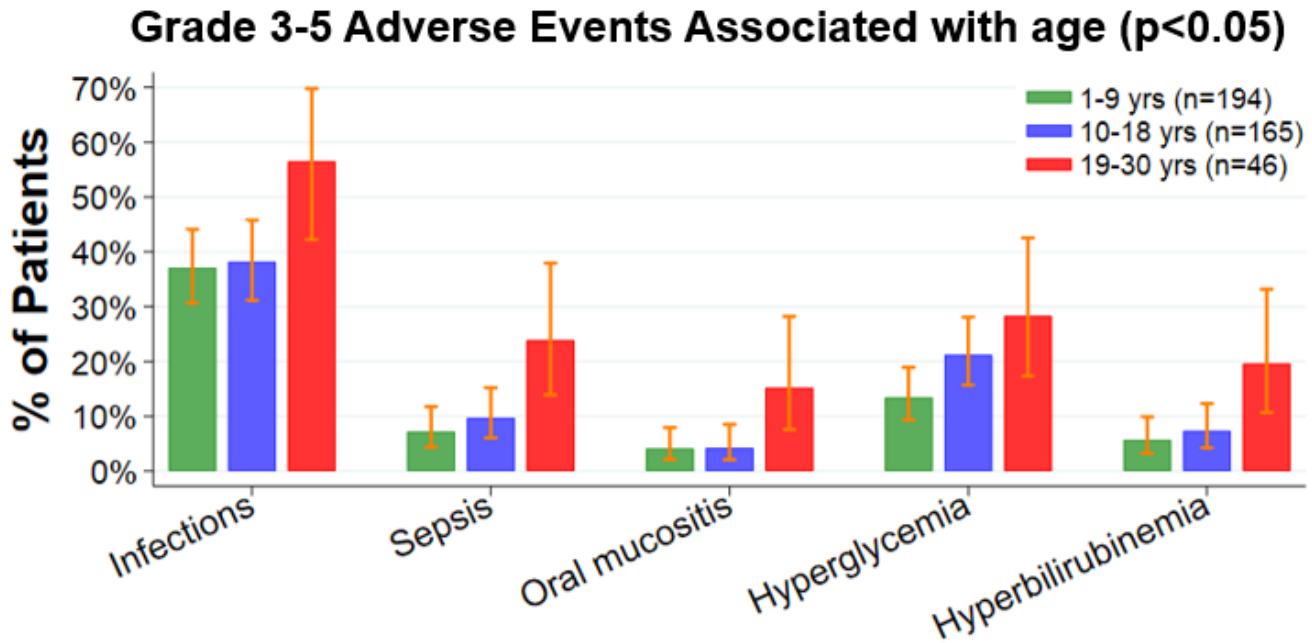
None	12	14

CHILDREN'S ONCOLOGY GROUP

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

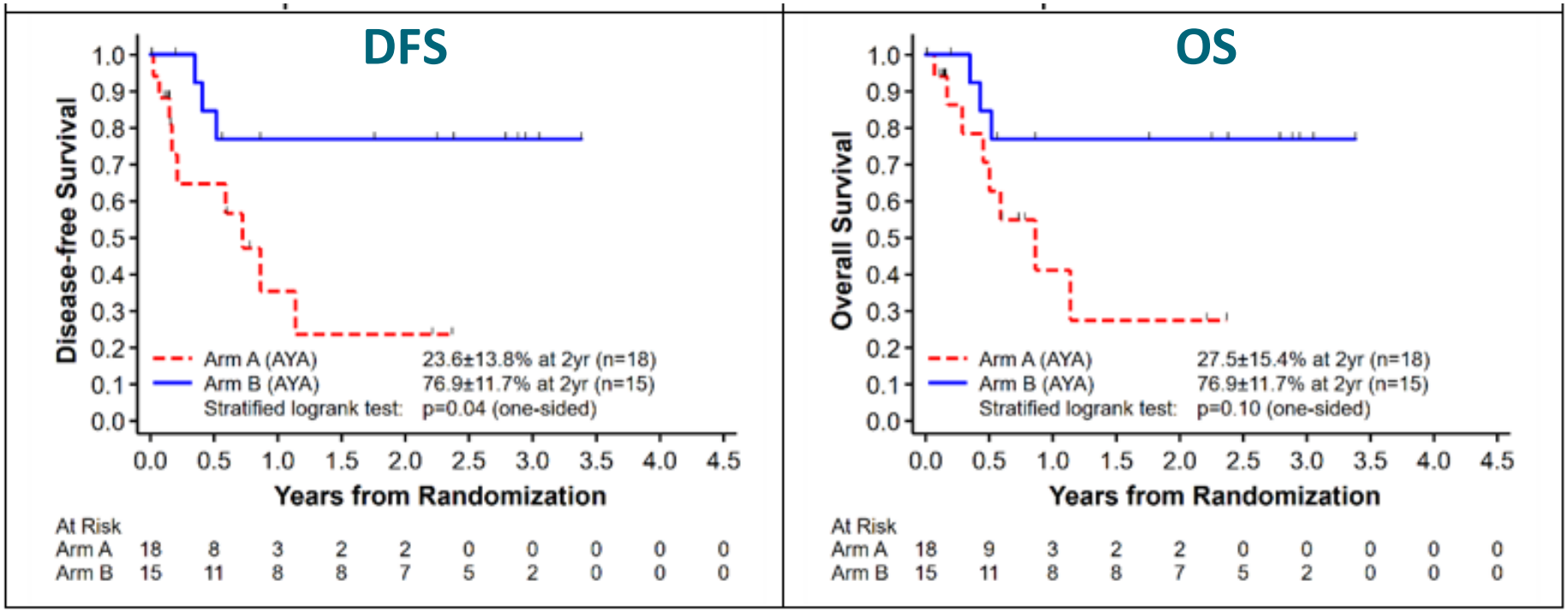
Results AYA Patients (Ages 18-30 at Relapse)



CHILDREN'S ONCOLOGY GROUP

Hogan LB, et al. *Blood*. 2018;132(Suppl_1):1382.

Results AYA Patients (Ages 18-30 at Relapse)



CHILDREN'S ONCOLOGY GROUP

Median follow up 1.4 years

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 (especially AYA)
  - 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

CHILDREN'S ONCOLOGY GROUP

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

Question 1

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

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
  - Mike Pulsipher
  - Sue Rheingold
  - Teena Bhatla
  - Sarah Tasian
  - 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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Brown PA, et al. *Blood*. 2019;134(suppl_2):LBA-1.

Funding

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

CHILDREN'S ONCOLOGY GROUP

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

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Discussion

APTITUDE HEALTH®

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Break

APTITUDE HEALTH

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Panel discussion on the role of HSCT

APTITUDE HEALTH

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%

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Pros and cons of transplantation

Patrick Brown

APTITUDE HEALTH

Pros and Cons of Transplantation

Patrick Brown, MD

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

Define “transplantation”

- Allogeneic hematopoietic stem cell transplantation
- Possible allogeneic donors
  - Related
    - HLA identical sibling
    - Haploidentical relative
  - Unrelated
    - HLA “matched” living donor
    - Umbilical cord blood
- Possible stem cell sources: bone marrow, PBSC
- Other variables: prep regimen, GVHD ppx, graft processing, post-HSCT relapse prevention, etc

Personal communication from Dr Brown.

Pros and cons: Compared to what?

> Typical comparator is continued systemic therapy (multiagent chemotherapy, TKI, immunotherapy, etc)

Putative Pros	Putative Cons
Improved survival • Median survival, or proportion of “cures”? • Competing events: relapse vs TRM ?	Increased toxicity • Short term: Infection, aGVHD, VOD • Long term: Infection, cGVHD, growth, fertility, SMN, endocrine
Shorter duration of treatment • On paper, yes . . . but what about chronic medical issues?	More resource-intensive
	Age and comorbidity limitations
	Limited access / need for travel

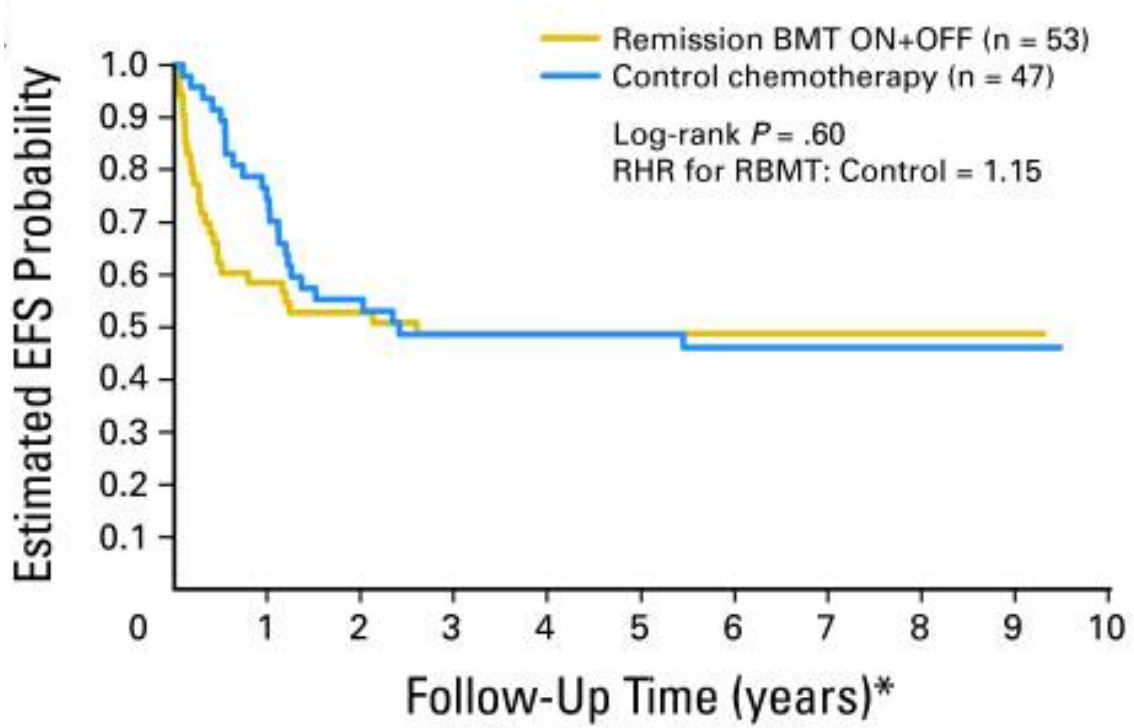
Personal communication from Dr Brown.

Does transplant improve survival in ALL?

- Yes and no (maybe)
- Depends on a multitude of complicated factors
  - Patient-related
    - Age (infant; child; AYA; adult; elderly)
    - Comorbidities
  - Disease-related
    - Timing: CR1 vs CR2+
    - Genetic subset (Ph+, hypodiploid, etc)
    - MRD response to induction/reinduction
    - MRD status at time of transplant
  - Treatment-related
    - Evolving effectiveness of non-transplant therapy (eg, TKI, immunotherapy)
    - Relative effectiveness of various transplant strategies (eg, TBI vs non-TBI prep)

Personal communication from Dr Brown.

Infant ALL, CR1



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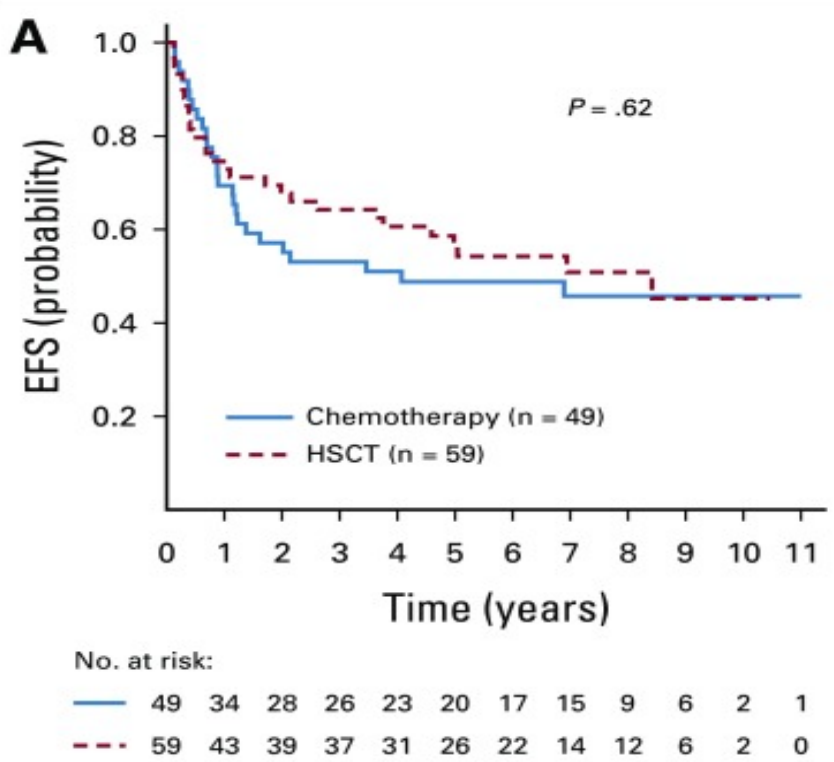
Dreyer ZE, et al. *J Clin Oncol.* 2011;29(2):214–222.

Hypodiploid ALL, CR1



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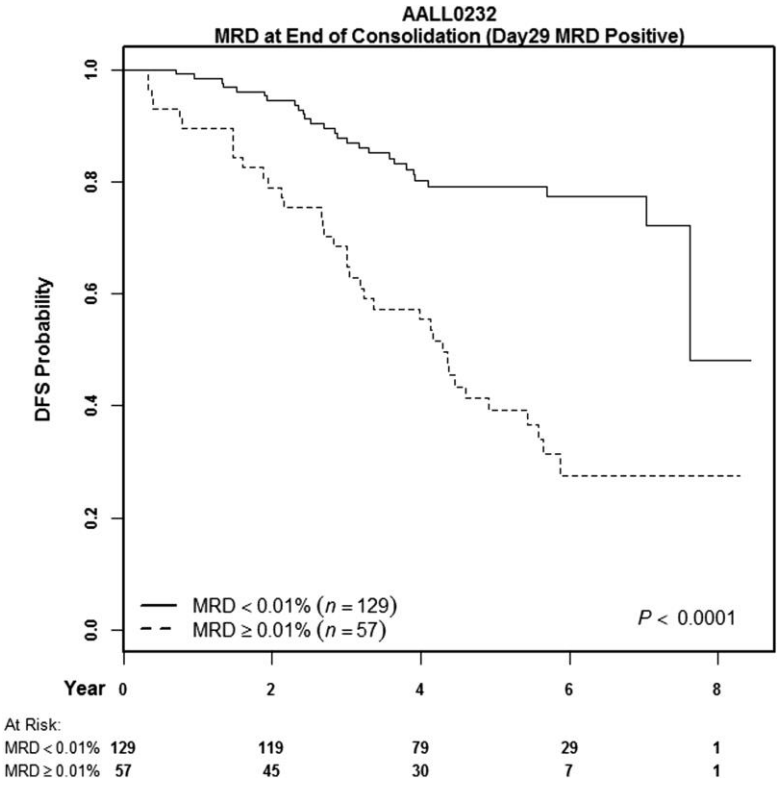
McNeer JL, et al. *J Clin Oncol.* 2019;37(10):780-789.

End-consolidation MRD+, CR1



Patients with HR B-ALL treated on AALL0232

MRD determined by multiparameter flow cytometry

Day 29 MRD >0.1%

5-year DFS by EOC MRD

MRD <0.01%: 79% ± 5%

MRD ≥0.01%: 39% ± 7%

CAR T cells?
Blina?
HSCT?

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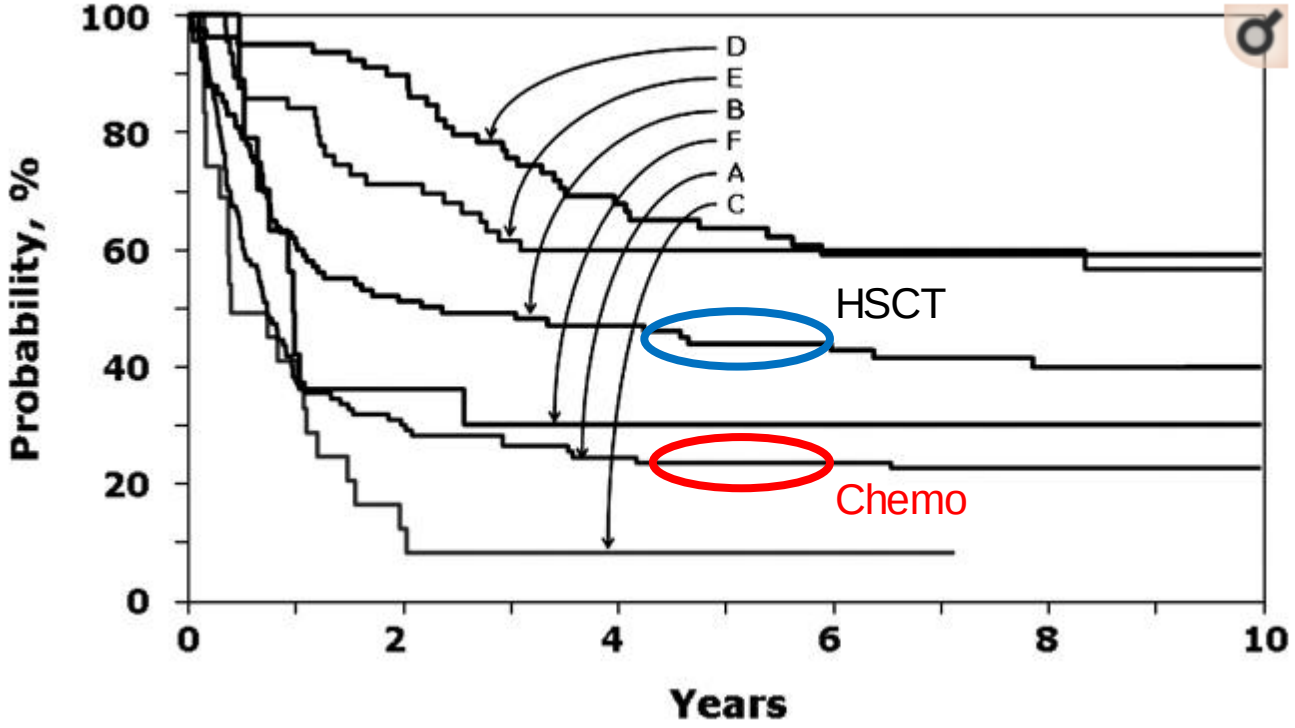
Borowitz MJ, et al. *Blood.* 2015;126:964-971.

CR2, early relapse



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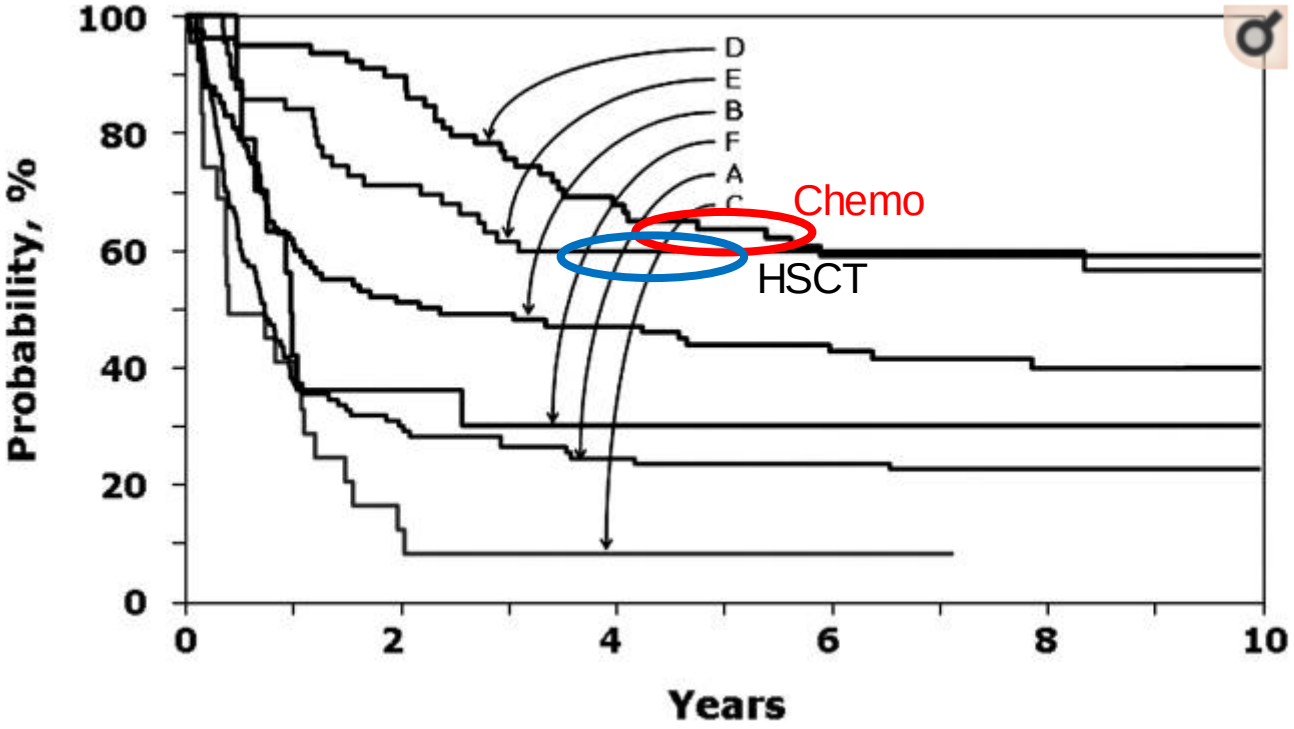
Eapen M, et al. *Blood.* 2006;107(12):4961–4967.

CR2, late relapse



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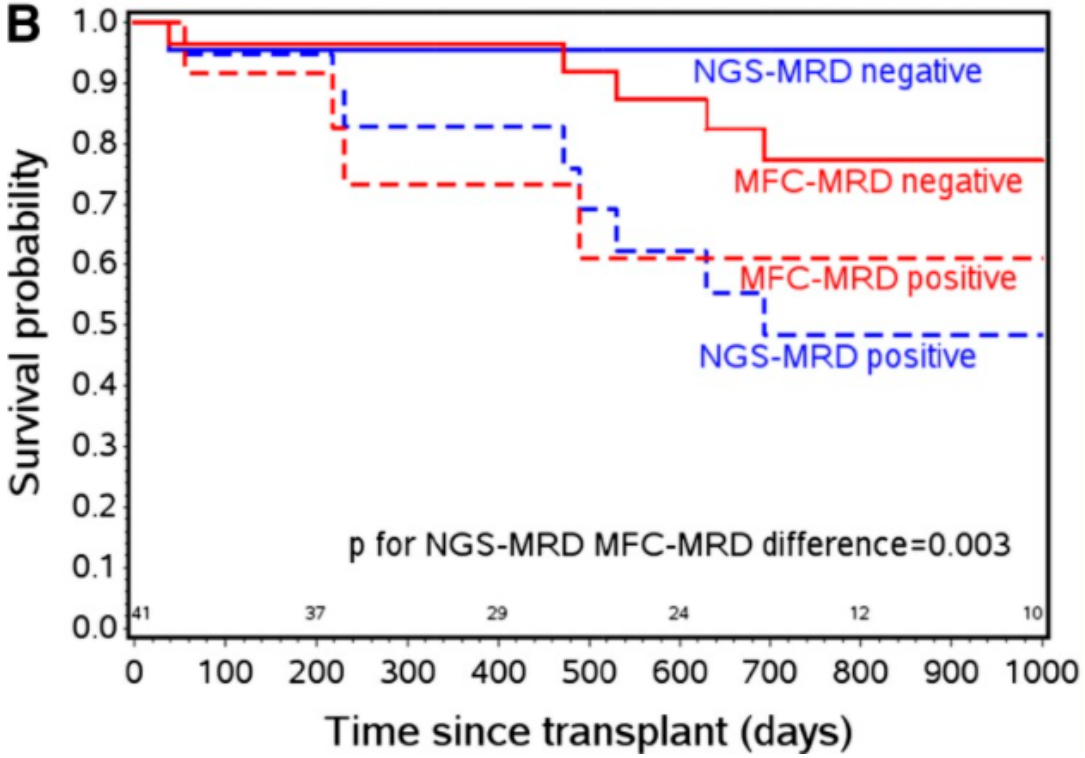
Eapen M, et al. *Blood.* 2006;107(12):4961–4967.

MRD status pre-transplant



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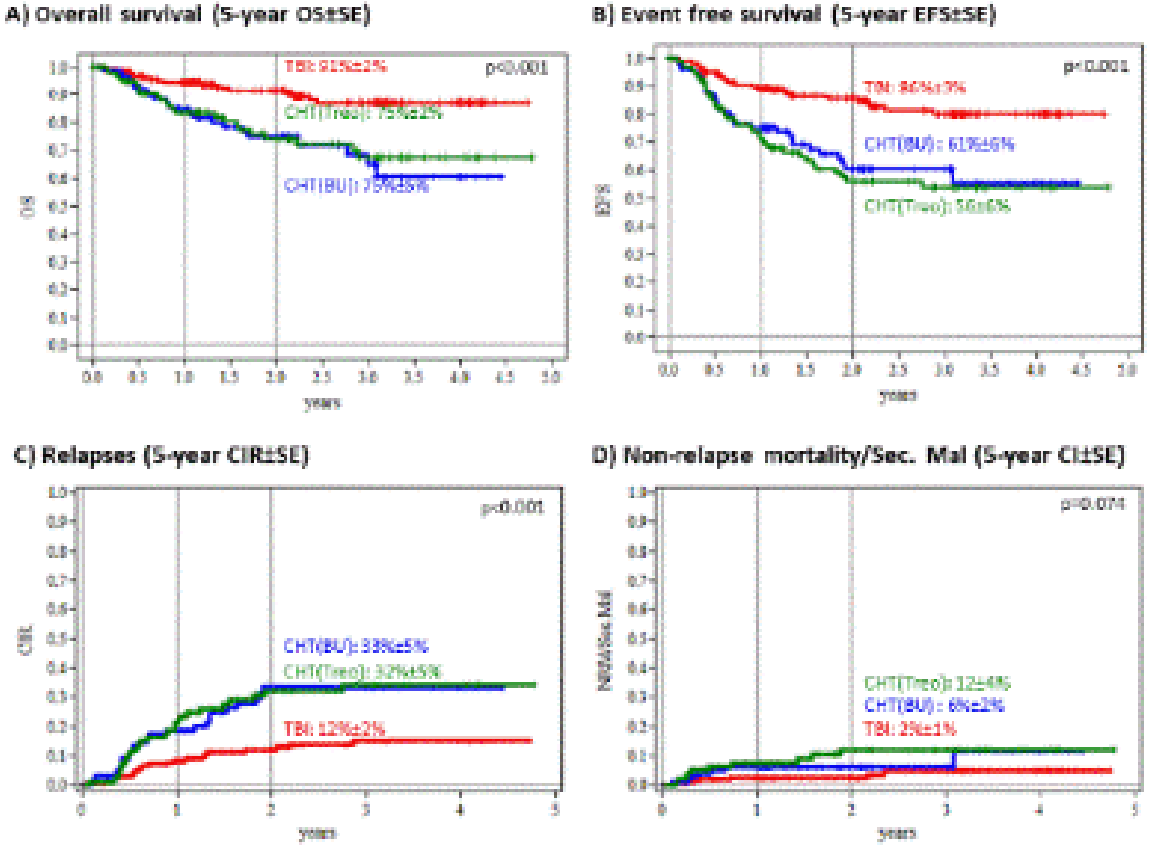
Pulsipher MA, et al. *Blood.* 2015;125(22):3501–3508.

TBI vs chemo prep



Peters C, et al. EHA 2020. Abstract: 294922;S102.

Summary

- Transplant in ALL is currently widely accepted therapy for high-risk CR2 (ie, early first relapse), preferably after achieving MRD negative status
- However, this may change based on evolving experience with immunotherapy (especially CAR T-cell products with potential for long-term persistence and blinatumomab)
- All other indications for transplant in ALL are controversial and evolving
  - Ph+ in CR1: questionable benefit of transplant in TKI era
  - Adult ALL in CR1: questionable benefit of transplant given enhance efficacy of pediatric-inspired regimens
  - All other high-risk CR1 (late MRD+, hypodiploid, KMT2A-r, etc): poor outcomes, but no data showing transplant better than alternative
- Prospective, randomized clinical trials are desperately needed!

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Role of transplant in MRD+ population

Josep-Maria Ribera

APTITUDE HEALTH

One simple answer:

Yes, always

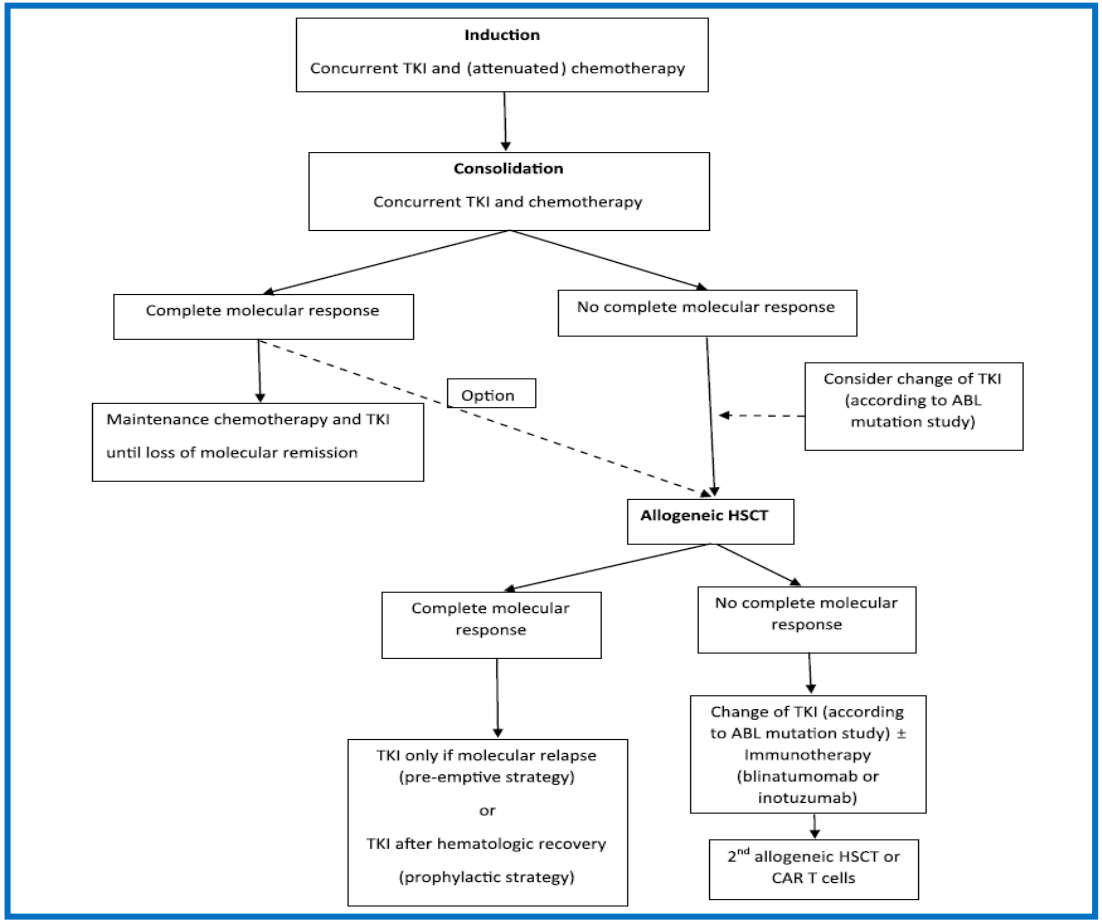
However . . . things are not so simple!

Aspects to be considered

- **Patient**: fitness, comorbidities, feasibility of HSCT
- **Type of ALL**: Ph-positive or -negative
- **ALL status**
  - CR1 or CR ≥1
  - Previous HSCT
- **MRD characteristics**: persistent positivity or MRD reappearance
- **MRD level**
- **Possibility of effective therapies** (targeted therapies, immunotherapy) in MRD+ status

HSCT in MRD+, Ph+ ALL

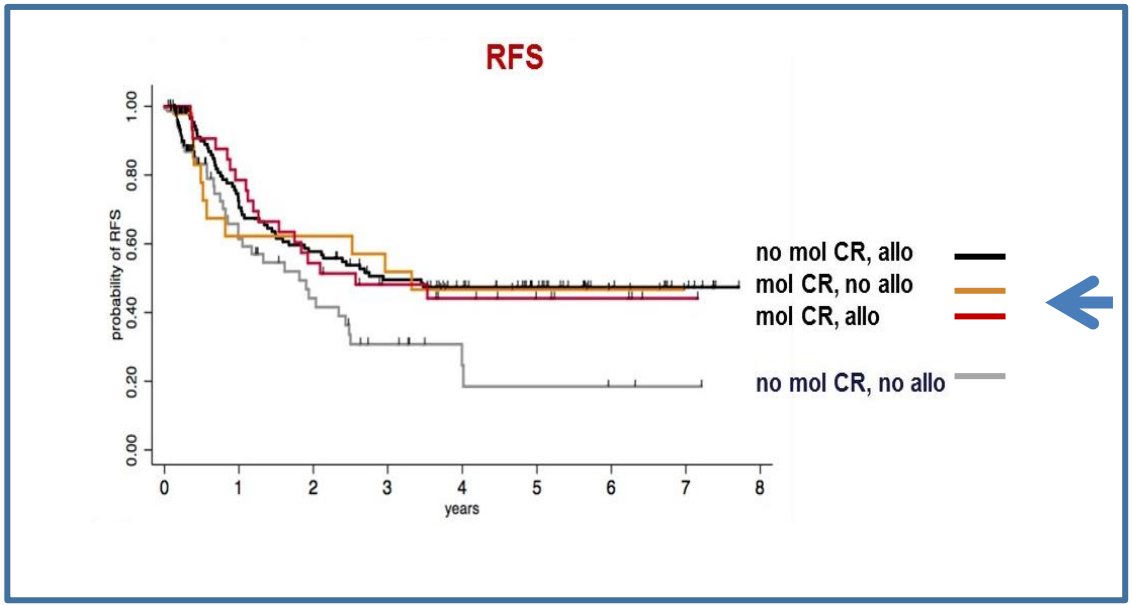
Indication of HSCT in Ph+ ALL: "Standard" approach



Ribera JM, et al. *Ther Adv Hematol*. 2018;9:357-368.

MRD after consolidation can modulate the HSCT indication

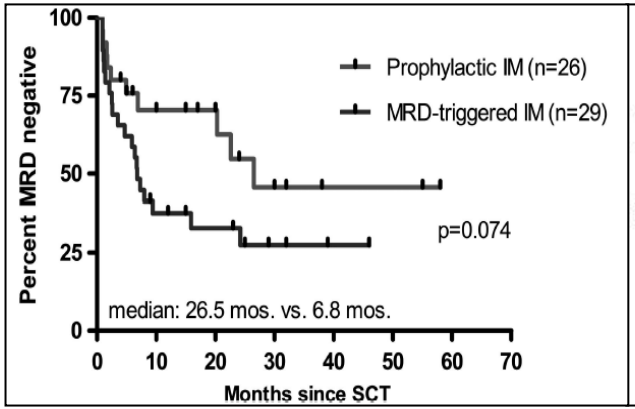
- Time-dependent analysis; Simon-Makuch plots; *t0*, MRD2 assessment
- HR, 1.02 [95% CI, 0.47–2.21]; *P* = .96 in molecular CR patients
- HR, 0.62 [95% CI, 0.40–0.96]; *P* = .034 in patients with detectable MRD2



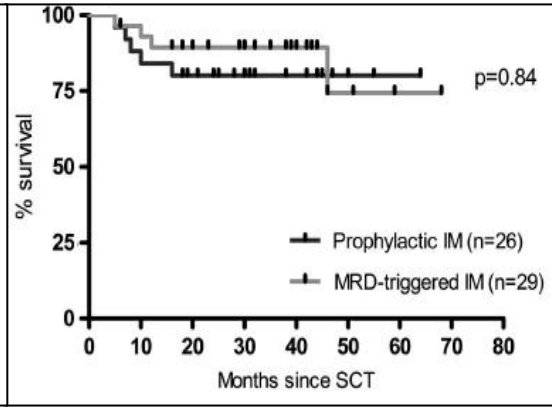
Chalandon Y, et al. *Blood*. 2015;125:3711-3719 and supplementary appendix.

Prophylactic vs MRD-triggered imatinib after allogeneic HSCT

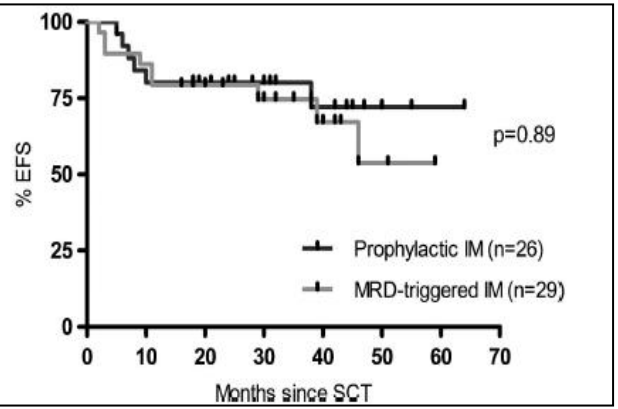
Duration of molecular remission by treatment arm



Survival after HSCT by treatment cohort

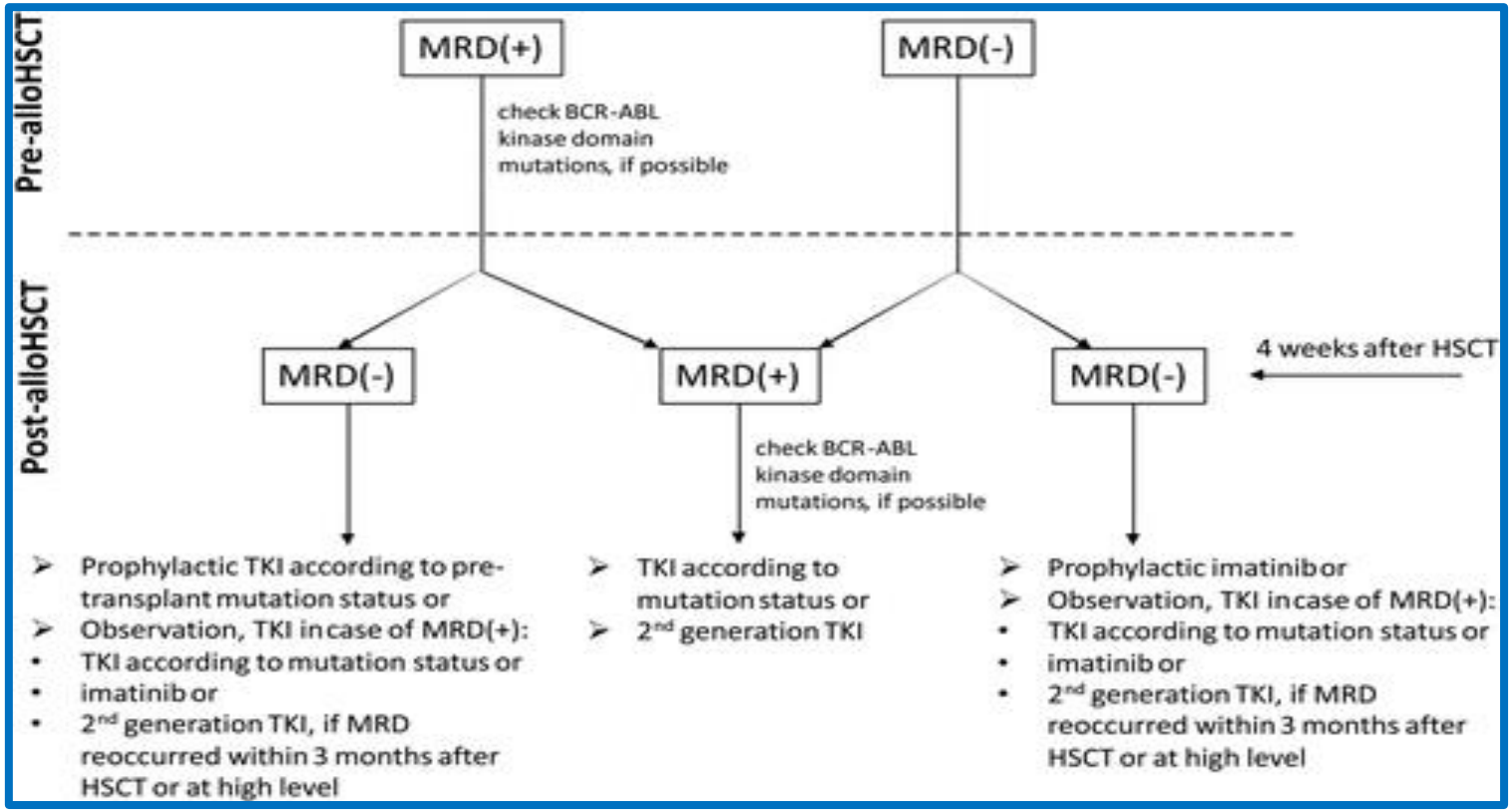


EFS after HSCT by treatment cohort



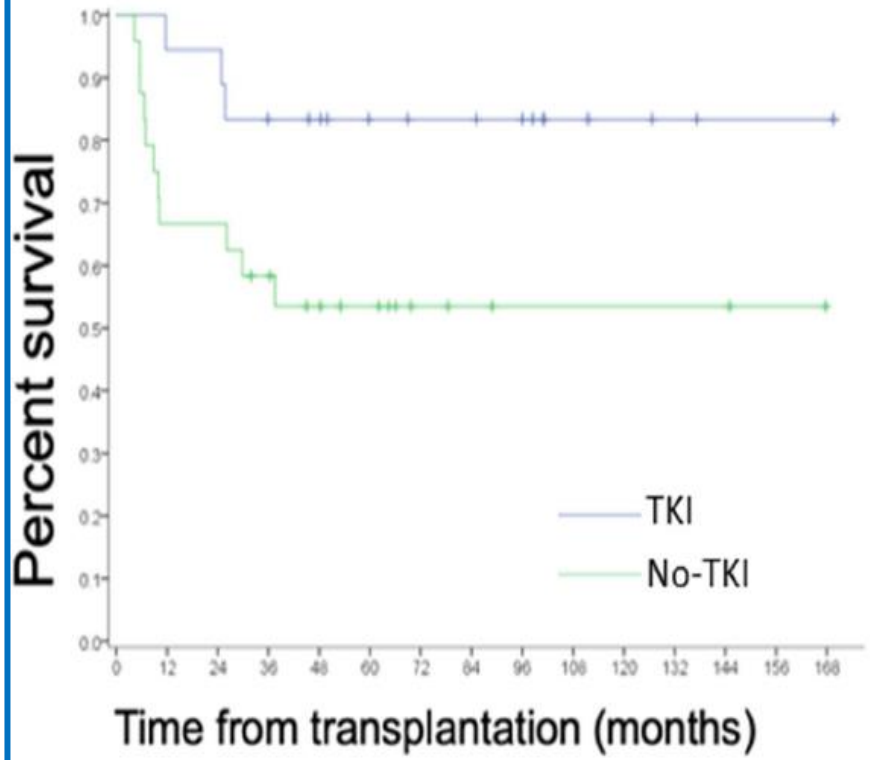
Pfeifer H, et al. *Leukemia*. 2013;27:1254-1262.

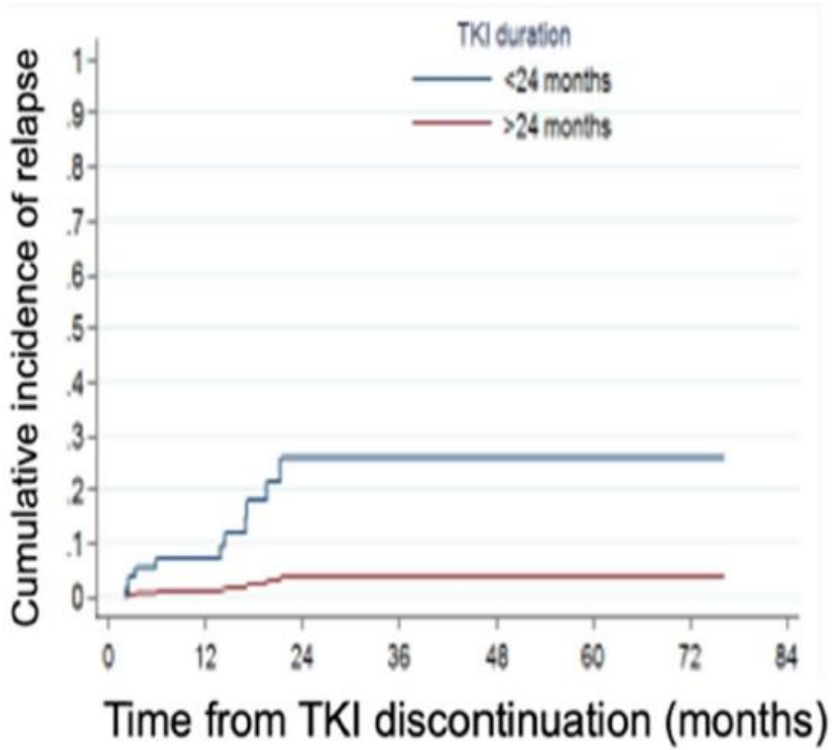
TKI to prevent relapse after allogeneic HSCT: EBMT position statement



Giebel S, et al. *Cancer*. 2016;122:2941-2951.

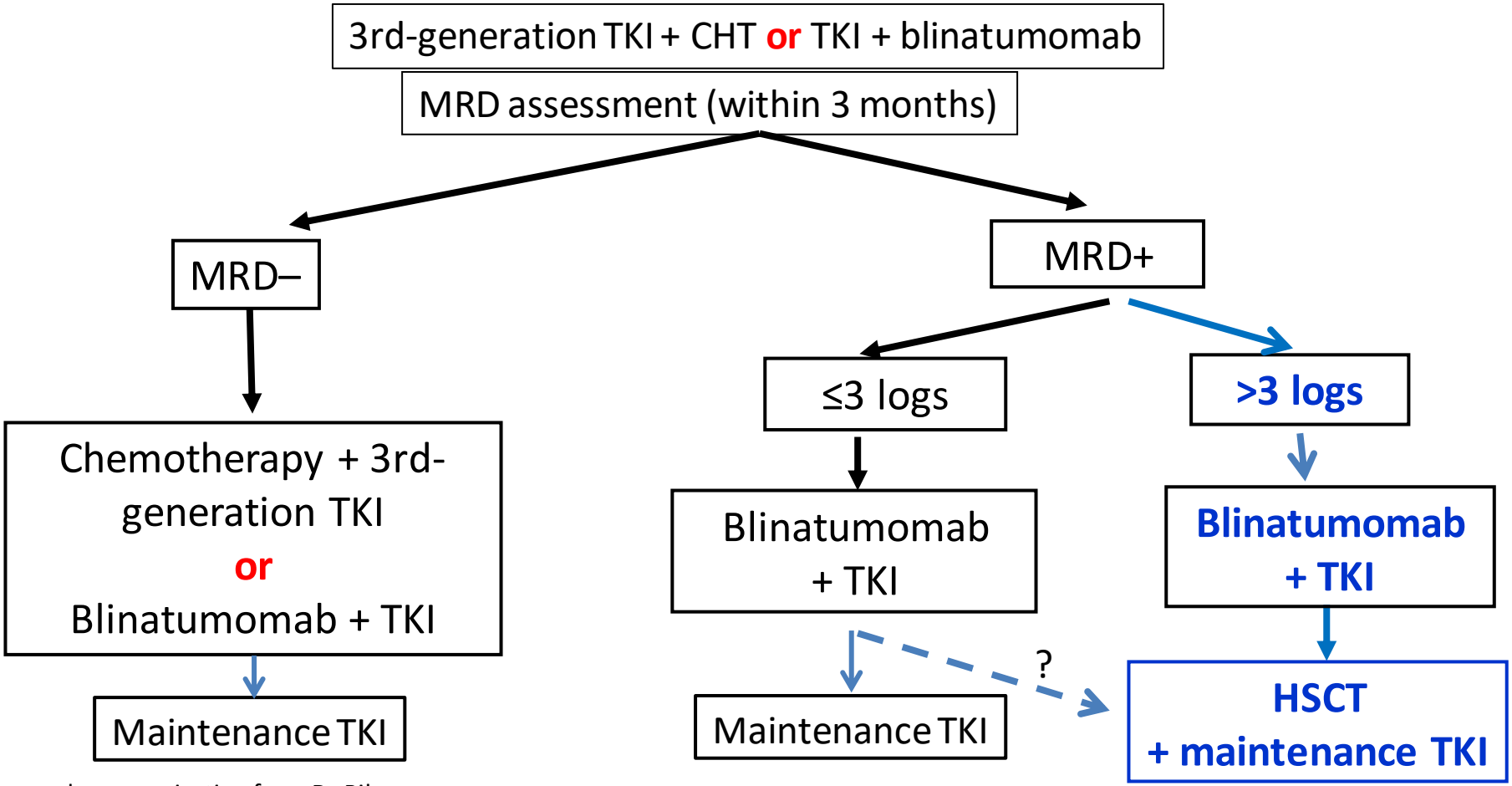
TKI after alloHSCT: MDACC experience





Saini N, et al. *Blood*. 2020;136:1786-1789.

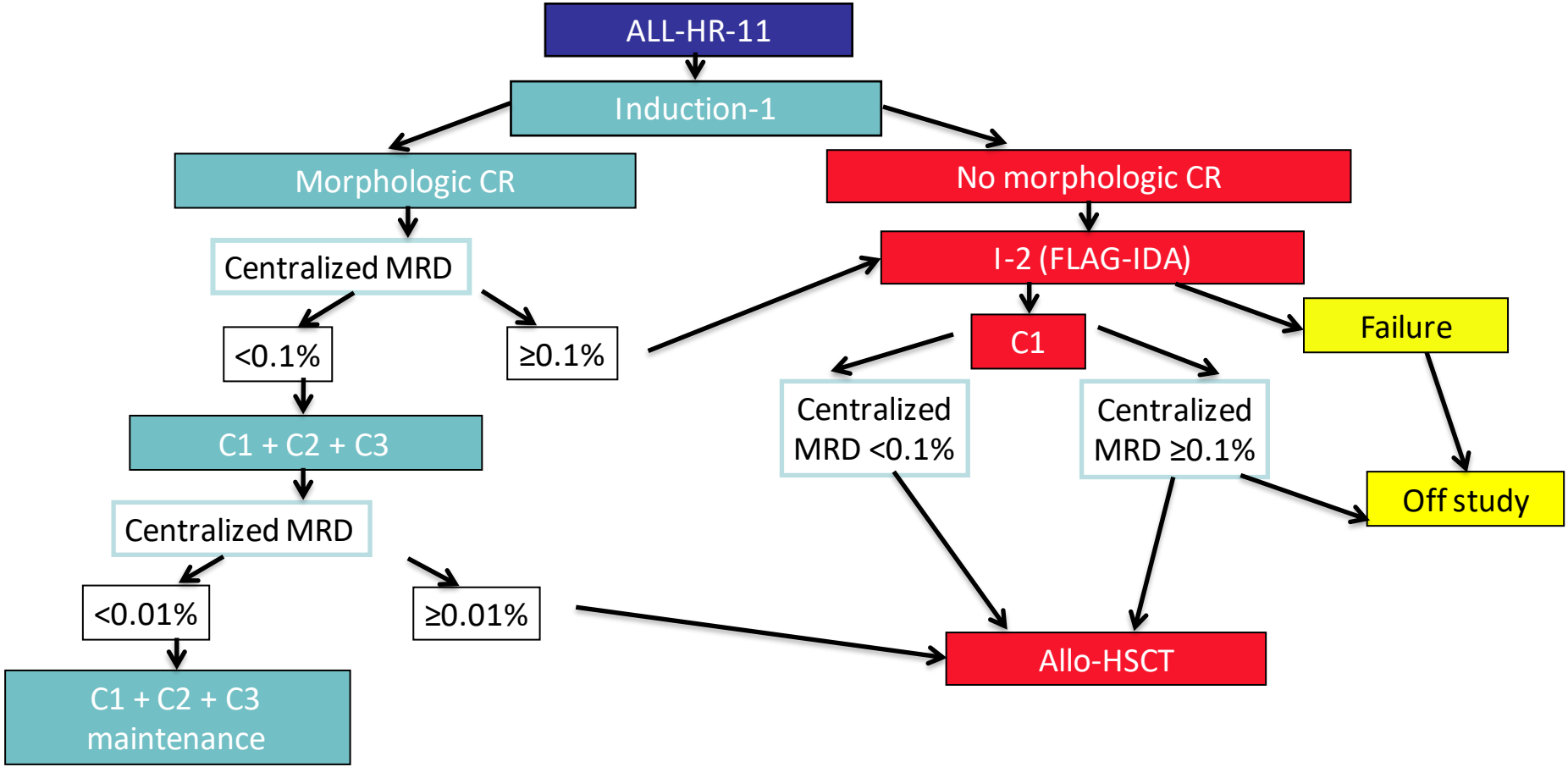
Indications for HSCT in Ph+ ALL: "Improved" approach



Personal communication from Dr Ribera.

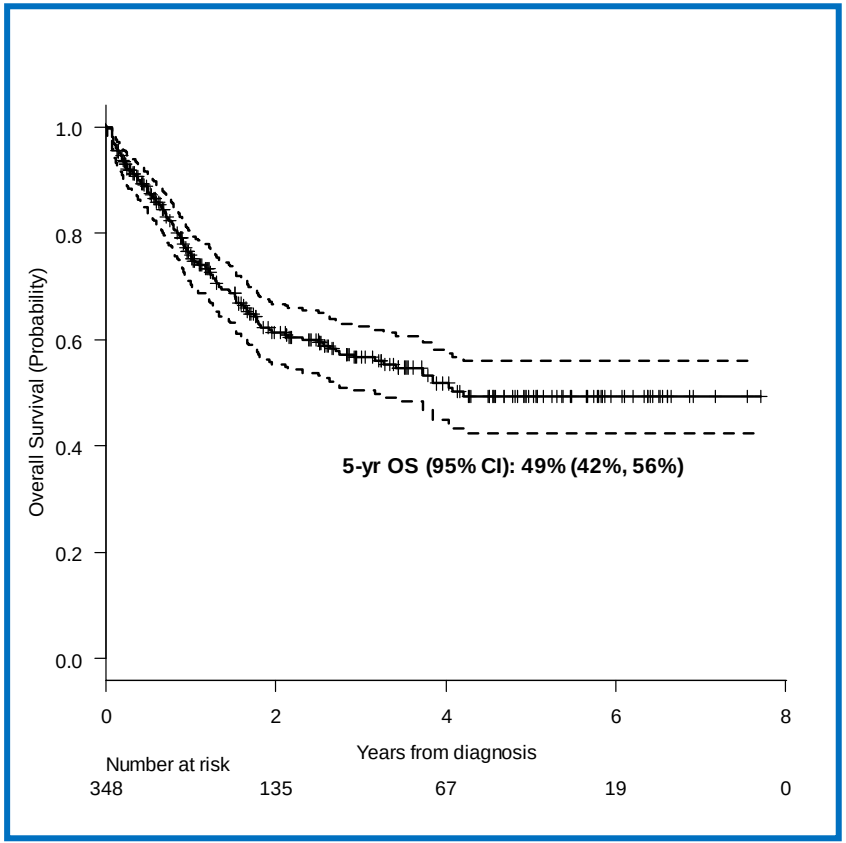
HSCT in MRD+, Ph– ALL

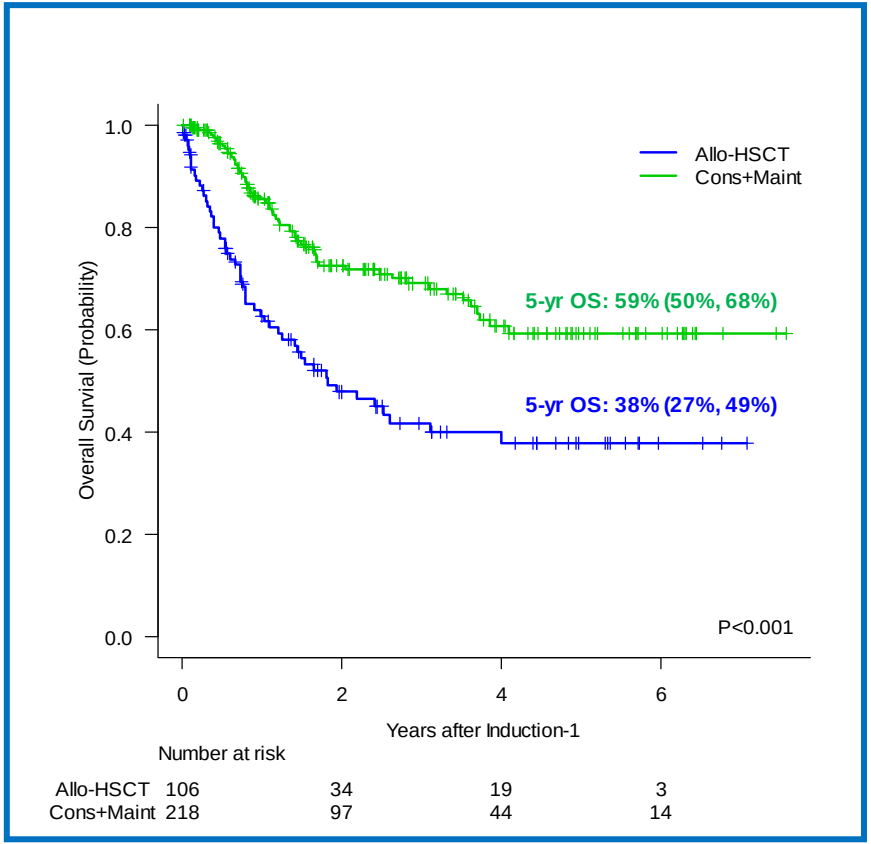
HSCT in Ph– ALL: "Standard" approach (PETHEMA ALLHR11)



Personal communication from Dr Ribera.

Overall survival

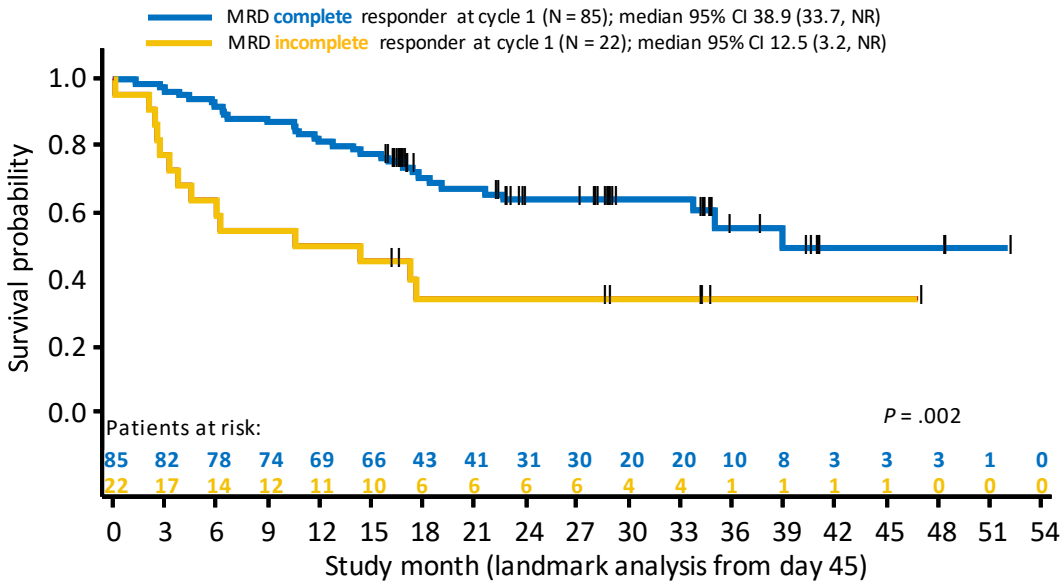




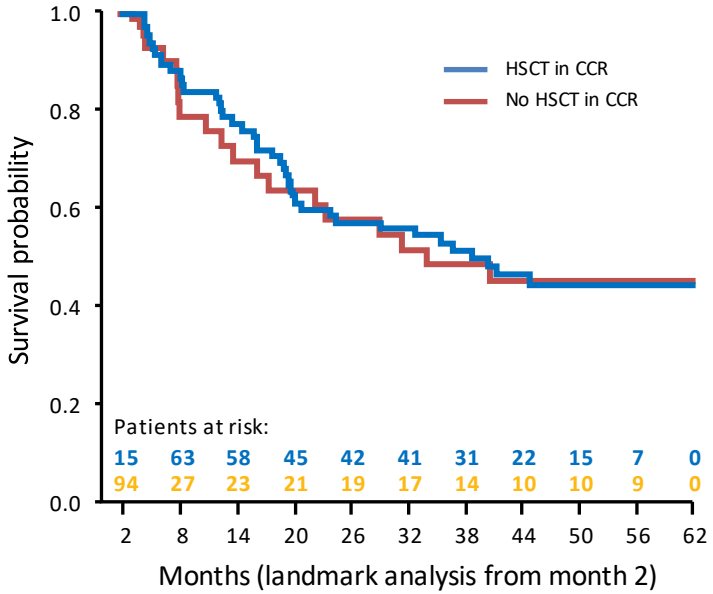
Ribera JM, et al. *Blood*. 2020 (in press).

Indication in CR1 after clearance of MRD with immunotherapy: Data from BLAST trial

Overall survival according to MRD response[1]



Overall survival according to allogeneic HSCT in CCR[2]

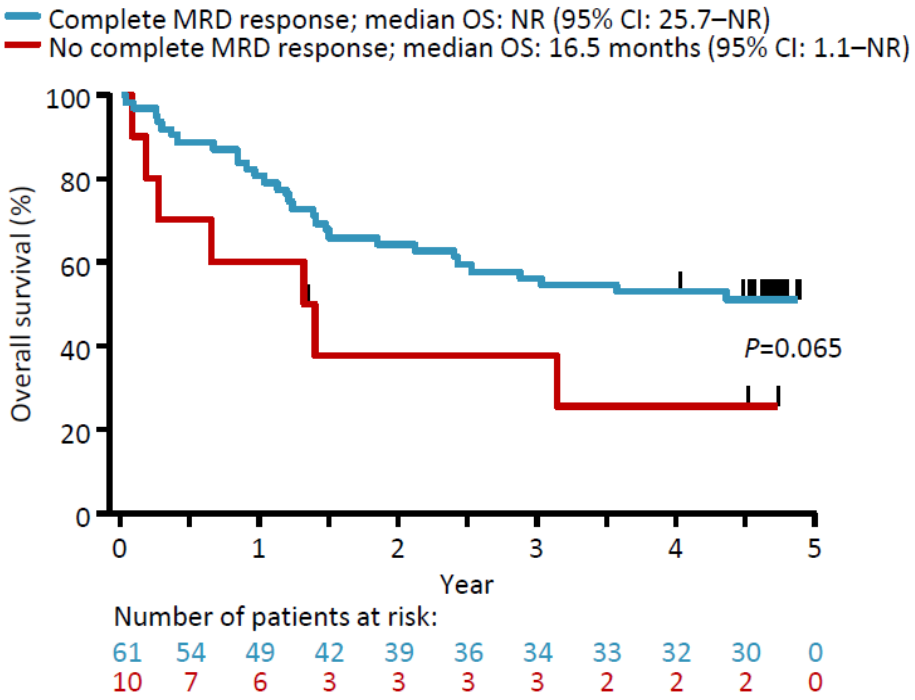


1. Gökbuget N, et al. *Blood*. 2018;131:1522-1531; 2. Gökbuget N, et al. ASH 2018. Abstract 554 and oral presentation.
https://clinicaltrials.gov/ct2/show/NCT02003222

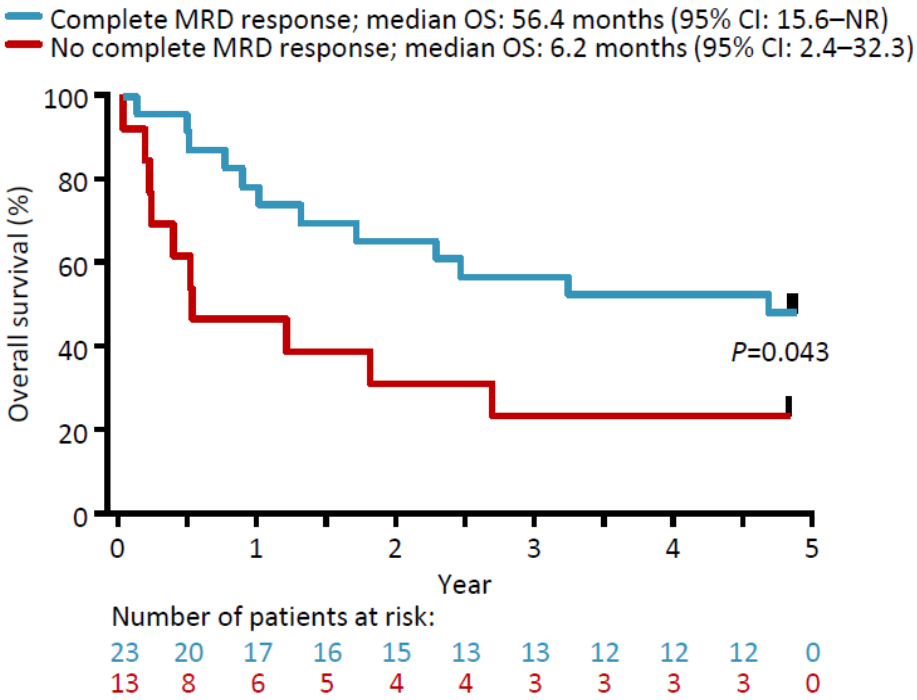
BLAST trial: Overall survival

According to complete MRD response, in patients with/without HSCT in CCR

Patients with HSCT in continuous CR (starting at day of HSCT)

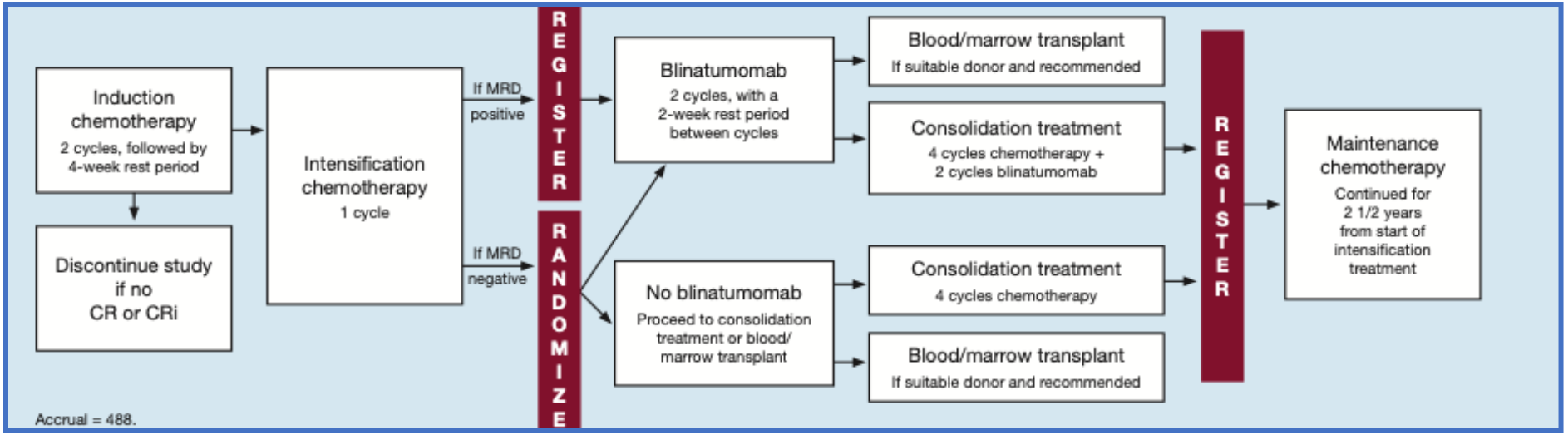


Patients without HSCT in continuous CR (starting at Day 45, after MRD assessment)



Gökbuget N, et al. EHA 2019; Abstract S1619 and oral presentation.

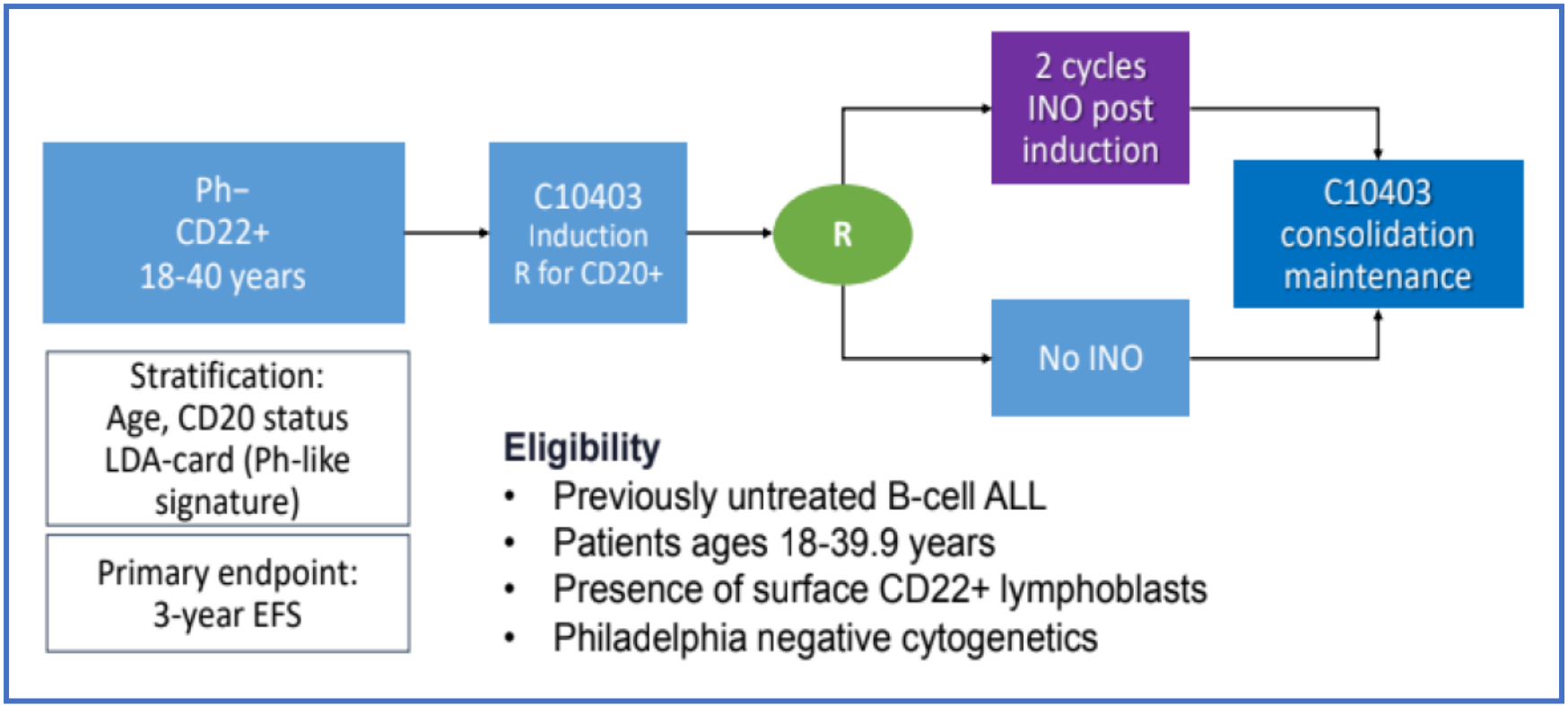
A phase III randomized trial of blinatumomab for BCR-ABL– BCP ALL in adults (ECOG ACRIN 1910)*



*Accrual completed.

https://clinicaltrials.gov/ct2/show/NCT02003222

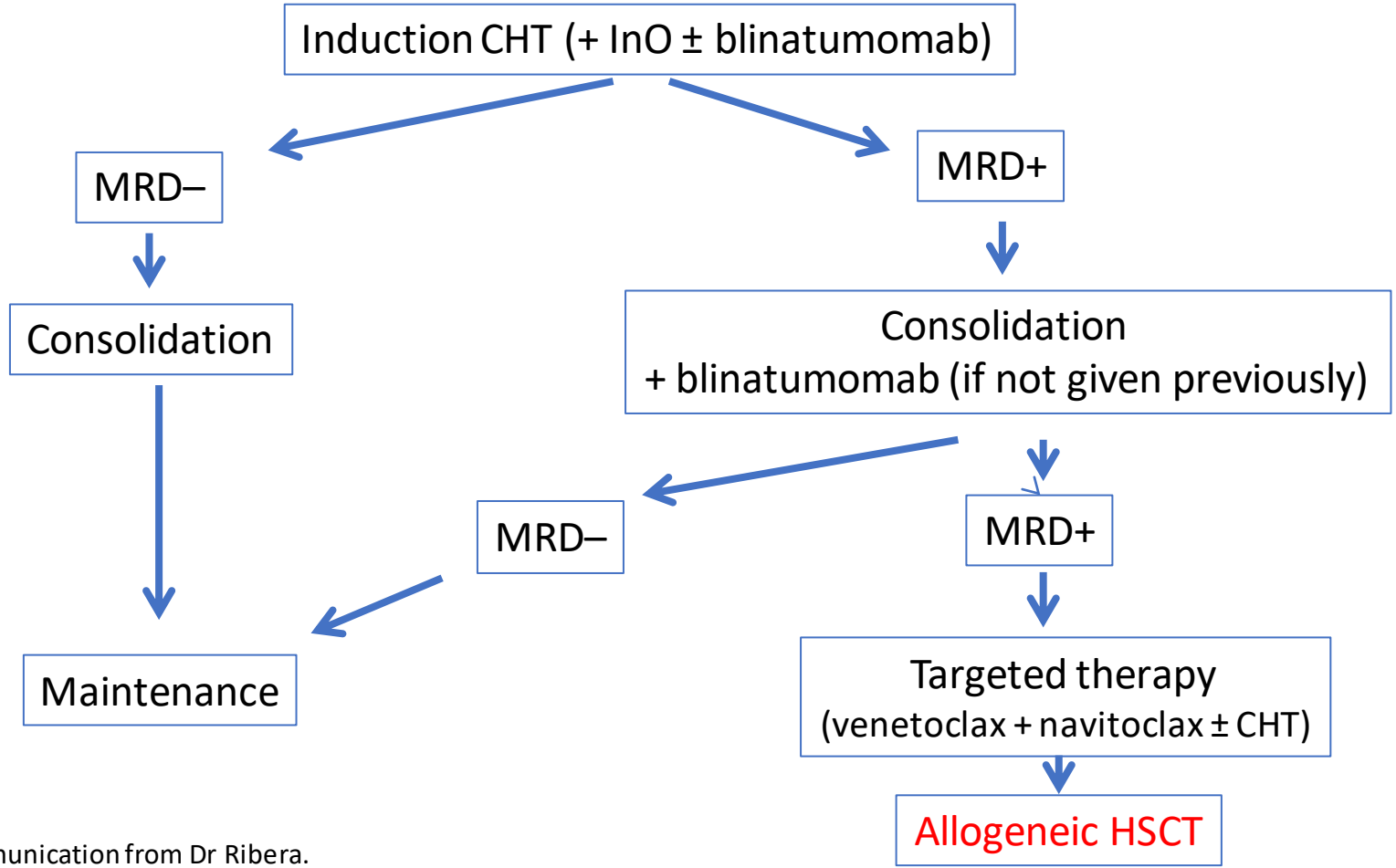
Inotuzumab in AYA with BCP ALL (phase 3 Alliance 041501 trial)



Trial ongoing

https://clinicaltrials.gov/ct2/show/NCT03150693

Indications for HSCT in Ph– ALL: "Improved" approach



Personal communication from Dr Ribera.

Concluding remarks

- MRD is an essential tool to guide therapy in ALL
- MRD+ status is a general indication for allogeneic HSCT
- The introduction of immunotherapy ± targeted therapies in CR1 will decrease the frequency of MRD positivity and could modulate the general indication of allogeneic HSCT in MDR+ patients
- MRD+ beyond CR1 should be managed with immunotherapy ± targeted therapies and should be followed by alloHSCT

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Panel discussion on the role of HSCT: Discussion and voting

APTITUDE HEALTH

Question 1

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

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

Question 2

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

a. Yes, as patients who achieve MRD negativity are on the way to cure and do not require HSCT
b. No, as HSCT is the SOC today and should be part of the treatment algorithm of patients independently of MRD
c. I do not know

Question 3

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

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

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Debate on CD19-targeted approaches

Josep-Maria Ribera and Elias Jabbour

APTITUDE HEALTH

Question 1

What is your preferred ALL treatment choice in salvage if these therapies were made available in your country?

a. CAR T therapies
b. 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

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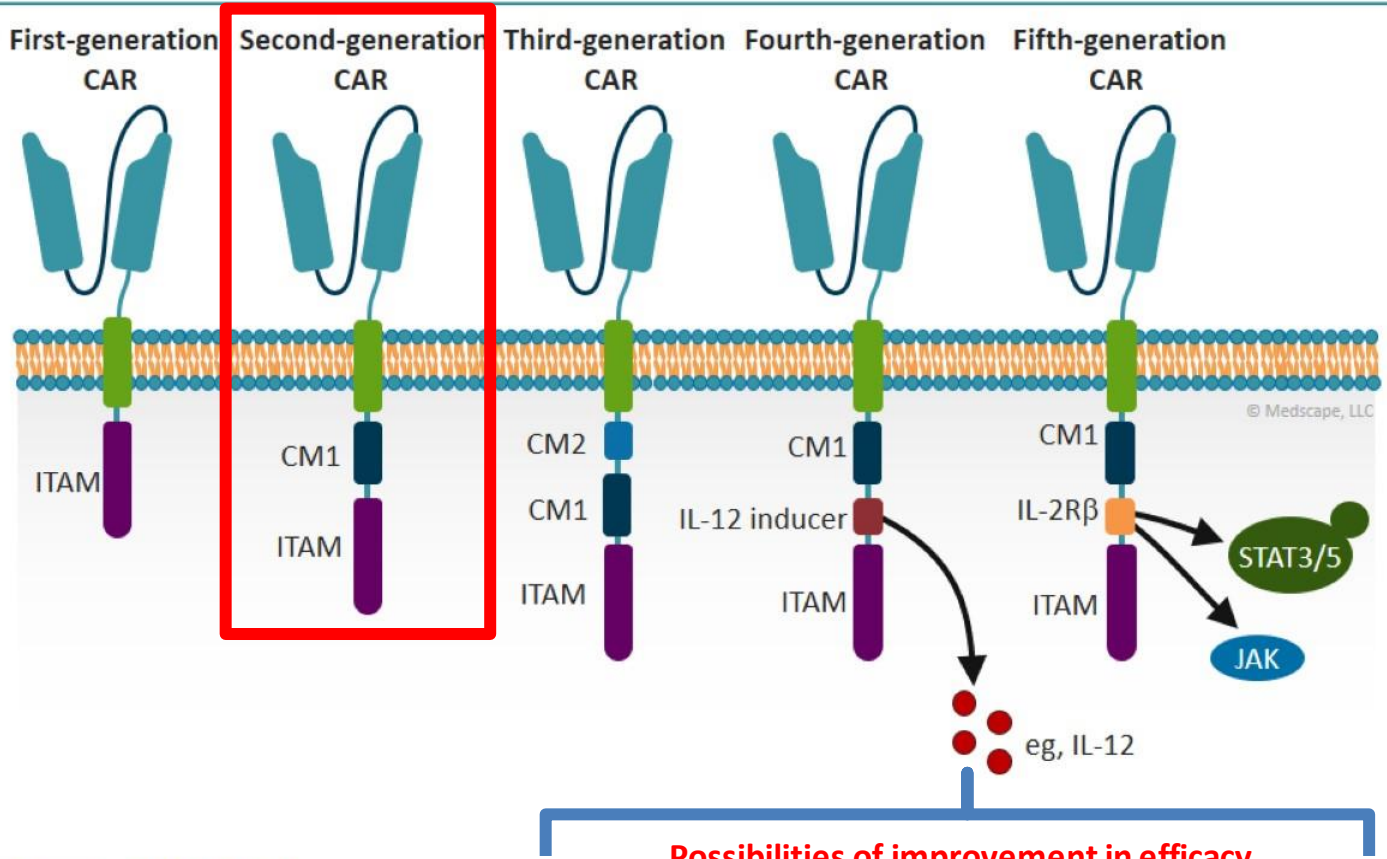
CD19 CAR T

Josep-Maria Ribera

APTITUDE HEALTH

Differences in CAR T Cell Therapies



Tokarew N, et al. *Br J Cancer.* 2019;120:26-37.

CD19 CAR T: Main results in R/R ALL

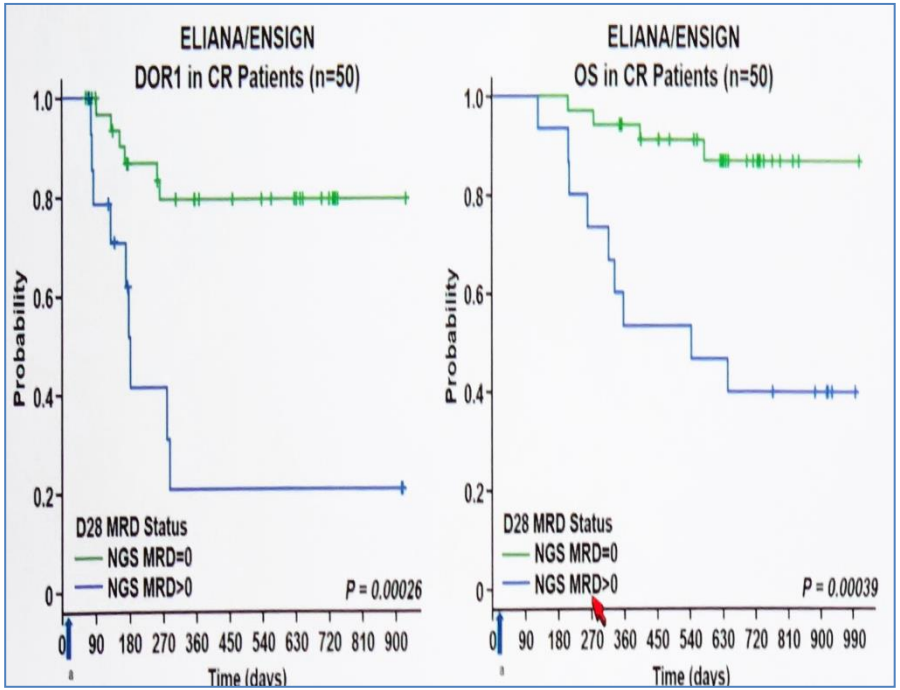
Author, reference	Institution	Costimulatory domain	Age (median, range)	Infused N	ORR %	CRS, %	Neurotoxicity, %	OS
Maude *et al.*[15]	UPenn	4-1BB	14 years (5–60)	30	90%	100% (severe, 27%)	43%	78% at 6 months
Davila *et al.*[16]	MSKCC	CD28	50 years (NA)	16	88%	severe, 44%	Gr 3/4, 25%	NA
Lee *et al.*[17]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

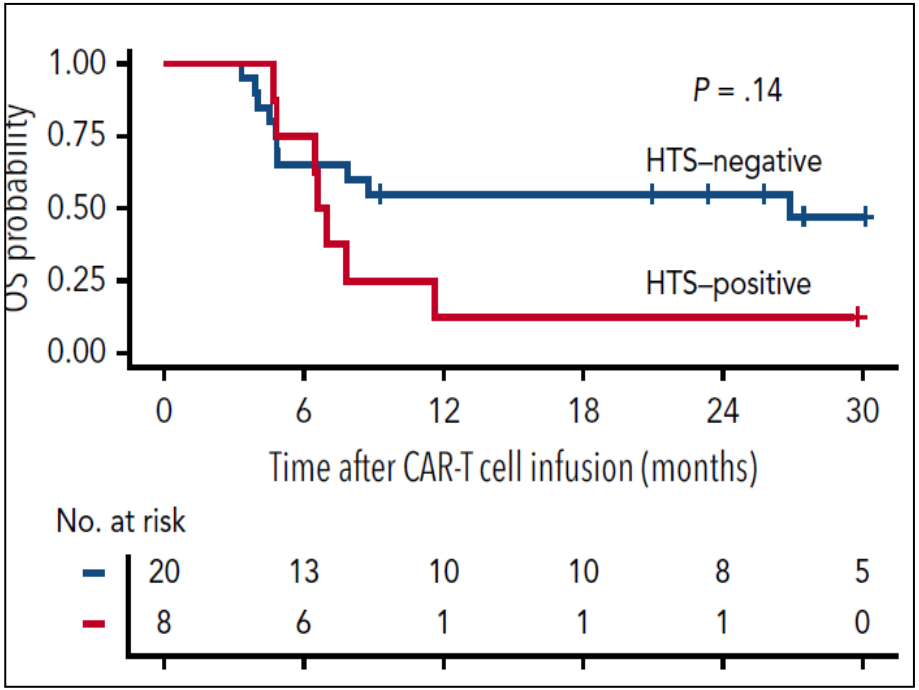
Ribera JM, et al. *Ther Adv Hematol.* 2020;11:1-15.

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

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

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.

CD19 CAR-T cells in relapsed/refractory adult ALL

CAR: CD19 4-1BB

59 pts apheresis

53 infused

Patient characteristics

Median age: 39 (20–76) years

21% Ph+

43% prior SCT

26% bridging

Disease at lymphodepletion:

64% (N=34) morphological BM relapse (≥5%)

- 13 extramedullary

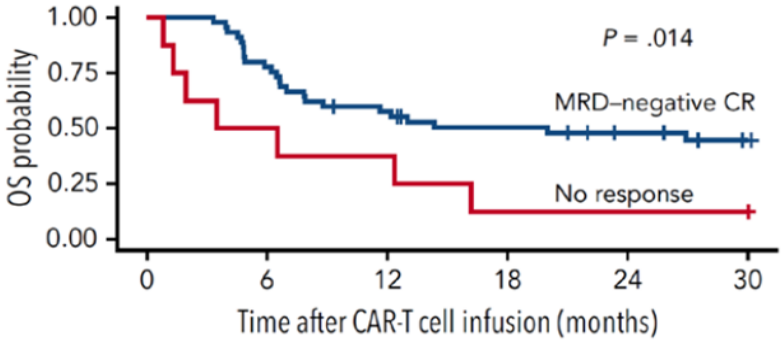
4% (N=2) extramedullary only

32% (N=17) MRD pos

- 3 extramedullary

85% in CR and MRD neg after infusion

Overall survival after infusion



Prognostic factors for EFS

Variable	Multivariable analysis		P
	HR	95% CI	
LDH prelymphodepletion (per 100 U/L increment)	1.39	1.11-1.73	.004
Platelets prelymphodepletion (per 50 000/μL increment)	0.74	0.53-1.03	.069
Fludarabine added to lymphodepletion	0.25	0.15-0.78	.003
HCT after CAR T-cell therapy	0.39	0.13-1.15	.088

Hay KA, et al. Blood 2019;133:1652–63.

EFS, event-free survival.

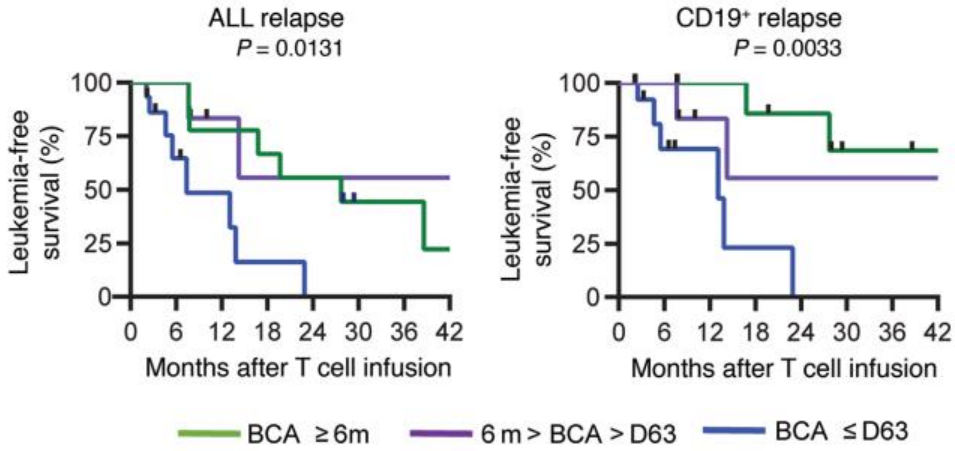
Challenges in CAR T for BCP ALL

- Broad and immediate availability
- Manufacturing failure
- Persistence
- CD19– relapses
- Need for subsequent alloHSCT
- Indication outside BCP ALL
- Economic issues

B-cell aplasia (BCA) and relapse

Table 1. Relapse rates in subjects who did not receive HSCT post–CAR T treatment

Relapse	CD19⁺, *n* (%)	CD19⁻, *n* (%)	No relapse	*N*
longBCA	2 (22.2)	4 (44.4)	3 (33.3)	9
mediumBCA	2 (50.0)	0 (0)	2 (50.0)	4
shortBCA	6 (75.0)	2 (25.0)	0 (0.0)	8



Finney OC, et al. *J Clin Invest*. 2019;129:2123-2132.

Tumor antigen escape from CAR T-cell therapy

MINI REVIEW

Table 1. A summary of antigen escape in CD19 CAR trials for ALL

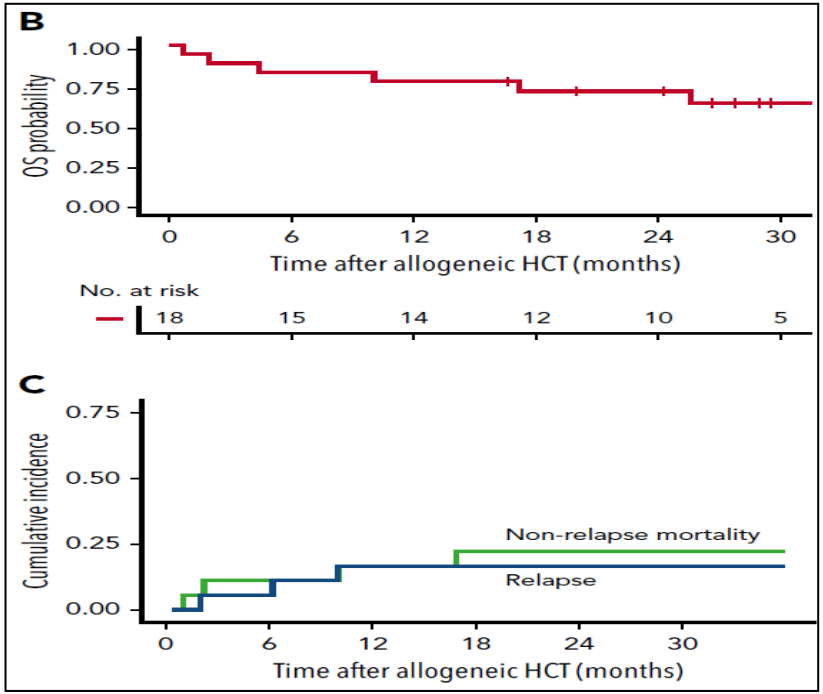
Trial	Population	CD19 CAR construct	Relapse rate	CD19-negative relapse rate
Children's Hospital of Philadelphia phase I	Pediatric	FMC63-4-1BB-ζ	36% (20/55)	24% (13/55)
Novartis phase II (ELIANA)	Pediatric	FMC63-4-1BB-ζ	33% (20/61)	25% (15/61)
Seattle Children's Research Institute phase I	Pediatric	FMC63-4-1BB-ζ	45% (18/40)	18% (7/40)
NCI phase I	Pediatric	FMC63-CD28-ζ	29% (8/28)	18% (5/28)
Memorial Sloan Kettering phase I	Adult	SJ25C1-CD28-ζ	57% (25/44)	9% (4/44)
Fred Hutchinson Cancer Center phase I	Adult	FMC63-4-1BB-ζ	31% (9/29)	7% (2/29)

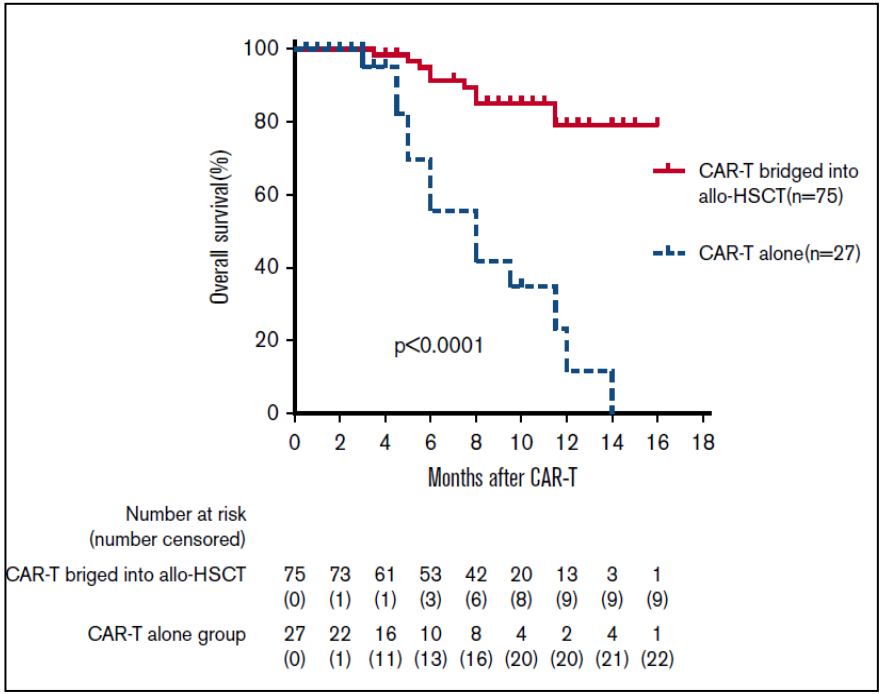
Overall, 50% of relapses are CD19–
CD19+ relapses are more frequent in adults

Majzner RG, Mackal CL. *Cancer Discov.* 2018;8:1219-1226.

HSCT after CAR T

AlloHSCT in MRD– patients after CAR T





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

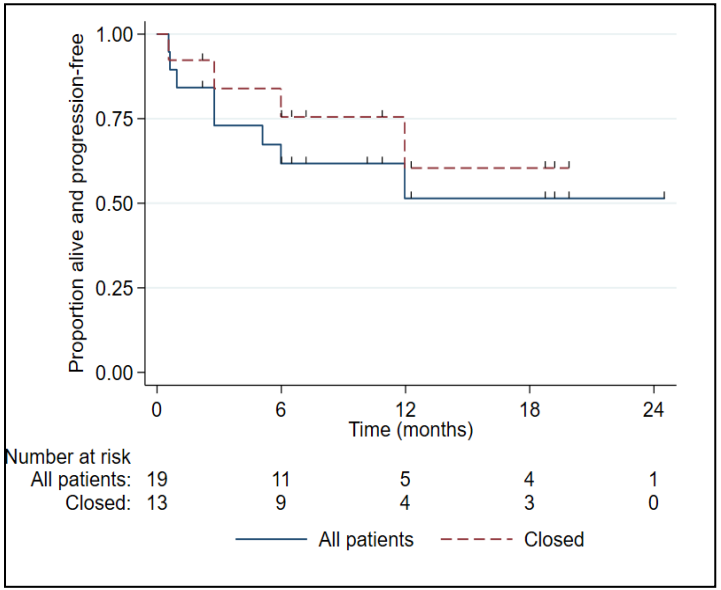
Zhang X, et al. *Blood Adv.* 2020;4:2325-2338.

Strategies to improve outcomes of CD19 CAR T-cell Tx

- **Beyond CD19 target: prevent CD19– relapse**
  - CD22
  - CD19+CD22
  - CD19+CD20+CD22
  - CD123
- **Improve CAR T-cell persistence/efficacy**
  - Fully human/humanized scFv to prevent immune rejection
  - Combination with checkpoint inhibitors (eg, Tisa-Cel + pembro/nivolumab)
  - Apheresis of T cells in earlier phases of the disease, especially in older patients
- **Improve availability**
  - Off-the-shelf CAR T
- **Expand indications beyond BCP ALL**
  - CAR T (CD7, CD1a)
  - NK CAR

AUTO-1, a novel fast-off rate CD19 CAR in R/R BCP ALL

- Phase 1 of AUTO1 ALLCAR19 study in R/R BCP ALL
- **AUTO1**: Second-generation CD19 CAR T with lower affinity for CD19 and shorter target interaction time (more physiologic T-cell activation and reduced toxicity)
- **19 pts infused (additional 13 in a closed process)**
  - Median age 43 yr (18-62), 6/19 with Ph+ ALL
  - Prior tx with blinatumomab or inotuzumab: 73%
  - Prior HSCT: 63%
  - Refractory: 4; 1st rel: 8; 2nd rel: 5; 3rd rel: 2. >50% blasts: 42%
  - Median f/u: 11 mo (0.5-21)
- **Efficacy** (15 pts evaluable)
  - MRD– CR: 84%, 11/19 in continuous MRD– CR (median 12 mo)
  - 6-mo EFS: 62%
  - Subsequent alloHSCT: 1
- **Safety**
  - No grade ≥3 CRS
  - Grade ≥3 neurologic toxicity: 16%



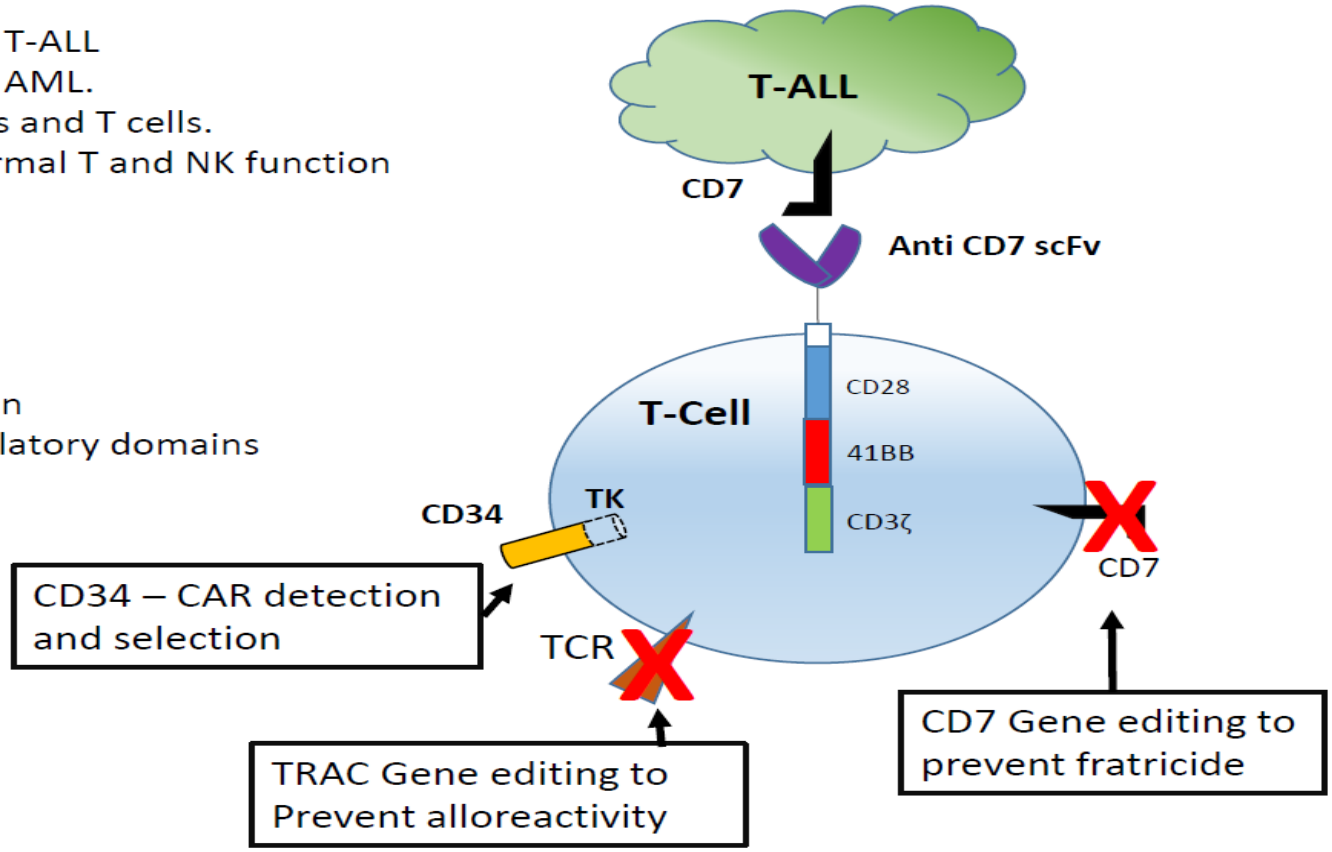
Roddie C, et al. EHA 2020. Abstract S119, and SOHO 2020.

CD7 CAR Design

- **CD7 as a target.**
  - Expressed on 98% of T-ALL
  - Expressed on 24% of AML.
  - Expressed on NK cells and T cells.
  - CD7-/- mice have normal T and NK function

- **CAR Design**
  - 3rd generation CAR
  - Anti CD7 scFv
  - CD3ζ signaling domain
  - 4-1BB, CD28 costimulatory domains
  - CD34

- **Gene editing**
  - CRISPR/Cas9



Courtesy of Dr Perales.

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Bispecifics

Elias Jabbour

APTITUDE HEALTH

Bispecifics in R/R ALL

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

Autumn 2020

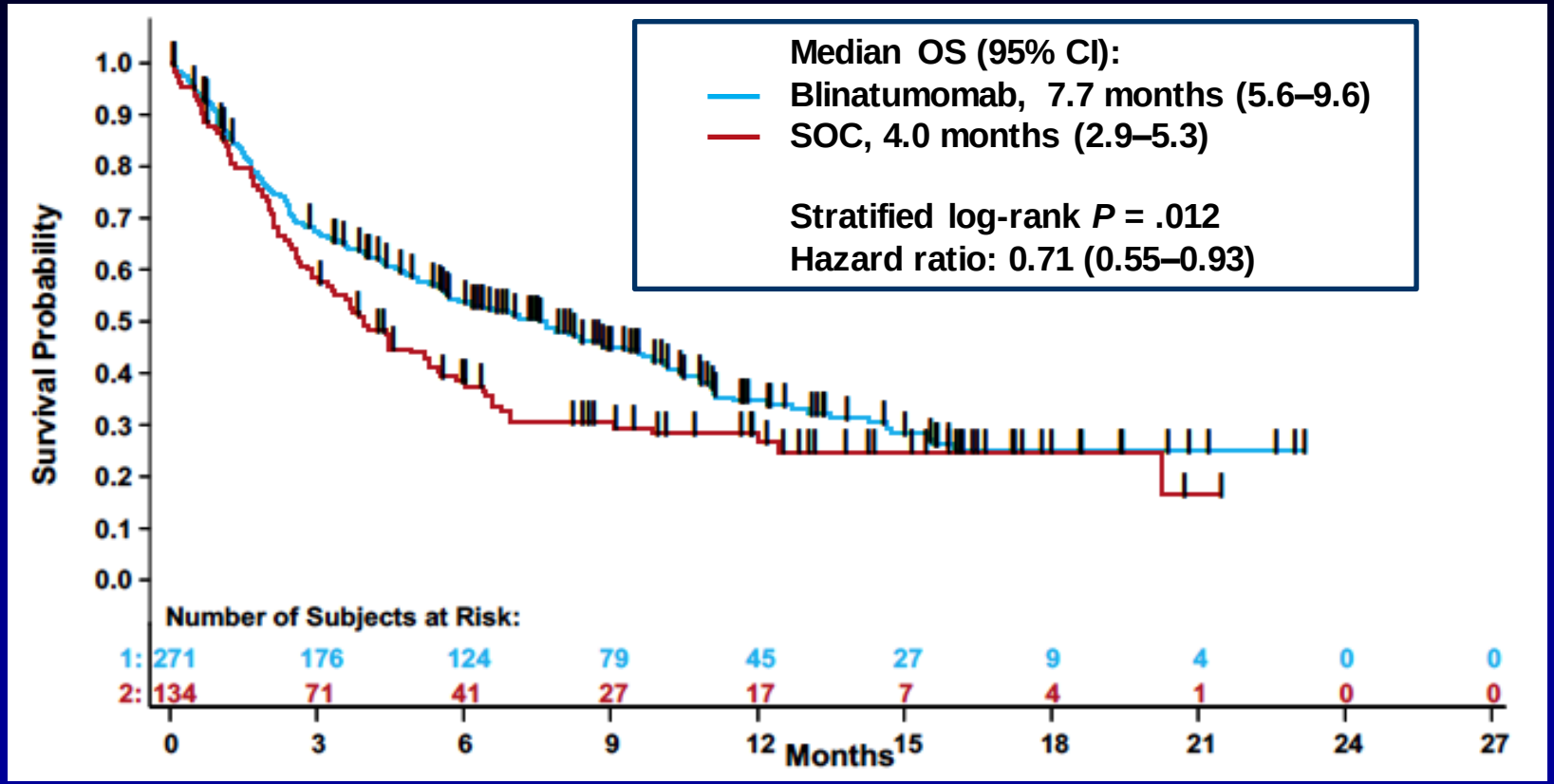
Historical Results in R-R ALL

- 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

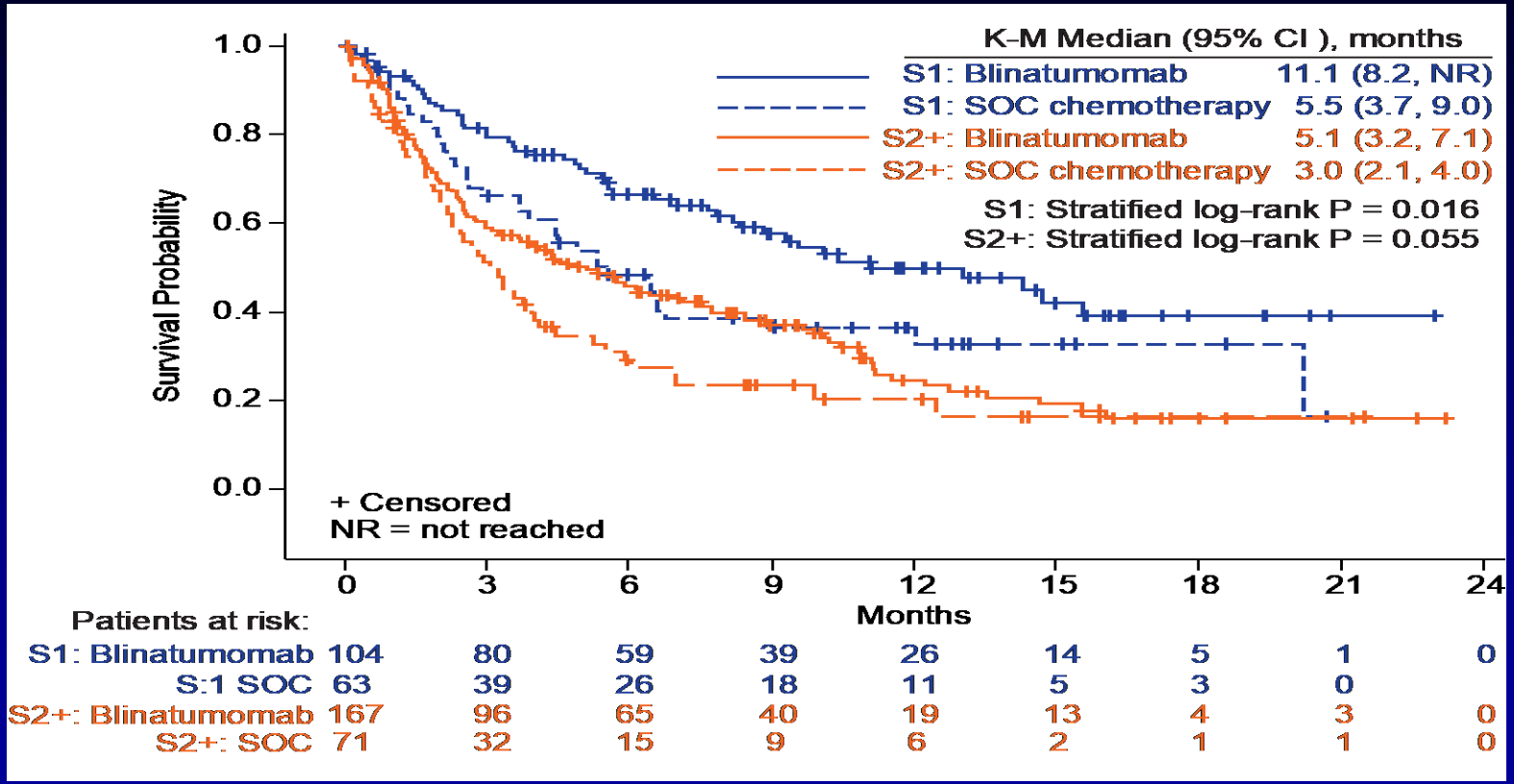
Gökbuget N, et al. *Haematologica*. 2016;101:1524-1533.

Blinatumomab vs Chemotherapy in R-R ALL



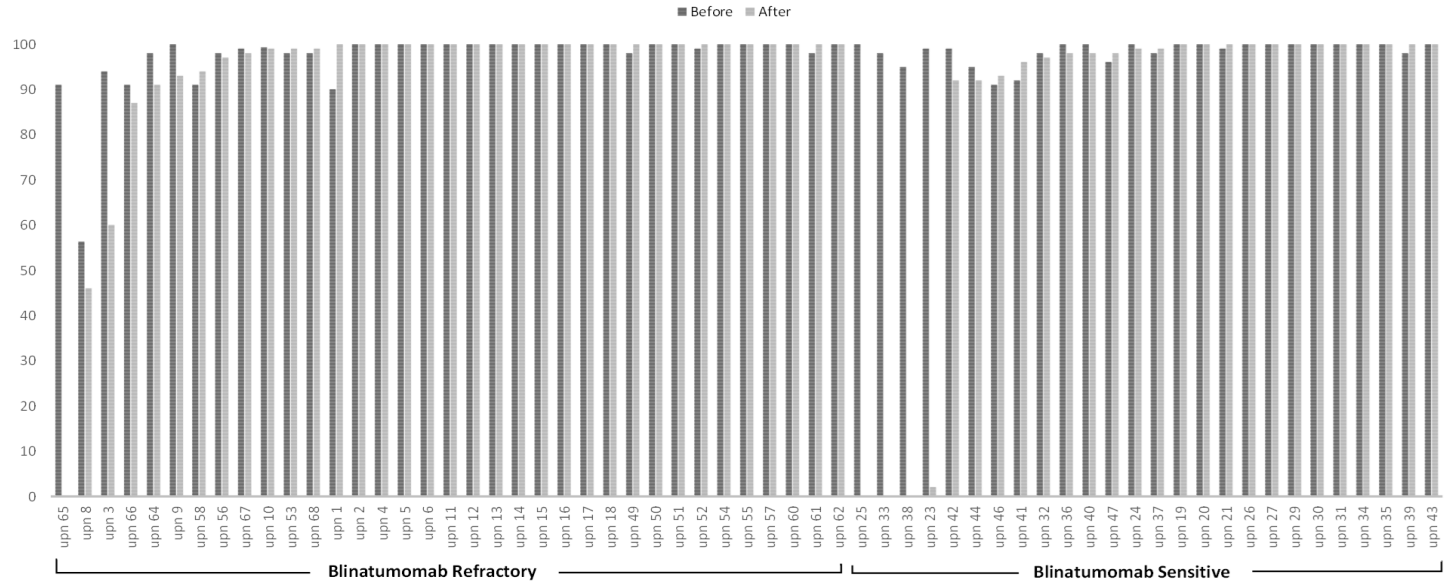
Kantarjian. *N Engl J Med.* 2017;376:836-847.

Phase III TOWER Study: Survival by Salvage



Dombret. *Leuk Lymphoma*. April 2019.

CD19 (%) Expression Before and After Blinatumomab Therapy

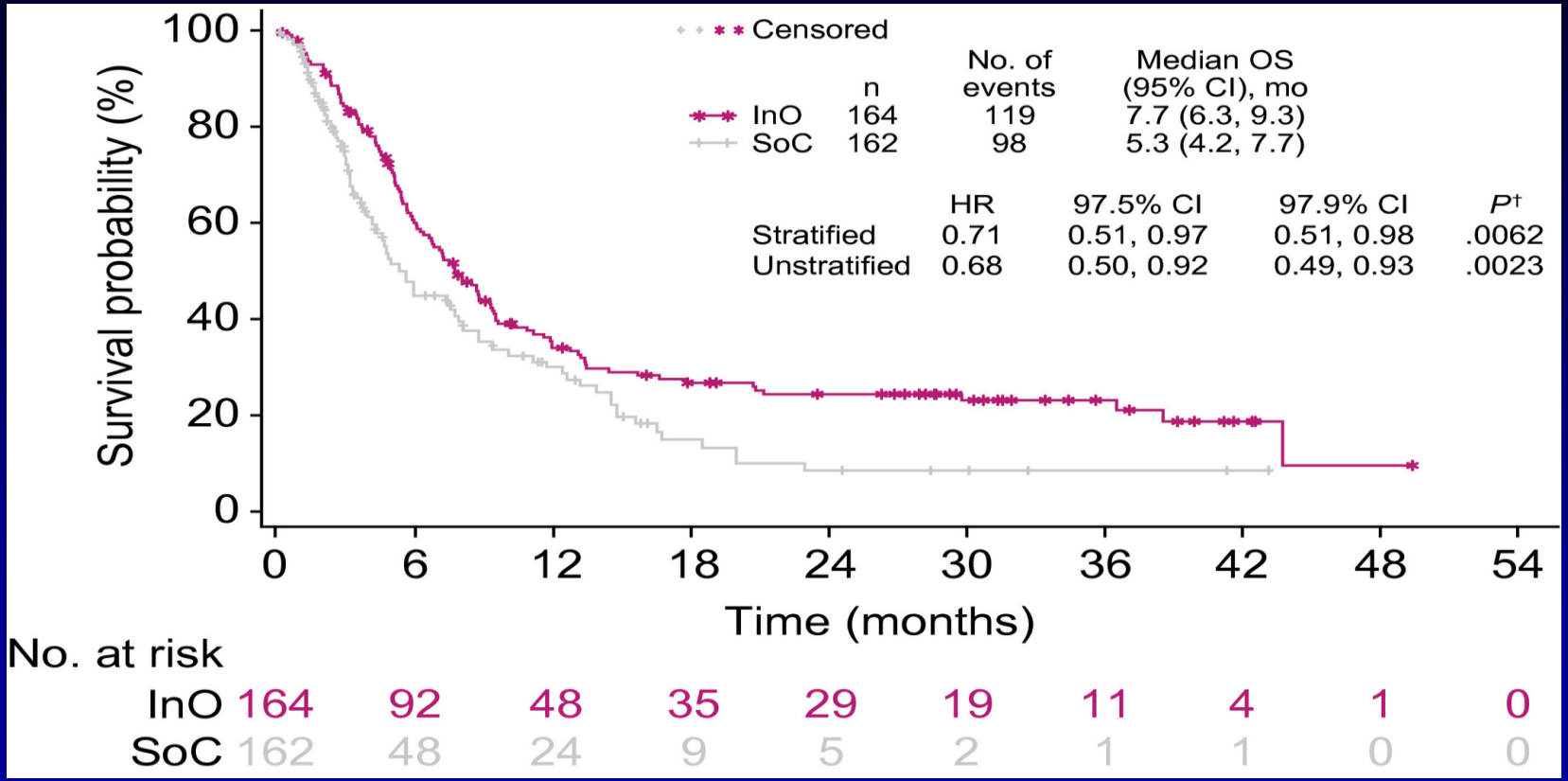


61 patients evaluated for immunophenotype; 56 (92%) had CD19+ disease

- **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.

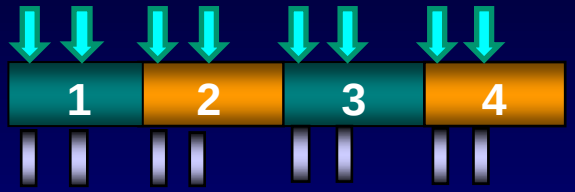
Mini-HCVD–Ino–Blina in ALL: Design

- 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/m^2)	Dose per Day (mg/m^2)
C1	0.9	0.6 D1, 0.3 D8
C2–4	0.6	0.3 D1 and D8

Total Ino dose = 2.7 mg/m^2

Maintenance phase

18 months

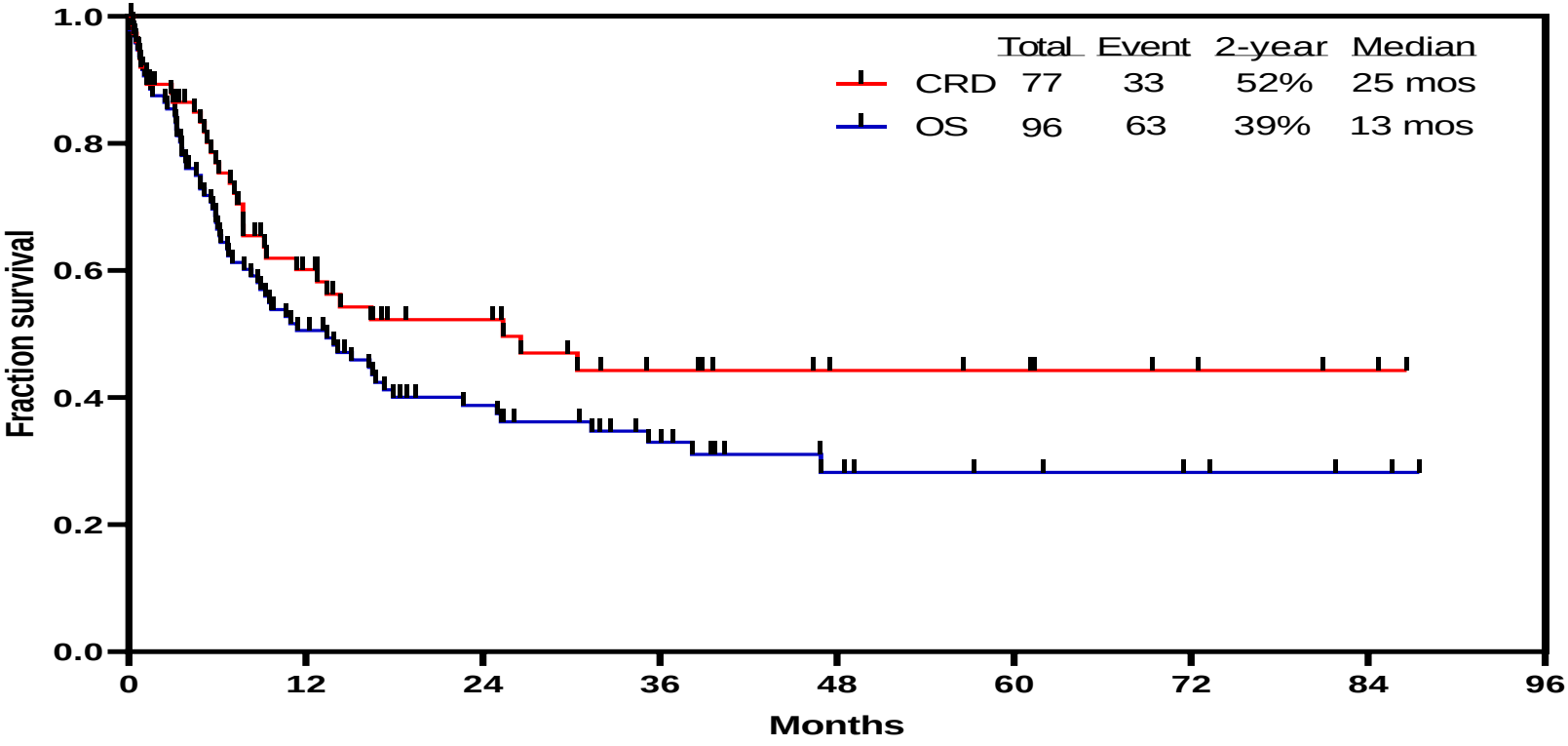
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Sasaki K, et al. *Blood.* 2018;132:abstract 553.

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

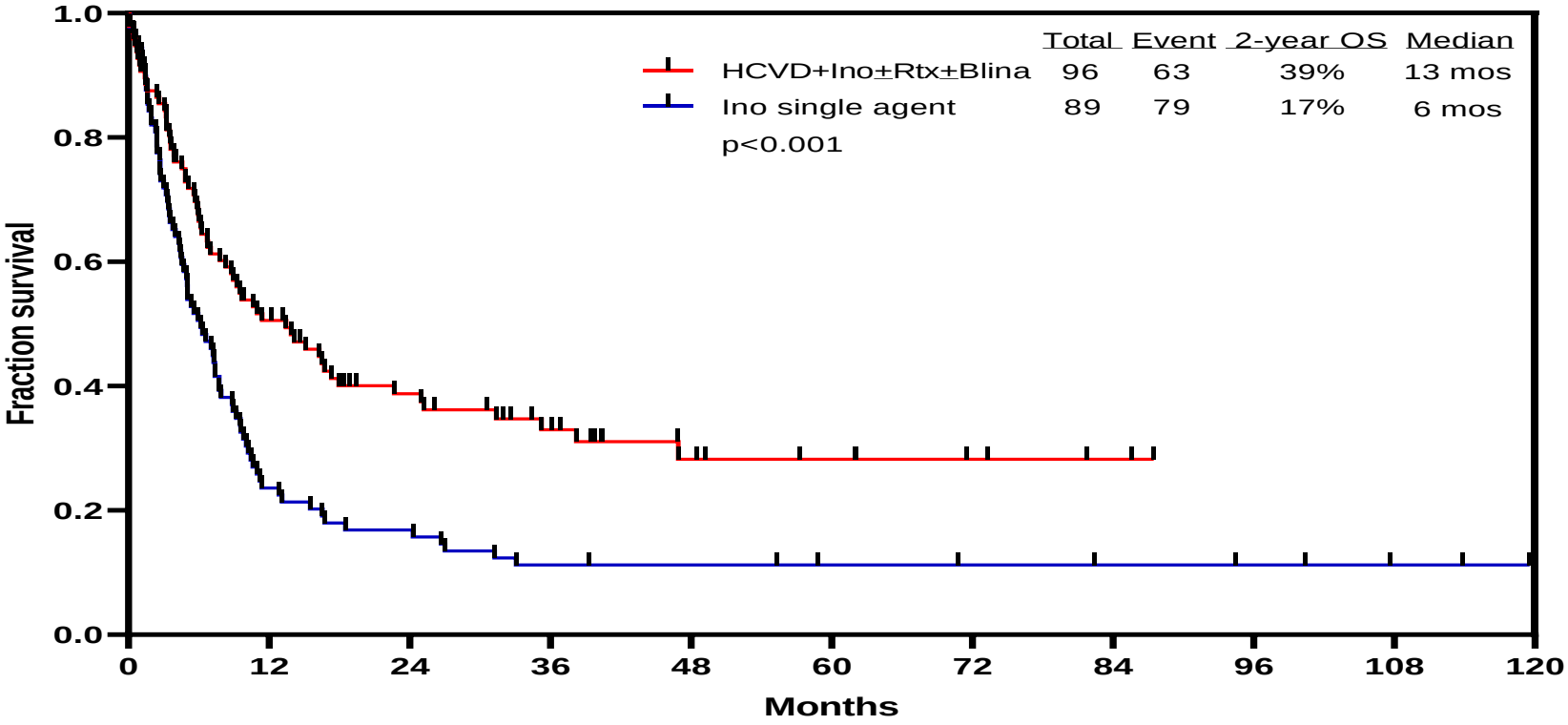
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055.

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



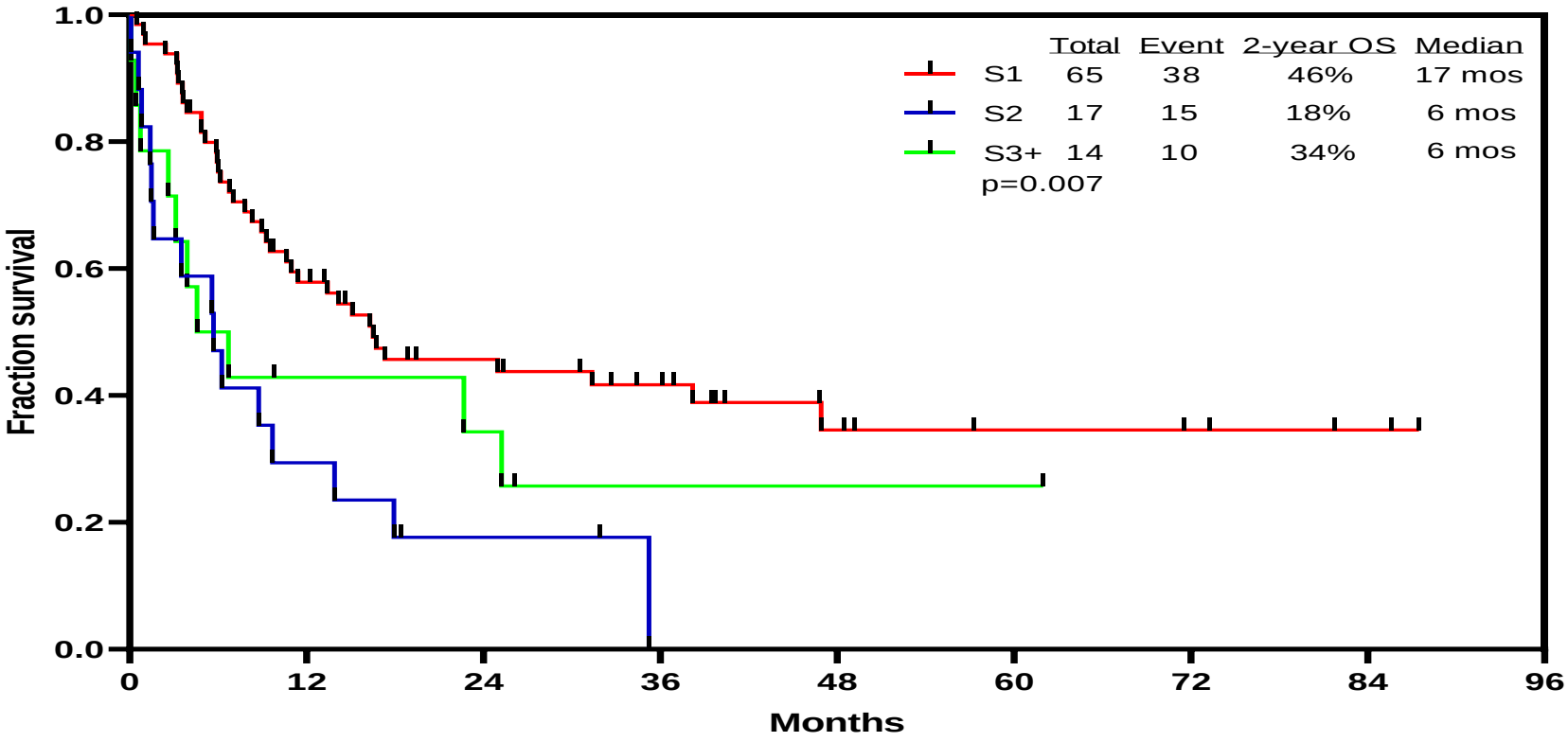
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Sasaki K, et al. *Blood*. 2018;132(suppl):553.

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

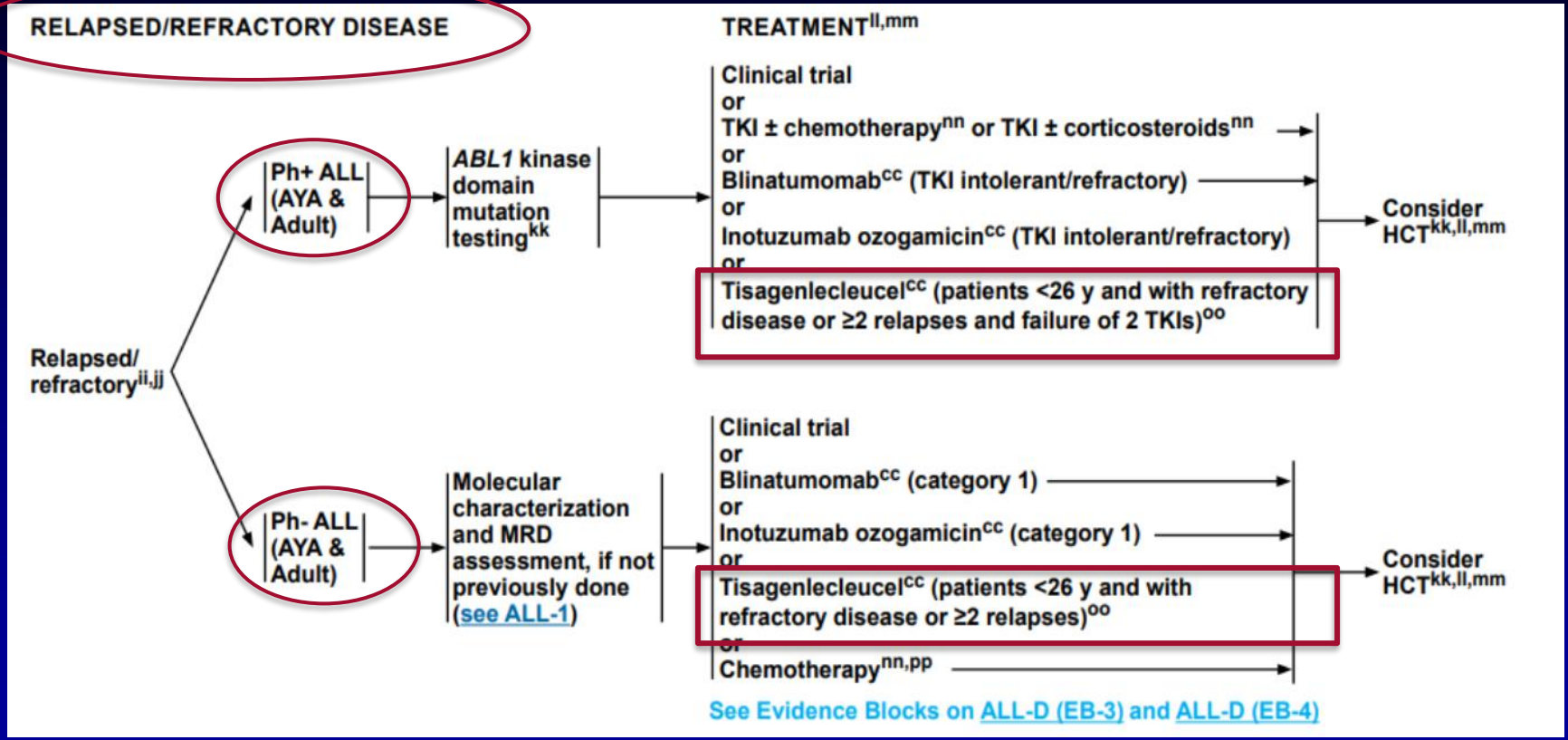


Sasaki. *Blood.* 2018;132:abstract 553; Jabbour E. *JAMA Oncol.* 2018;4:230.

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%)

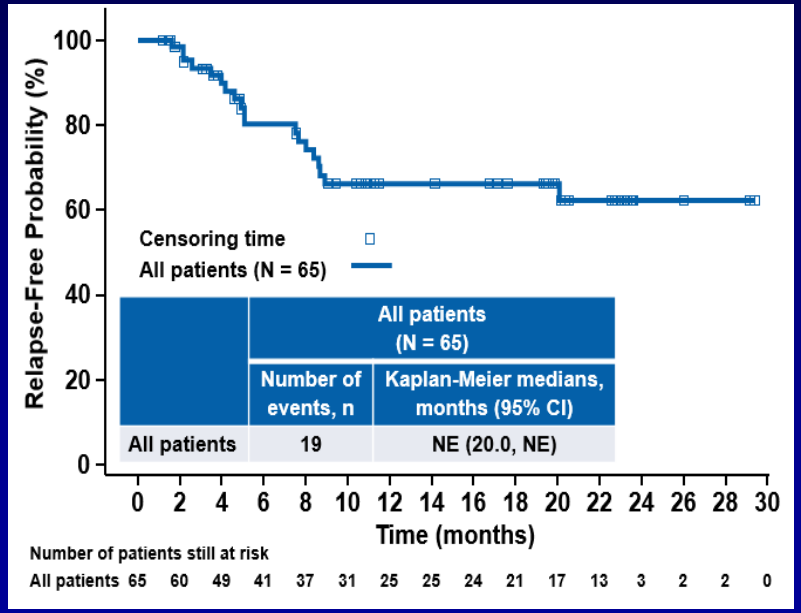
Where Does CAR T-Cell Therapy Stand?

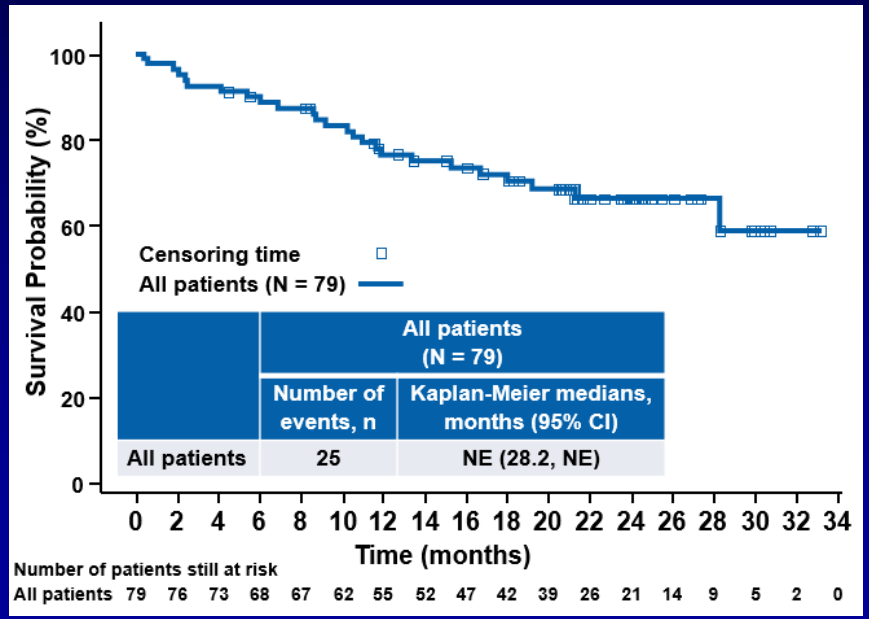


NCCN Guidelines ALL version 1.2020: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

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%

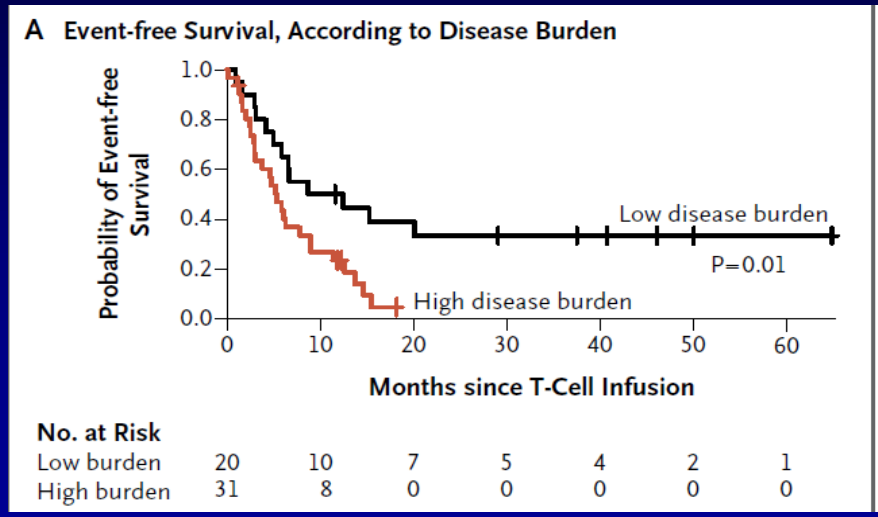


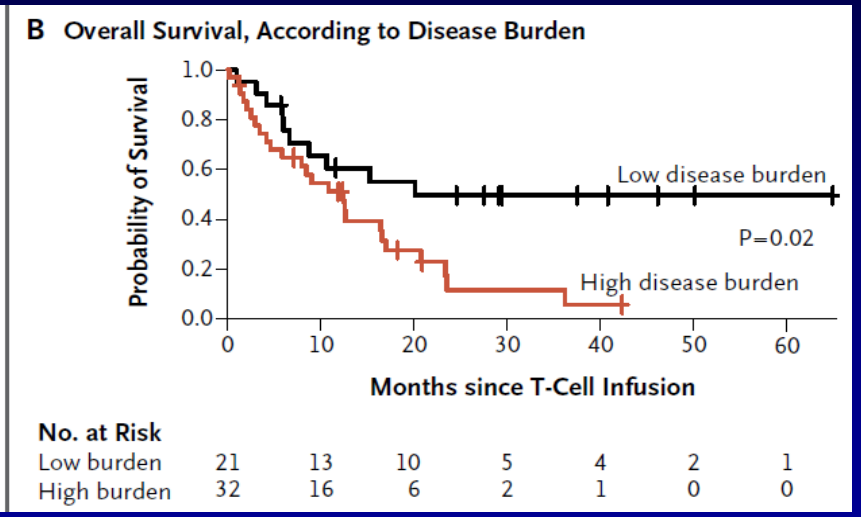


Grupp. EHA 2019. Abstract S1618.

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

Question 1

After listening to the debate, what is your preferred ALL treatment choice in salvage?

a. CAR T therapies
b. Bispecifics

Question 2

After listening to the debate, 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

After listening to the debate, 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

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

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

Autumn 2020

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

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**

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Hypercoagulable state	X	X	
Organ dysfunction (cardiac, renal, liver, pulmonary)	X	X	X
Comorbid conditions			X
Age			X

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

Treating Leukemia in the Time of COVID-19

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

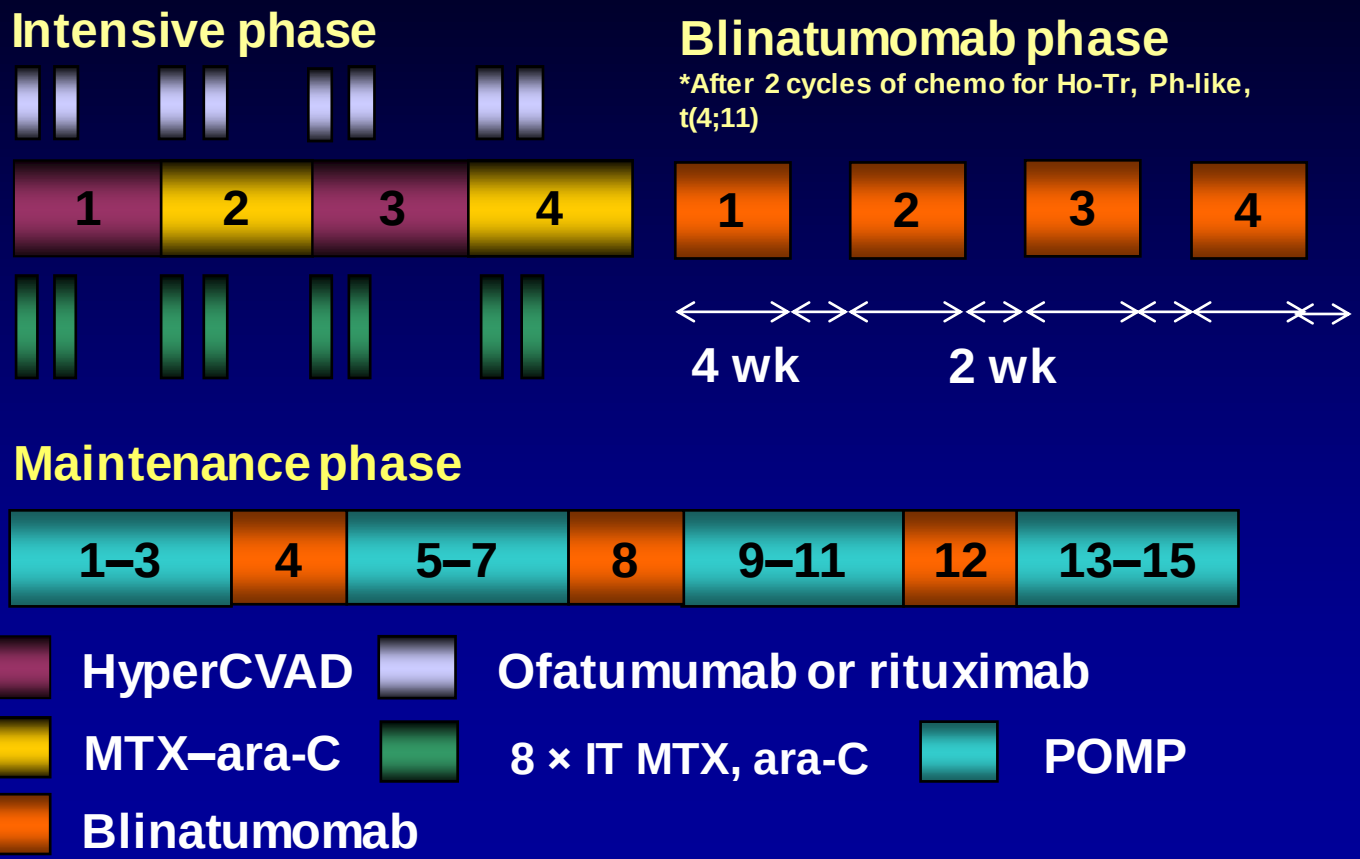
Treating ALL in the Time of COVID-19

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

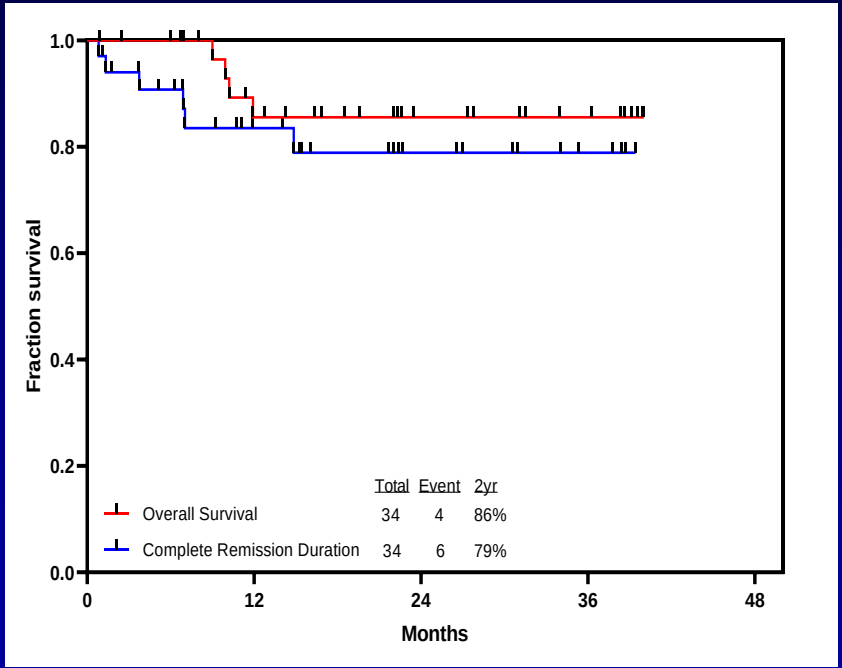


Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

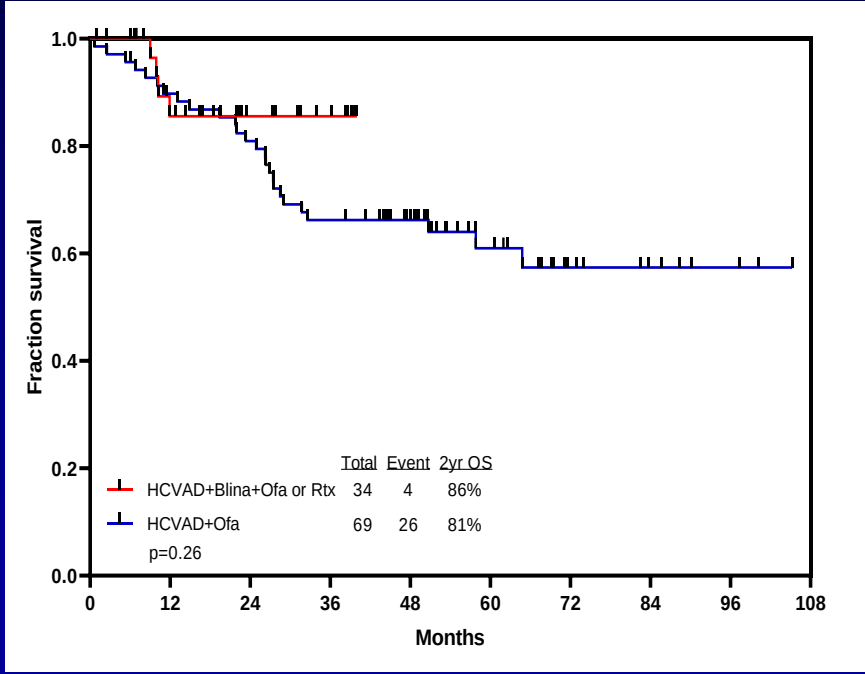
HyperCVAD + Blinatumomab in FL B-ALL (N = 34)

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

CRD and OS Overall

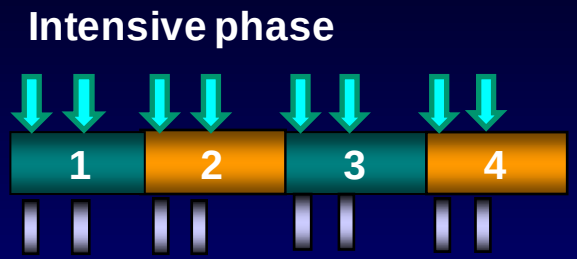


OS – HCVAD-Blina vs O-HCVAD



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)**

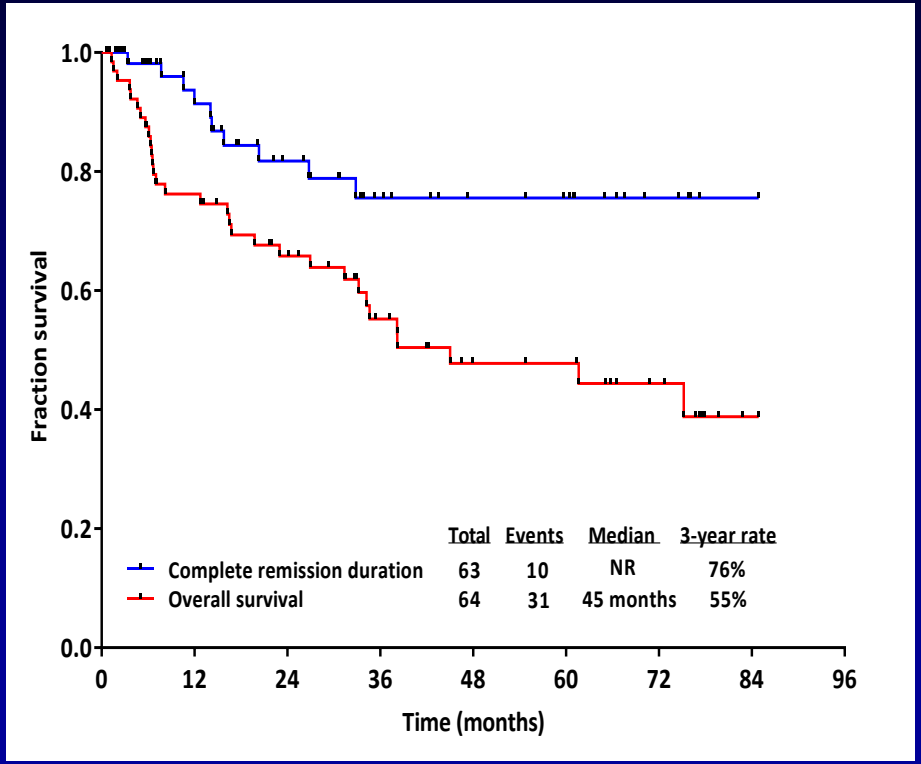
Response (N = 59)	N (%)
ORR	**58 (98)**
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	**0**

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

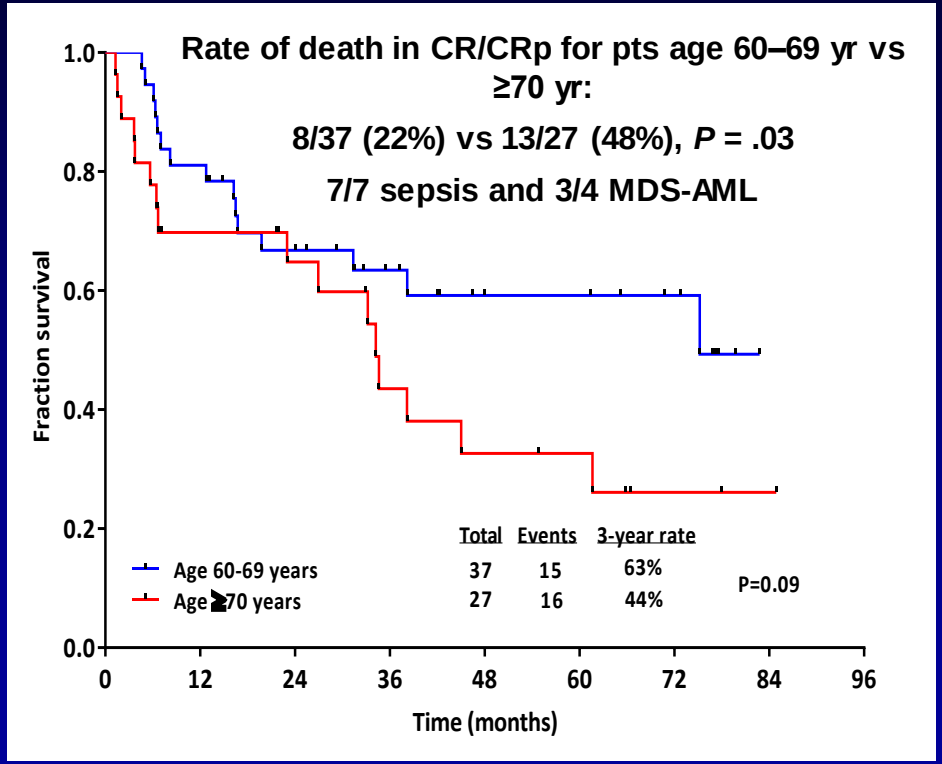
Short. *Blood.* 2019;134:abstract 823.

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

CRD and OS overall



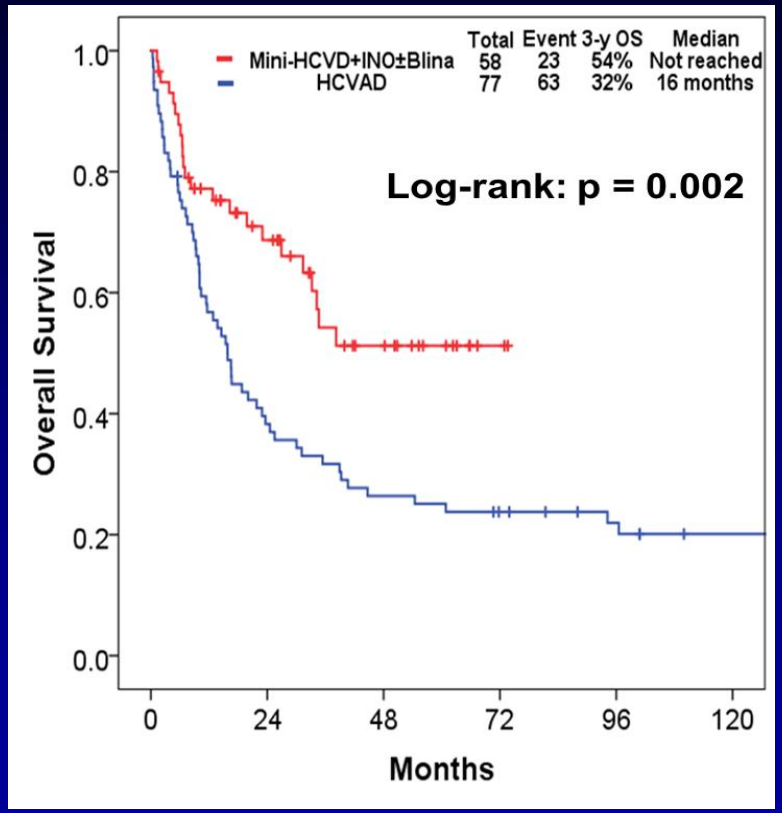
OS by age



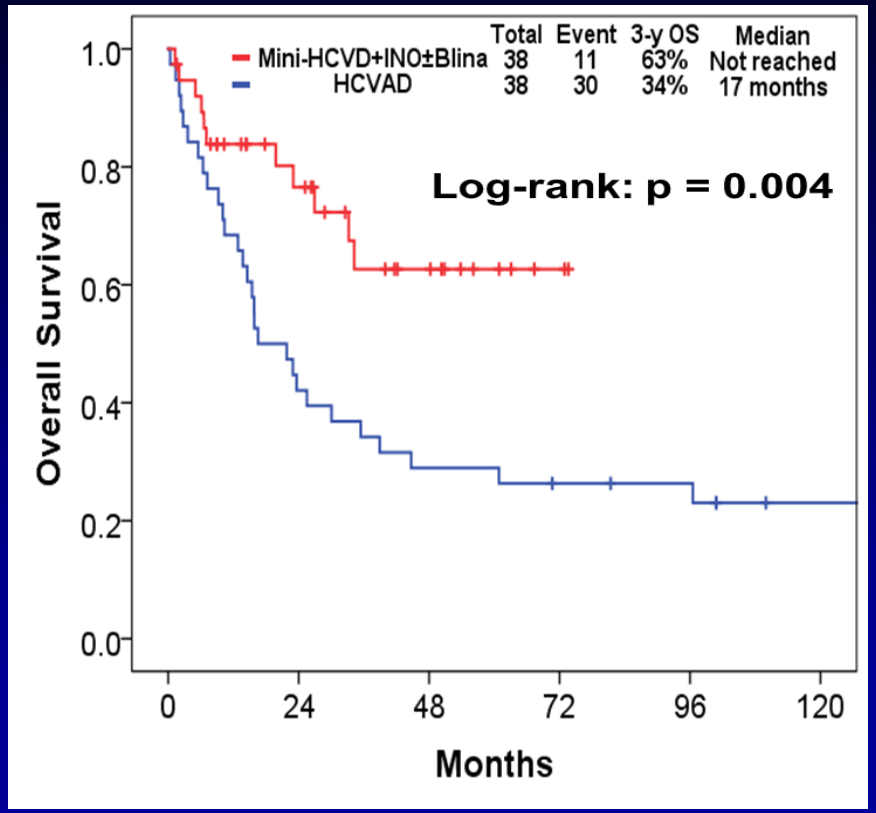
Short. *Blood.* 2019;134:abstract 823.

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

Prematched

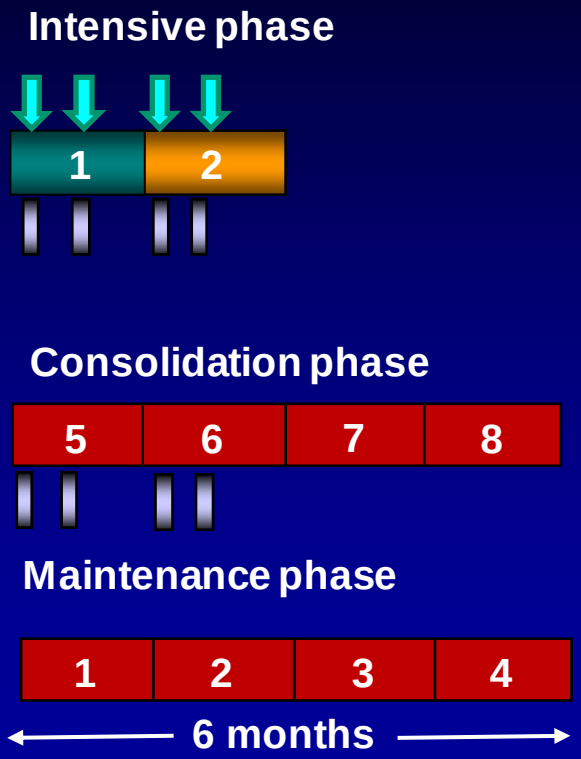


Matched



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

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



Mini-HCVD

Mini-MTX–cytarabine

IT MTX, ara-C

Blinatumomab

POMP

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

Total Ino dose = 1.5 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

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

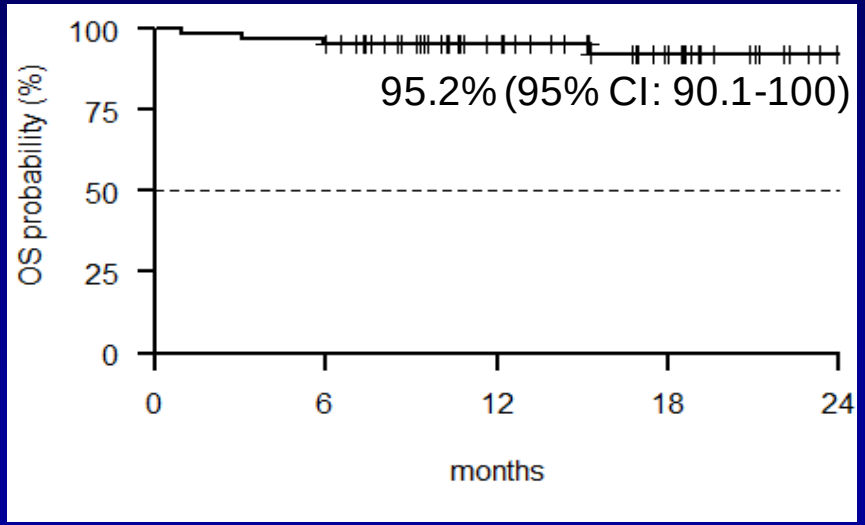
Treating ALL in the Time of COVID-19: Advantage of These Regimens

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

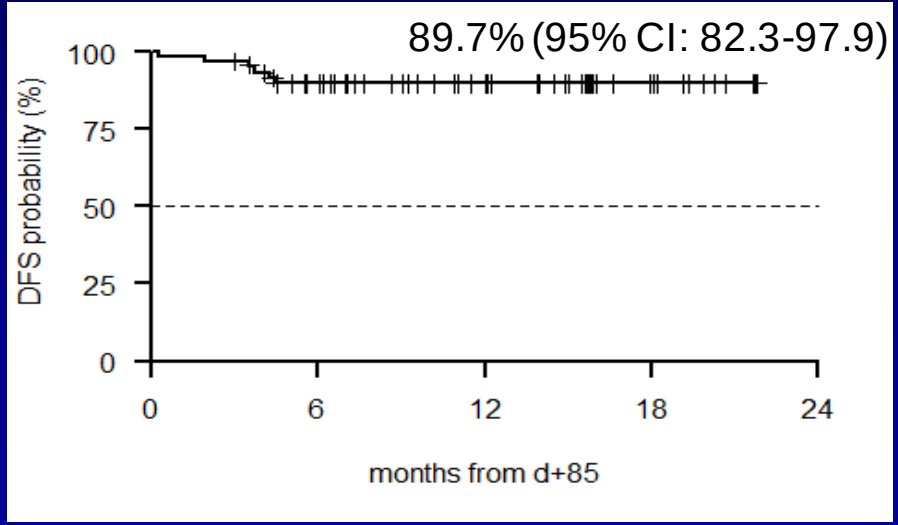
Dasatinib-Blinatumomab in Ph+ ALL

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

OS

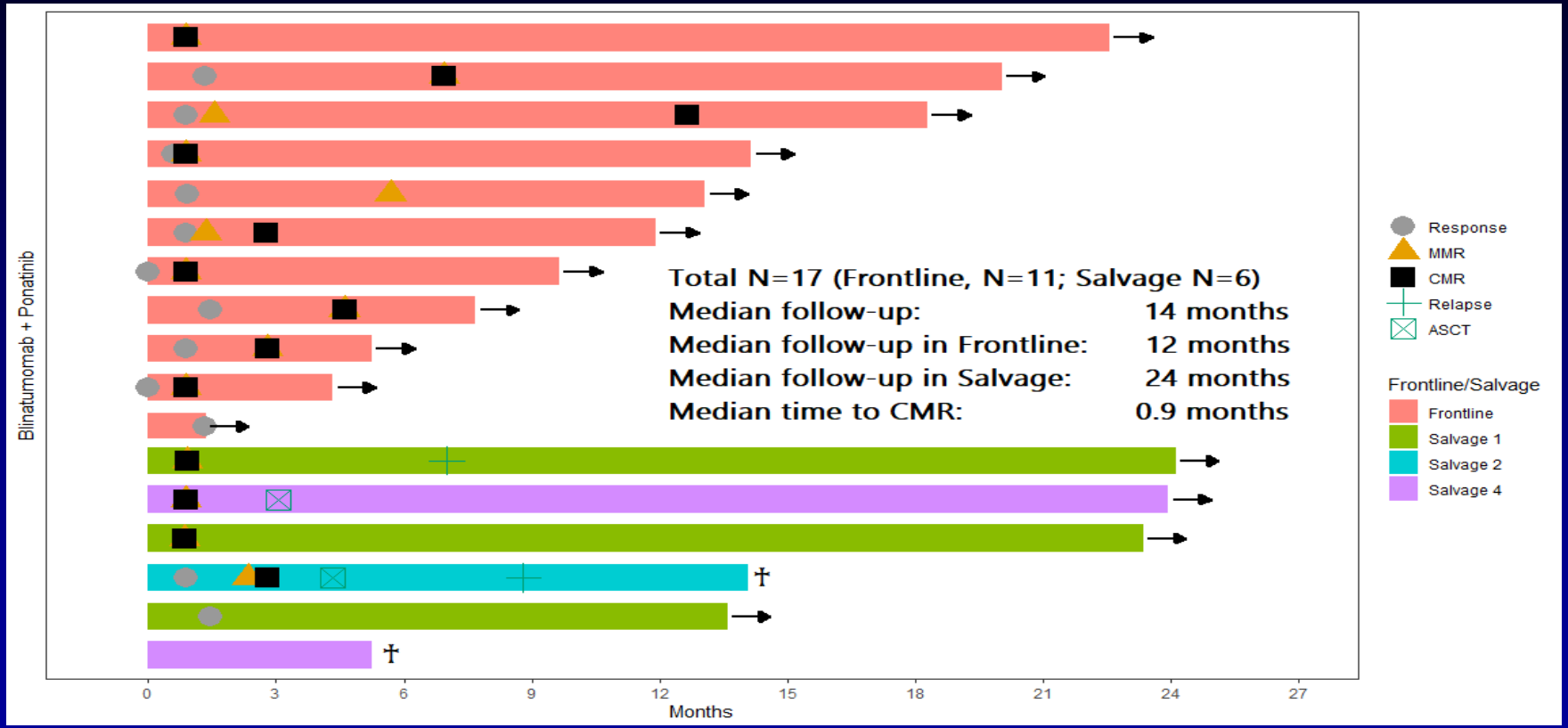


DFS



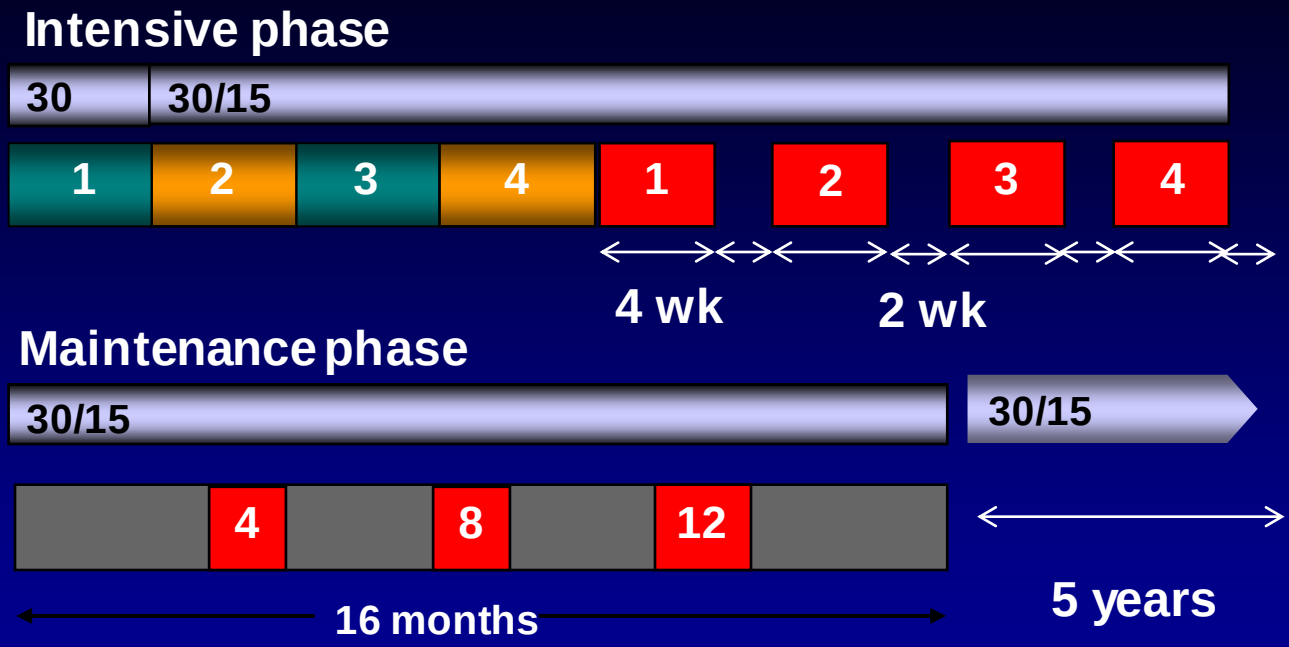
Chiaretti. *Blood.* 2019;134:abstract 615.

Blinatumomab + Ponatinib Swimmer Plot (N = 17)



Personal communication from Dr Jabbour.

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

APTITUDE HEALTH

Global Leukemia Academy

Session close

Elias Jabbour and Franco Locatelli

APTITUDE HEALTH

Thank you!

- Please complete the **evaluation survey** that will be sent to you by email
- The meeting recording and slides presented today will be shared on the www.globalleukemiaacademy.com website
- You will also receive a certificate of attendance by email by October 30

THANK YOU!

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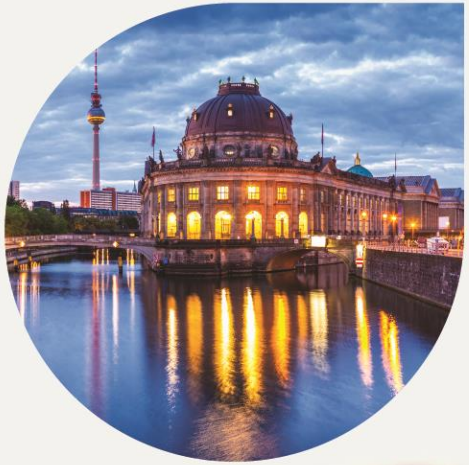

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

SEE YOU TOMORROW AT THE BREAKOUT SESSIONS!

APTITUDE HEALTH