Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

Bridging Science and Practice: From Newest Clinical Approaches to Real-World Clinical Cases

September 18–19, 2025 – Europe

Meeting sponsors AMGEN Autolus

APTITUDE HEALTH®

Global Leukemia Academy

Welcome and meeting overview

Elias Jabbour

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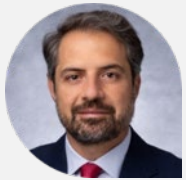
Meet the Faculty

CHAIR



Elias Jabbour, MD
MD Anderson Cancer Center, Houston, TX, USA

FACULTY

Nicola Gökbuget, MD
University Hospital Frankfurt
Frankfurt, Germany

Nicolas Boissel, MD
Saint-Louis Hospital
Paris, France

Josep-Maria Ribera, MD, PhD
Catalan Institute of Oncology
Hospital Germans Trias i Pujol
Badalona, Spain

Objectives of the program (ALL)

- 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 biomarkers in managing and monitoring ALL
- Share insights into antibodies and bispecifics in ALL
- Discuss the evolving role of ADC therapies in ALL
- Review promising novel and emerging therapies in ALL
- Explore and discuss regional challenges in the treatment of ALL across the EU

Day 1: Virtual Plenary Sessions

Thursday, September 18, 2025
18.00 – 21.00 UTC +2 (Central European Summer Time)

Time (UTC -5)	Time (UTC +2)	Title	Speaker
11.00 AM – 11.10 AM	18.00 – 18.10	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
11.10 AM – 11.35 AM	18.10 – 18.35	Latest achievements and developments in ALL	Elias Jabbour
11.35 AM – 11.55 AM	18.35 – 18.55	Review of prognostic and predictive markers in ALL	Josep-Maria Ribera
11.55 AM – 12.25 PM	18.55 – 19.25	Best practices for first-line treatment in ALL (including Ph+)	Elias Jabbour
12.25 PM – 12.40 PM	19.25 – 19.40	AYA patients with ALL: What is the current treatment approach for this diverse patient population? Special considerations for adolescents and young adults and how we can use this experience in adult patients	Nicolas Boissel
12.40 PM – 12.50 PM	19.40 – 19.50	Break	
12.50 PM – 1.25 PM	19.50 – 20.25	ALL case-based panel discussion for first-line therapy • Case ALL: Adult high risk (Dr Gökbuget/Dr Lang) • Case ALL: AYA (Dr Boissel)	Panelists: All faculty
1.25 PM – 1.50 PM	20.25 – 20.50	Panel discussion: How treatment in first line influences further therapy approaches in ALL • Differences in health care systems and clinical research in US and Europe and consequences for treatment approaches? • How have bispecifics changed the landscape of first-line therapy in adult ALL in Europe? • How to increase access to CAR-T-cells and study use in earlier phases of ALL treatment? • Is there any chance to agree on uniform prognostic factors for treatment stratification and transplant indication in adult ALL? • What is the difference in terms of treatment approach to AYA/Young adults, adults and older patients and how to stratify these approaches? • How to generate reliable clinical trial data in a rare and complex disease with more and more new compounds available? What can we learn from pediatric groups?	Moderated by Nicola Gökbuget Led by Elias Jabbour and all faculty
1.50 PM – 2.00 PM	20.50 – 21.00	Session close	Elias Jabbour

Day 2: Virtual Plenary Sessions

Friday, September 19, 2025
18.00 – 21.00 UTC +2 (Central European Summer Time)

Time (UTC -5)	Time (UTC +2)	Title	Speaker
11.00 AM – 11.10 AM	18.00 – 18.10	Welcome to Day 2	Elias Jabbour
11.10 AM – 11.40 AM	18.10 – 18.40	Current treatment options for relapsed/refractory (R/R) ALL in fit adults	Nicola Gökbuget
11.40 AM – 12.00 PM	18.40 – 19.00	Current treatment options for R/R ALL in elderly and frail patients	Josep-Maria Ribera
12.00 PM – 12.20 PM	19.00 – 19.20	Current and future role of transplantation in ALL in Europe	Nicola Gökbuget
12.20 PM – 12.30 PM	19.20 – 19.30	Break	
12.30 PM – 1.00 PM	19.30 – 20.00	ALL case-based panel discussion for R/R ALL • Case ALL: Young (Dr Ribera) • Case ALL: Elderly (Dr Gökbuget/Dr Lang)	All faculty
1.00 PM – 1.20 PM	20.00 – 20.20	Long-term safety considerations for ALL	Nicolas Boissel
1.20 PM – 1.50 PM	20.20 – 20.50	Panel discussion: Open questions in ALL – regional challenges (transplant, CAR T studies, and other) • Who are the ideal patients for CAR T therapy, bispecifics, and transplants in your practice? • What would be needed to make CAR T therapy available to all of your patients? • What would be needed to best position bispecifics in the continuum of care for ALL in adults? • How should transplant be strategically combined with the new therapy modalities?	Moderated by Nicolas Boissel Led by Elias Jabbour and all faculty
1.50 PM – 2.00 PM	20.50 – 21.00	Session close	Elias Jabbour

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Introduction to the voting system

Elias Jabbour

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Question 1

In which region of Europe do you currently practice?

A. Eastern Europe
B. Northern Europe
C. Southern Europe
D. Western Europe
E. Outside Europe

Question 2

Which captures the typical age range of most of your patients with ALL?
Select all that apply.

A. Adolescent/young adult (AYA; 15–39 years)
B. Adults (40–59 years)
C. Older adults (60–74 years)
D. Elderly (≥75 years)
E. I do not personally treat patients with ALL

Question 3

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

A. All patients with B-ALL relapsing within 18 months from diagnosis

B. Patients with hypodiploidy

C. Patients with t(17;19) or t(1;19)

D. Each of the 3 previous subsets

Question 4

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. Kinase inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. There are no effective consolidation treatments for patients who remain MRD+ after induction therapy

Question 5

If an elderly patient with Ph– ALL remains positive for MRD after dose-adjusted Hyper-CVAD induction, assuming full access, what is your preferred next intervention?

A. Proceed directly to transplant
B. Consolidation chemotherapy
C. Blinatumomab
D. Inotuzumab ozogamicin
E. CAR T-cell therapy
F. Other

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Latest achievements and developments in ALL

Elias Jabbour

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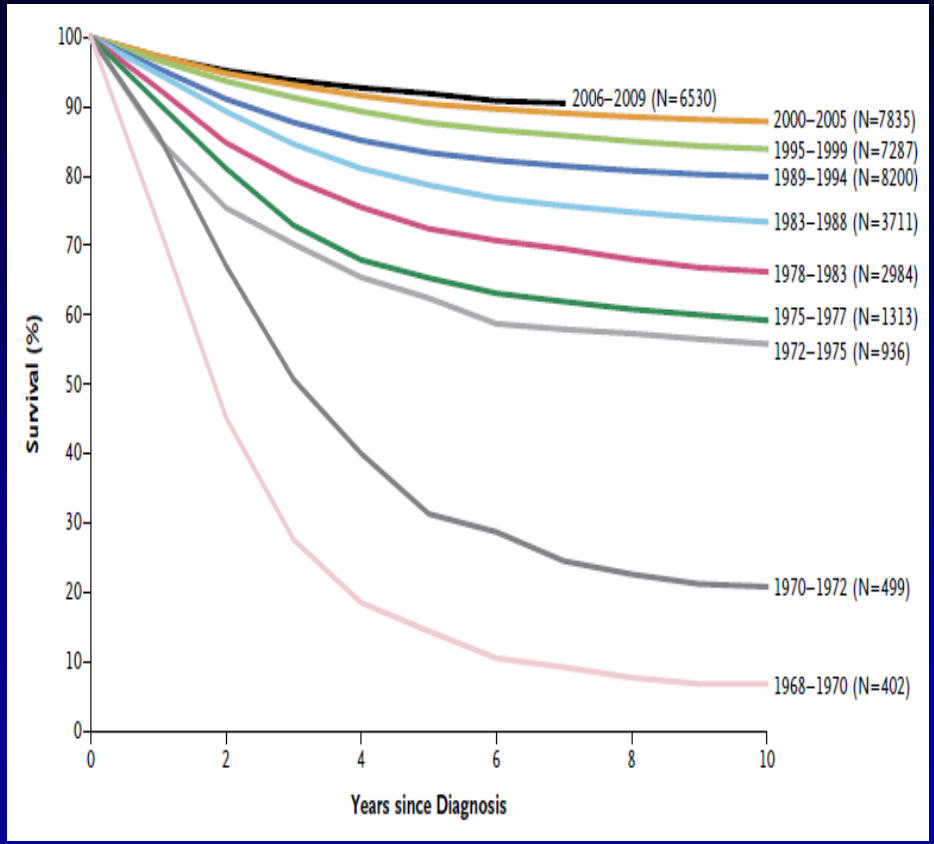
How I Treat Acute Lymphoblastic Leukemia in 2025: The Latest Updates

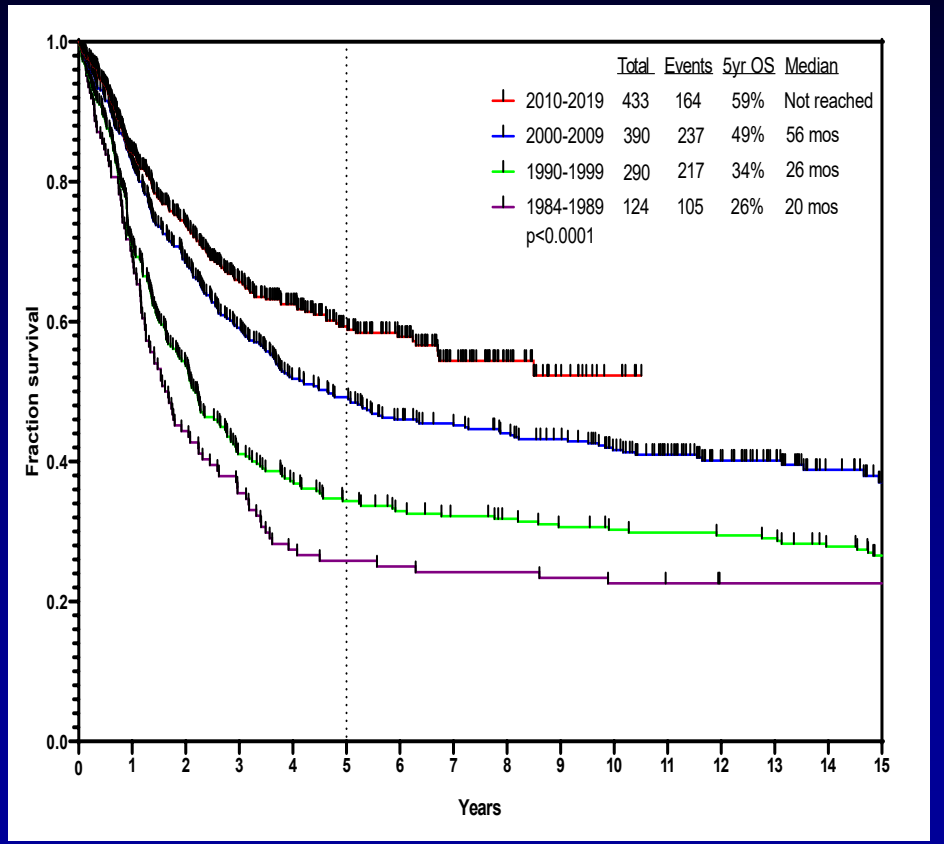
Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

Summer 2025

Survival in Pediatric and Adult ALL With Classical Intensive ChemoRx Regimens



Hunger SP, et al. *N Engl J Med*. 2015;373:1541-1552.

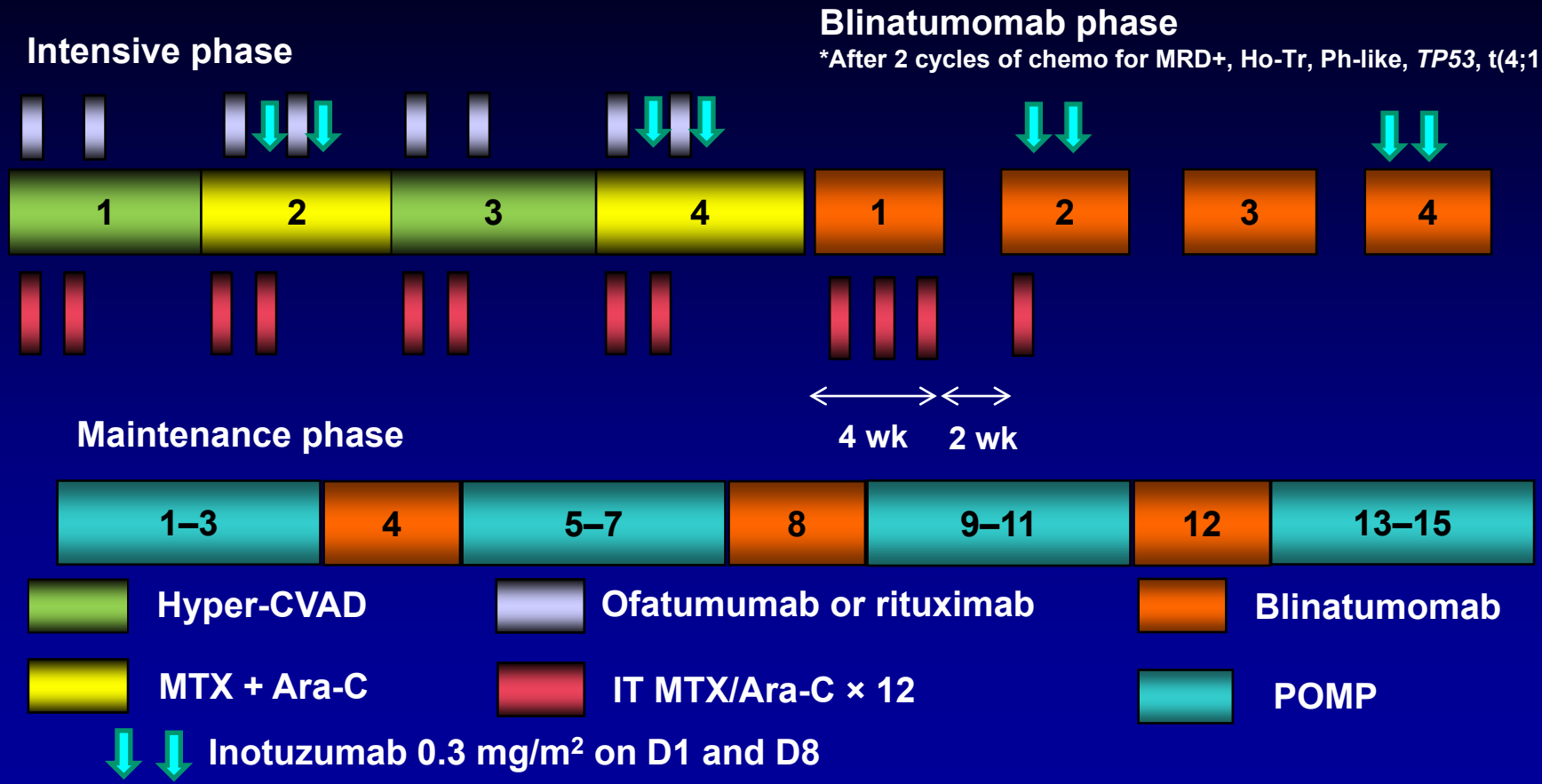


Kantarjian HM, et al. *Cancer*. 2022;128:240-259.

Reasons for Recent Success in Adult ALL

- Addition of TKIs (ponatinib) ± blinatumomab to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Addition of CD19 bispecific T-cell engager (BiTE) antibody blinatumomab, and of CD22 monoclonal antibody-drug conjugate (ADC) inotuzumab, to chemoRx in salvage and frontline ALL Rx
- CAR T therapy
- Importance of MRD in CR (at CR vs 3 mo; NGS)

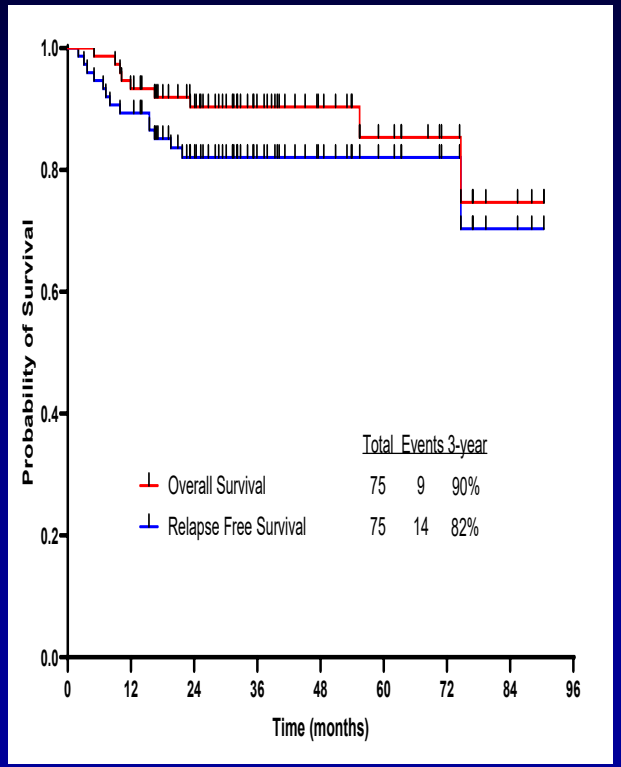
Hyper-CVAD + Blinatumomab in B-ALL: Regimen



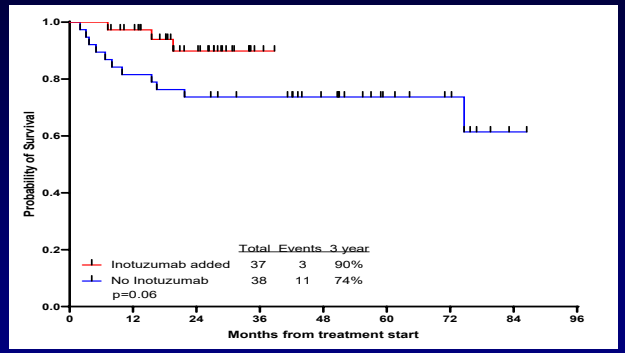
Jabbour E, et al. *Lancet Haematol.* 2022;9:e878-e885; Kantarjian H, et al. *Am J Hematol.* 2025;100:402-407.

Hyper-CVAD–Ino → Blina in Newly Dx Adult ALL

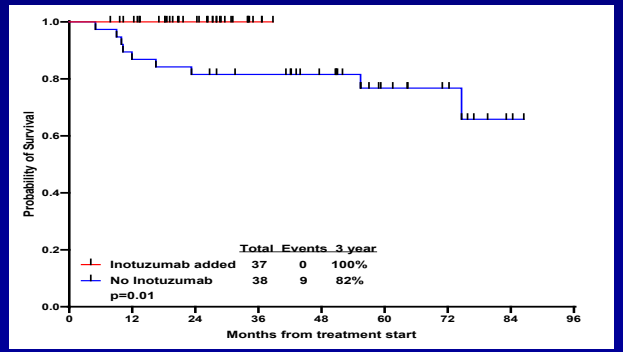
- 75 pts; median age 33 yr (18-59); median F/U 44 mo (13-90)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 76%; 60-day mortality 0%; 24 (32%) alloSCT



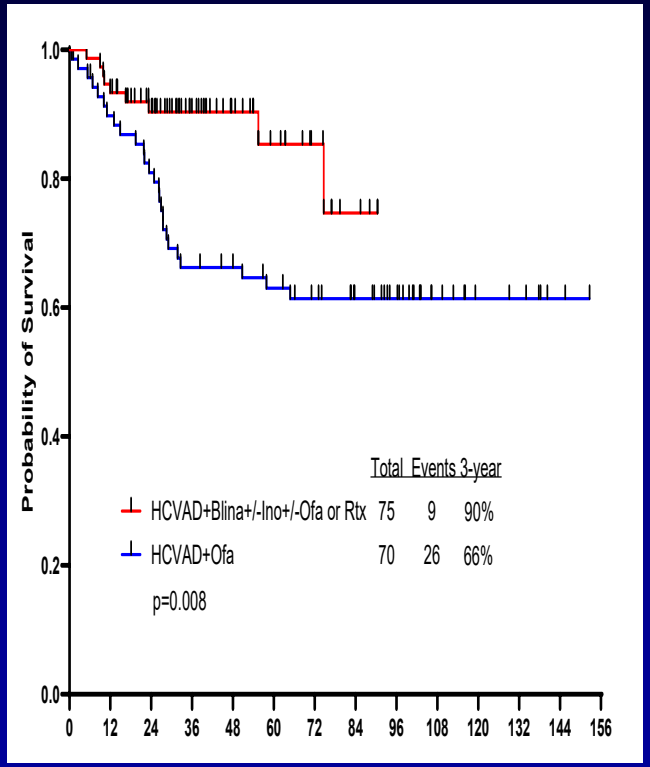
Relapse-free survival



Overall survival



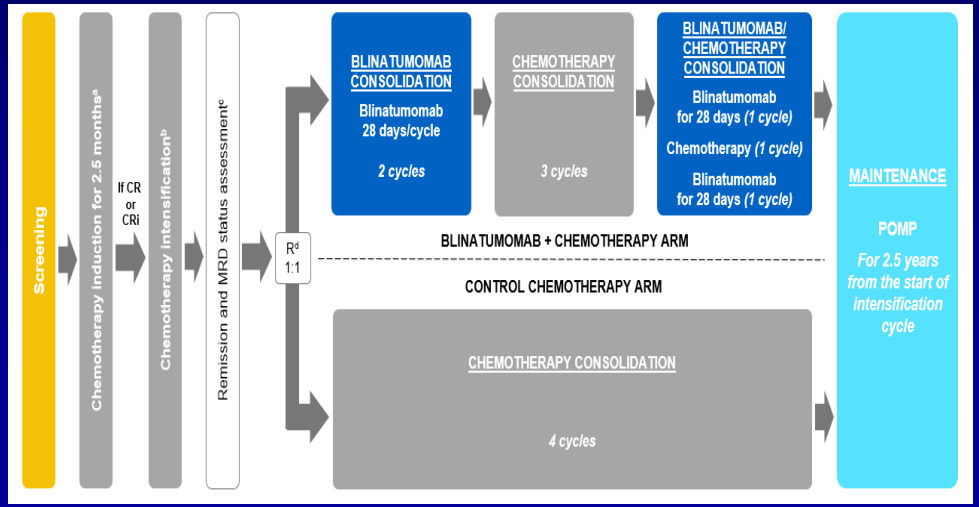
Overall survival

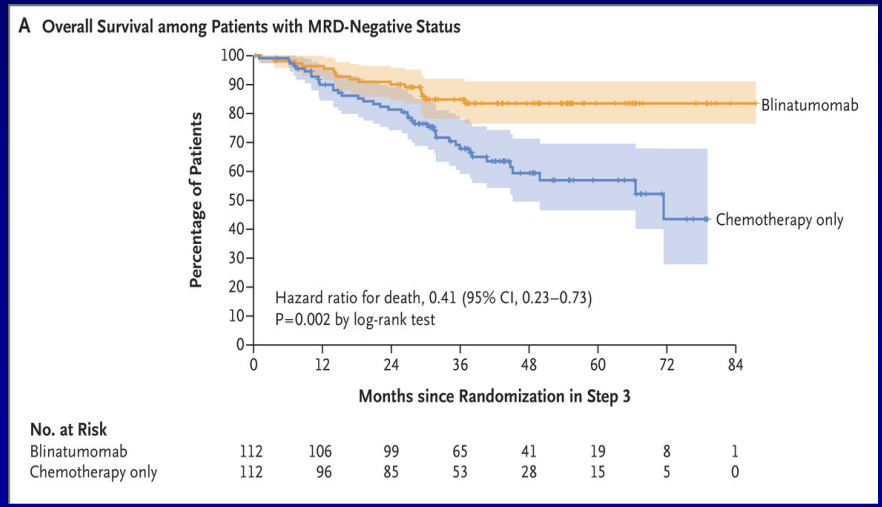


Jabbour E, et al. *Lancet Haematol.* 2022;9:e878-e885; Kantarjian H, et al. *Am J Hematol.* 2025;100:402-407.

E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD-Negative CR

- 488 pts median age 51 yr (30–70)
- 224 MRD-negative CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median F/U 43 mo; median OS NR vs 71.4 mo (HR 0.42; *P* = .003)
- No difference in OS if 1–2 cycles of blina vs control (HR 0.62; *P* = .22)
- OS: 1–2 cycles vs 4 cycles (HR 0.39; *P* = .07)

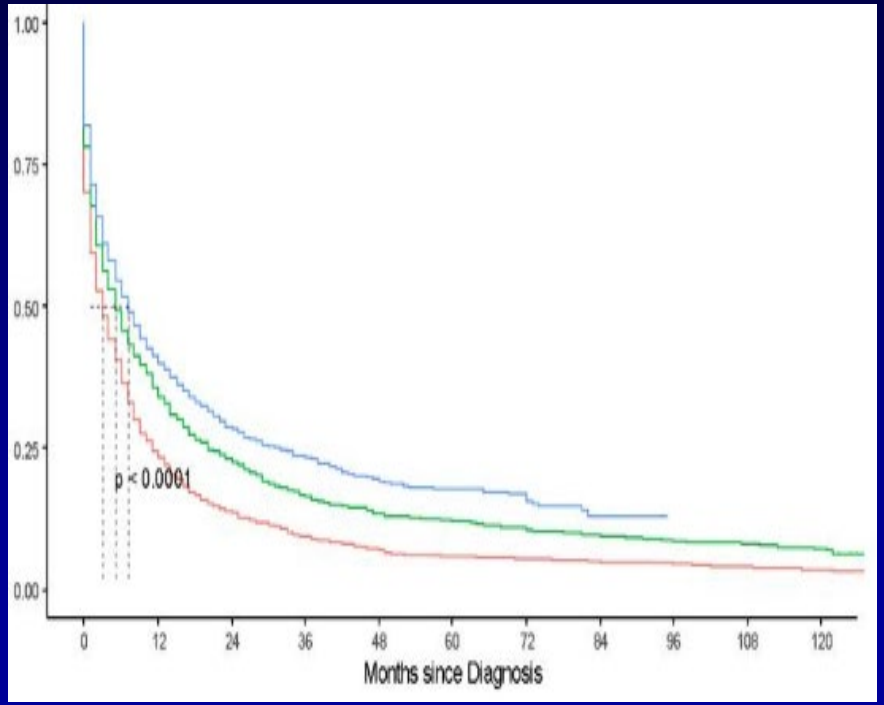


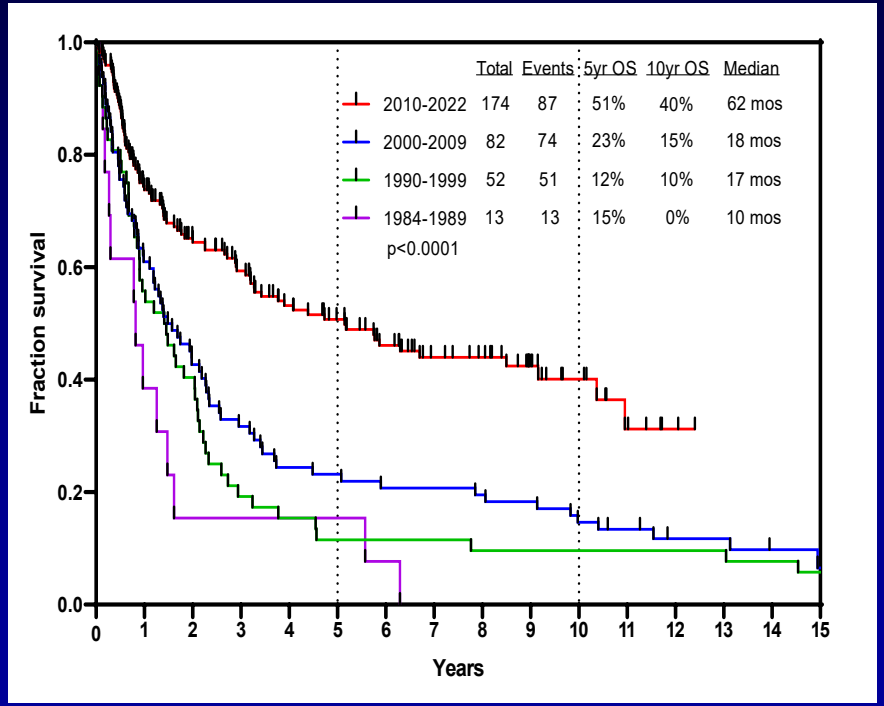


Litzow MR, et al. *N Engl J Med.* 2024;391:320-333.

MDACC vs SEER ALL: Survival by Decades for ≥60 Years

- 26,801 pts age 65+ yr; B-ALL 91%
- OS better in Ph+ (HR 0.68) and 2012-2018 (HR 0.64); worse in secondary ALL (HR: 1.15), AA (HR: 1.19), and Hispanic (HR 1.1)
- 5-yr OS <20%

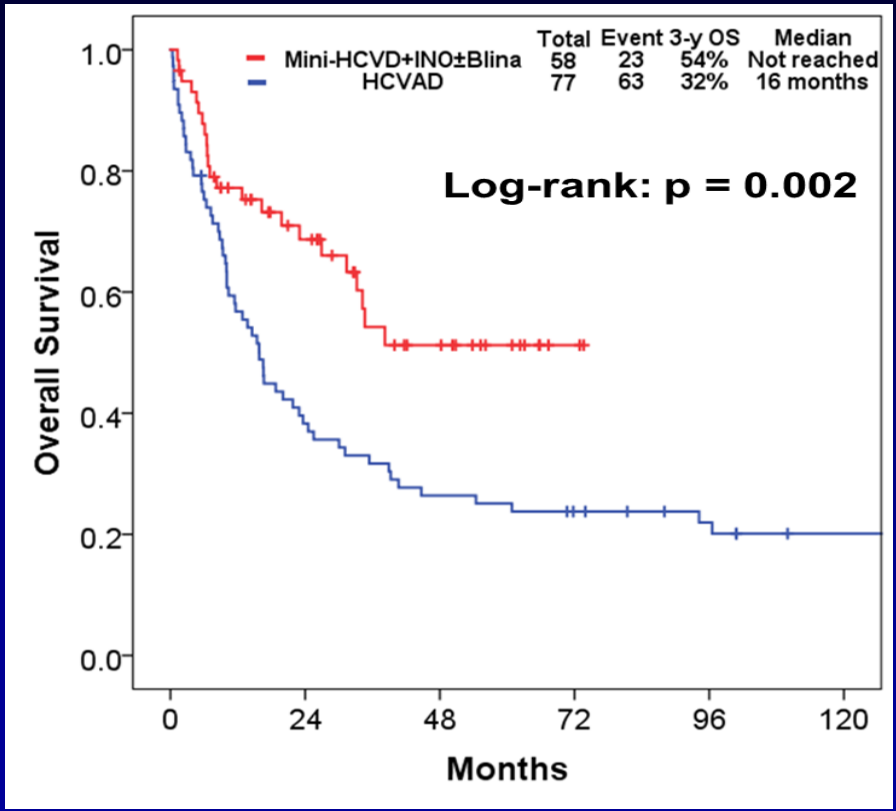




Gupta S, et al. *Blood.* 2022;140:1379.

Mini-HyperCVD + InO ± Blina vs HCVAD in Older ALL: Overall Survival

Prematched



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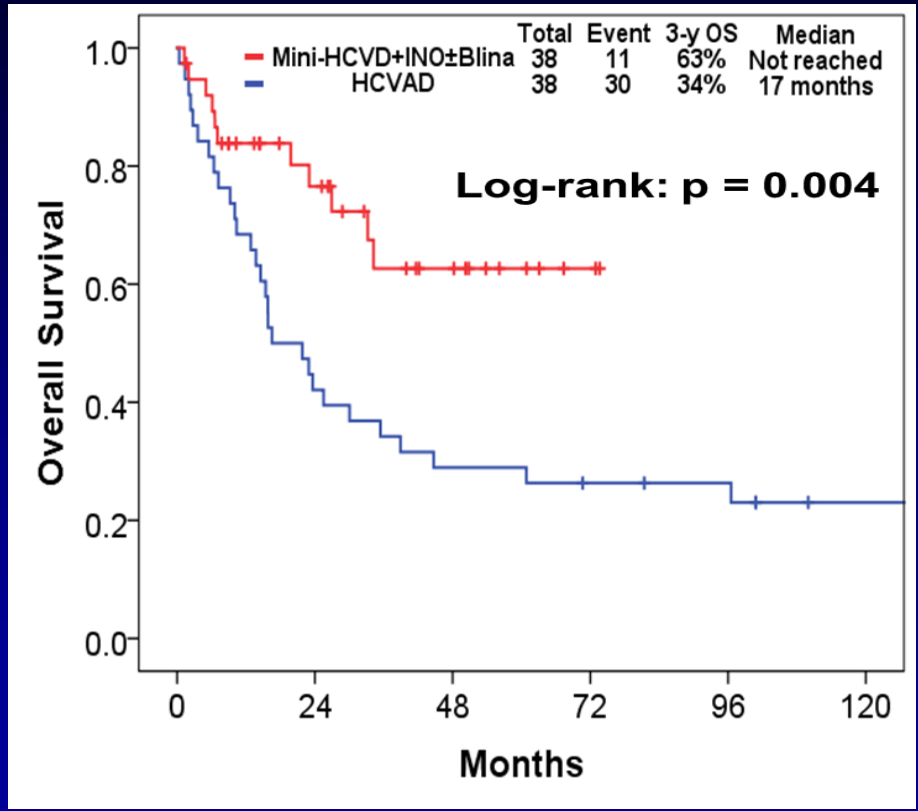


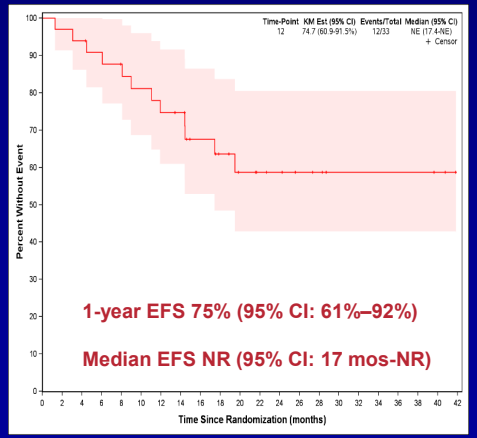
Jabbour E, et al. *Cancer.* 2019;125:2579-2586.

ChemoRx-Free InO + Blina in Pre–B-ALL (Alliance A041703)

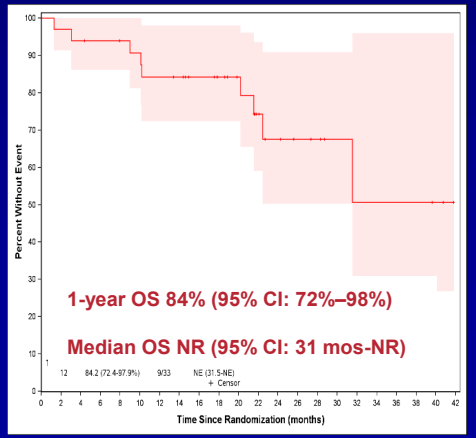
- 33 pts; median age 71 yr (60–84); median CD22 92%; F/U 22 mo
- Induction: InO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 and 15 (1.8 mg/m^2)
- Maintenance: if CR-CRi, InO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) × 2 then Blina × 2
- If no CR-CRi, Blina 28 µg/D × 21 then × 28 × 3
- IT × 8
- CR 85% post-InO × 3; cumulative CR 97%
- 1-yr EFS 75%; 1-yr OS 84%
- 9 relapses; 2 deaths in CR; 9 deaths, 6 post-relapse; ?1 SOS

	Induction With Inotuzumab (IA/B/C)	Consolidation With Blinatumomab
Cumulative CR (CR + CRh + CRi)	28/33 (85%)	32/33 (9%)
CR	15/33 (45%)	19/33 (58%)
CRh	11/33 (33%)	12/33 (36%)
CRi	2/33 (6%)	1/33 (3%)
Refractory	3/33 (9%)	-

EFS



OS



Wieduwilt M, et al. *HemaSphere.* 2023;7:S117.

CD19 CAR T-Cell Rx in Older ALL in CR1

- 20 pts ≥55 yr consented; minimal bridging followed by CAR T cells
- 14 evaluable (200 million CAR Ts)
- Median age 68 yr (55–79); 4 Ph positive; 2 hypodiploidy/*TP53* mutations
- 11 Rx Blina; 13/14 MRD-neg CR at LD
- No ICANS or G≥2 CRS
- Median F/U 244 days: 13/14 MRD-neg CR; 1 pt Ph positive ALL molecular relapse (alive in MRD-neg CR post-ASCT)
- No deaths
- CAR T cells expanded (peak 7–4 days; 14%)
- D28 10 pts LP CAR T cells expanded in CSF (median 0.28 × 10^3/mL)
- Baseline and D100 walk speed and cognitive function similar

Aldoss I, et al. *Blood.* 2024;144:966.

Hyper-CVAD, Venetoclax, Nelarabine–Peg-Asp in T-ALL/LL

- 145 pts (8/2007–12/2024) on 5 cohorts; median age 35.4 yr
- 46 pts (34%) with VEN
- 60% T-ALL; 18% ETP; median F/U 62 mo
- ORR 95%; CR 89%; 5-yr OS 64%. Cohorts 3–5: 3-yr OS 76%–88%
- OS shorter ETP/near-ETP vs non-ETP phenotype (71 mo vs NR; *P* = .08)
- VEN vs no VEN: 2-yr PFS 89% vs 64% (*P* = .03); 3-yr OS 88% vs 74% (*P* = .16)

Figure 1C: Overall survival (OS)

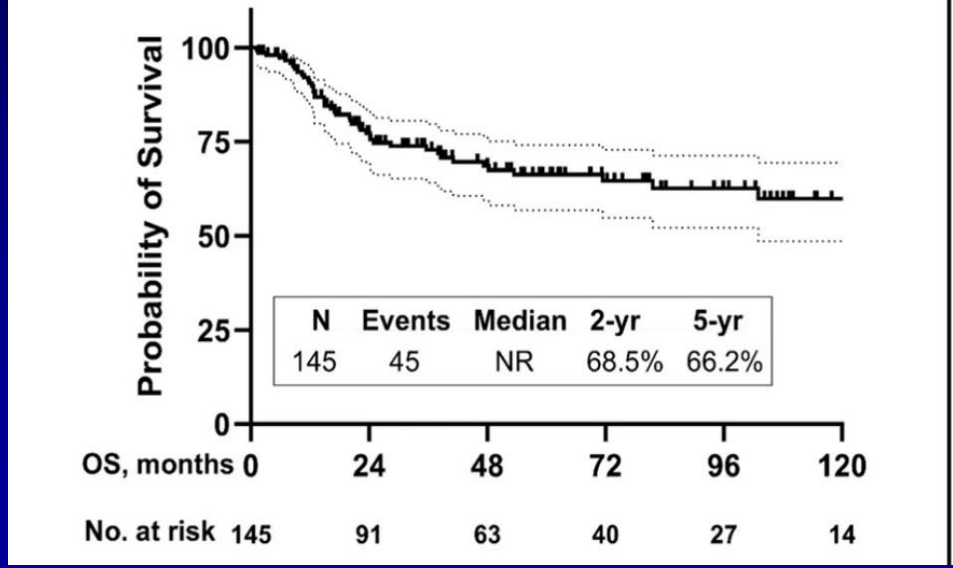
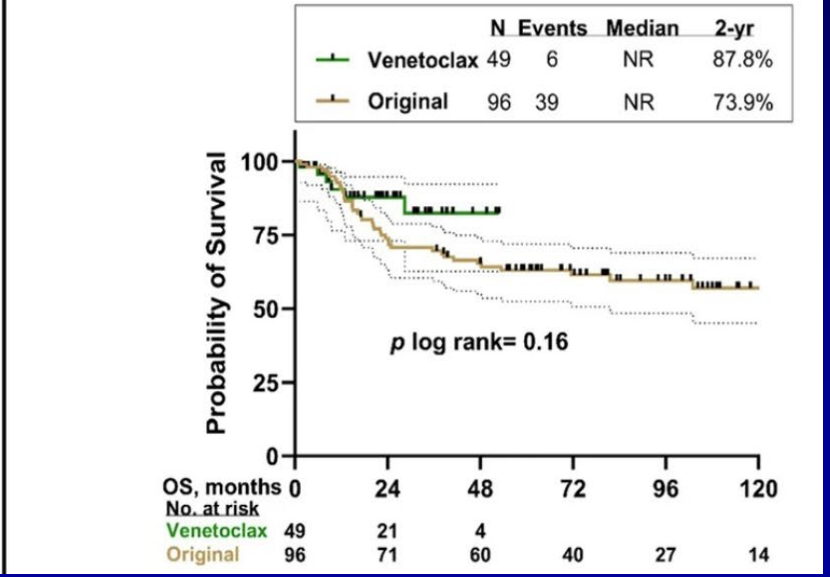


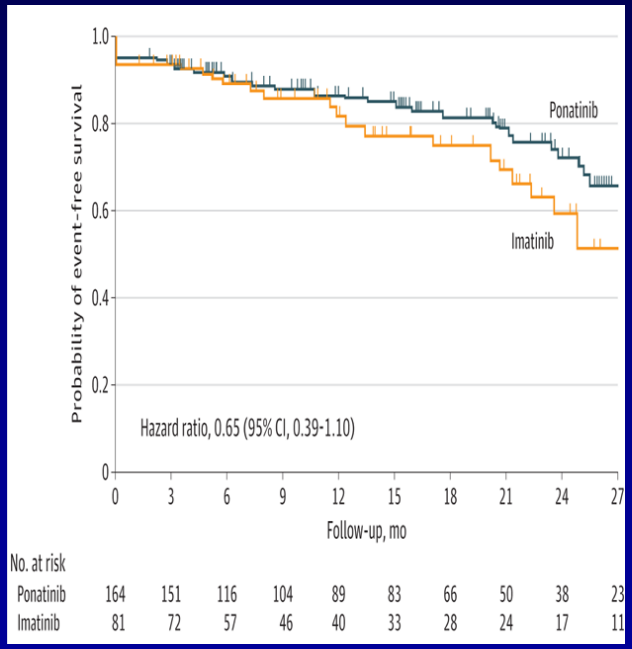
Figure 1F: Overall survival (OS)

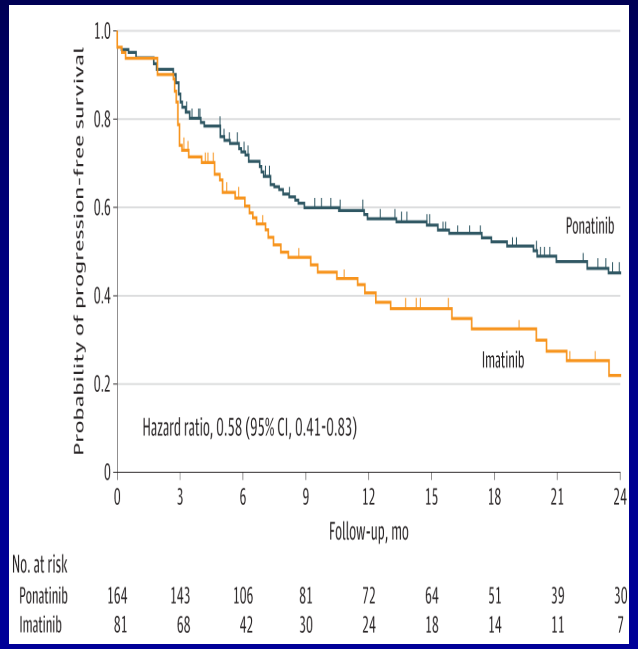


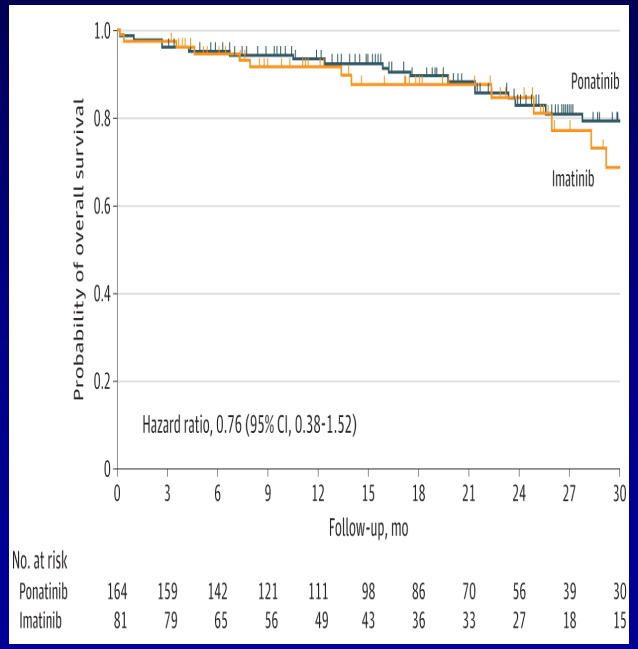
Ravandi F, et al. *Leukemia*. 2024;38:2717-2721.

Ponatinib vs Imatinib in Newly Dx Ph-Positive ALL: PhALLCON Phase III Trial

- 245 pts randomized (2:1) to ponatinib 30 mg/D (n = 164) or imatinib (n = 81), both with VCR-Dex for 90 days; then continuation of TKIs and chemoRx
- Primary endpoint MR4 CR at 90 days: 34.4% vs 16.7% (*P* = .002)
- Subsequent ASCT 30% vs 37%

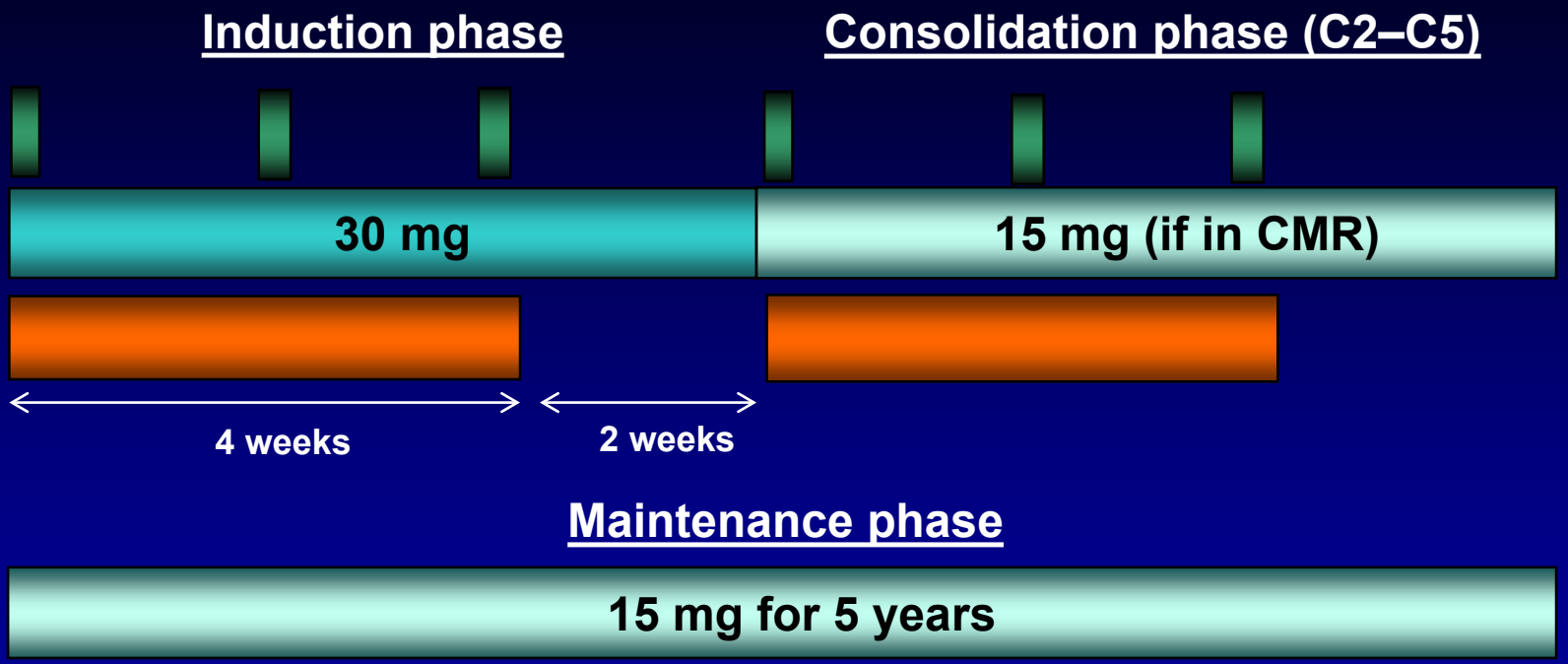






Jabbour E, et al. *JAMA*. 2024;331:1814-1823.

Ponatinib + Blinatumomab in Ph-Positive ALL: Regimen

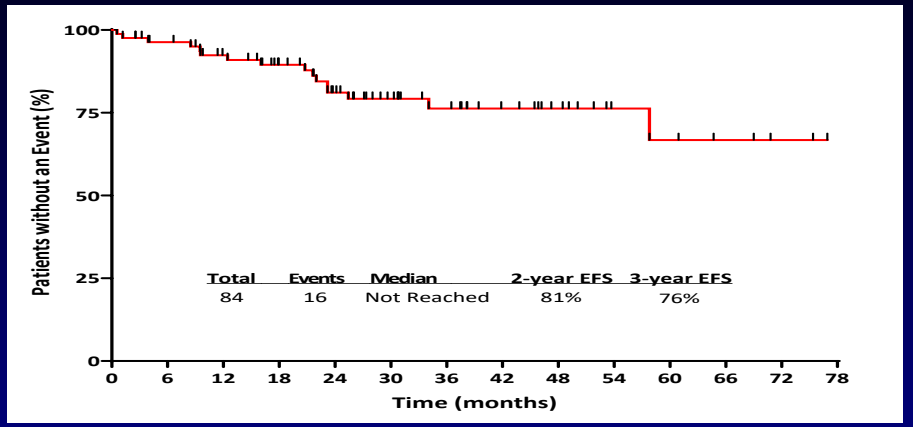


Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

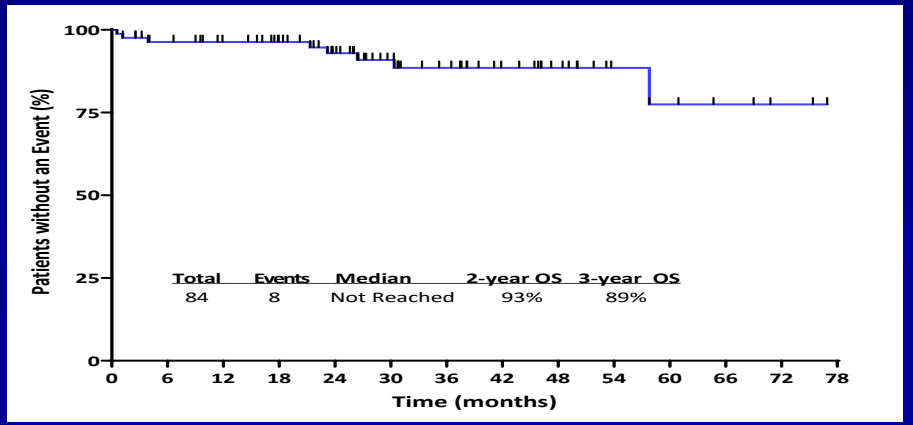
- 84 pts Rx with simultaneous ponatinib 30–15 mg/D and blinatumomab × 5 courses; 12–15 ITs. Median F/U 29 mo
- Only 2 pts had SCT (2%)
- Median F/U 29 mo; 3-yr EFS 76%, OS 89%
- 10 relapses (9 p190): 5 CNS, 4 BM, 1 *CRLF2*+ (Ph–); 3-yr cumulative relapse 12%

Parameter	%
CR-CRi	97
CMR	78
NGS-MRD negative	95
3-yr OS	89

Event-free survival



Overall survival



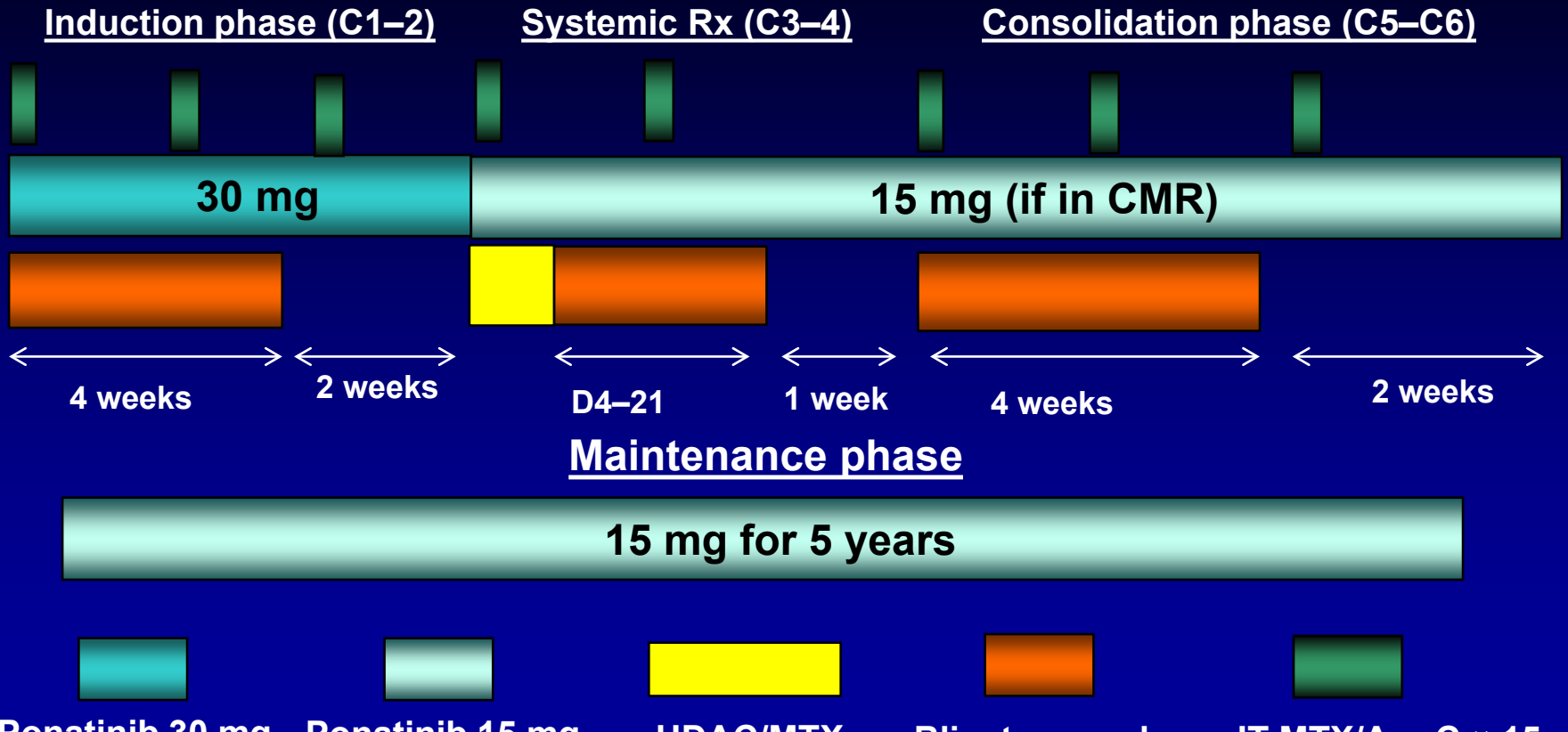
Jabbour E, et al. *Lancet Haematol*. 2023;10:e24-e34;
Kantarjian H, et al. *J Clin Oncol*. 2024;42:4246-4251.

Ponatinib vs Dasatinib + Blinatumomab in Ph-Positive ALL

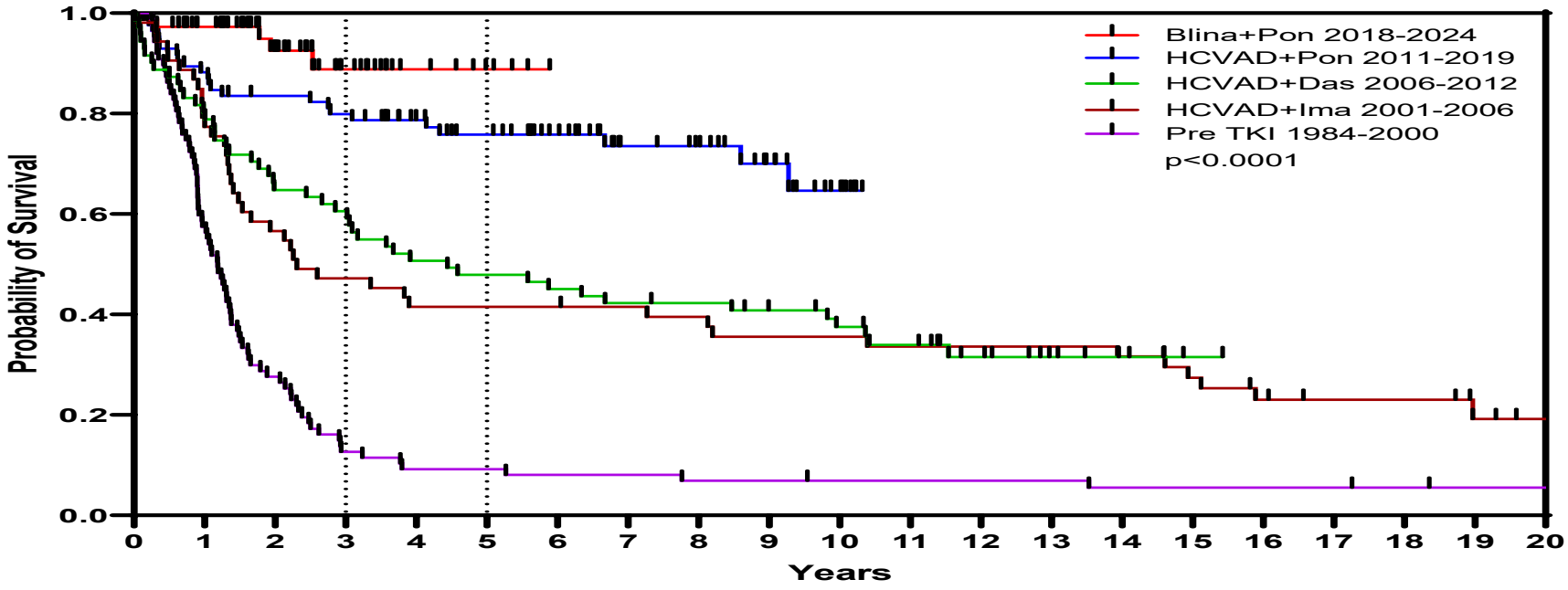
Parameter	Pona + Blina (n = 84; 5 blina)	Dasa + Blina (n = 63; 2+ blina)	Dasa + Blina (n = 24; 3 blina)	Pona + Blina (n = 133; 2-5 blina)
Median age, yr	50	54	73	57
PCR neg, % NGS clonoSEQ neg, %	78 95	93 (+ PNQ)	63	73
4-yr OS, %	89	82	75	18-mo OS 92%
AlloSCT, %	2	48	5	12
Relapses (CNS)	10 (5)	9 (4)	8 [3 T315I]	4 (1)

Kantarjian H, et al. *J Clin Oncol*. 2024;42:4246-4251; Foà R, et al. *J Clin Oncol*. 2024;42:881-885; Advani A, et al. *Blood*. 2023;142:1499; Chiaretti S, et al. *Blood*. 2024;144:835.

Ponatinib + Blinatumomab in Ph-Positive ALL: Regimen (WBC ≥70K)



ALL: Survival by Decade (MDACC 1984–2024)



	Total	Events	3yr OS	5yr OS	Median
Blina+Pon 2018-2024	76	5	89%	89%	Not reached
HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
Pre TKI 1984-2000	87	83	13%	9%	14 mos

p<0.0001

ChemoRx vs ASCT in HR Ph-Negative ALL With Early MRD Negativity: GMALL Trial 08/2013

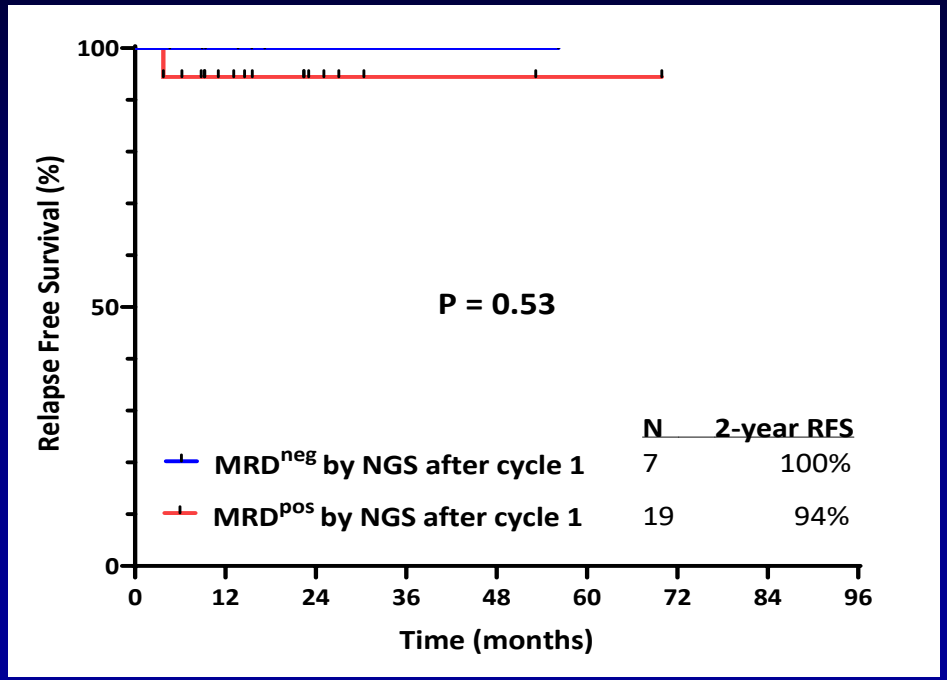
- 102/285 HR pts in CMR post-induction 2; randomized to ASCT vs SOC
- CMR rate post-induction 2: 36%
- Median age 31 yr (18-55); 63% B-ALL (26% pro-B); 37% T-ALL (19% early)
- 79% of total assigned to ASCT vs 88% of total assigned to SOC received intended Rx

Parameter, %	SOC (n = 42)	ASCT (n = 38)	*P* Value
3-yr DFS	71	76	NS
Relapses	15	10	
3-yr TRM	9	13	
3-yr OS	75	76	NS

Goekbuget N, et al. *Blood*. 2024;144:961.

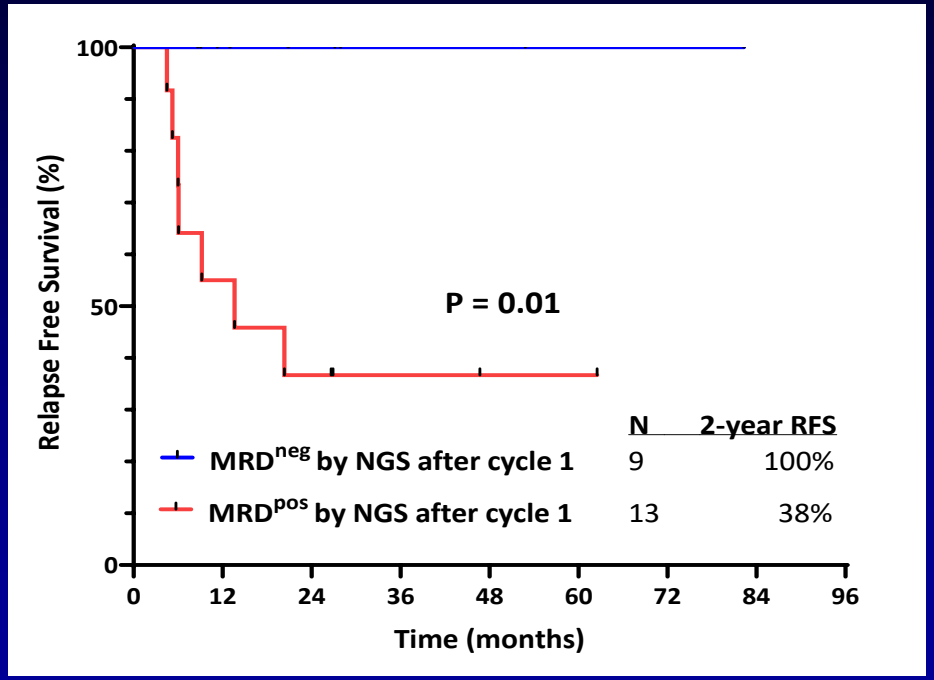
NGS MRD in B-Cell ALL: RFS by NGS MRD Response After Cycle 1 (Ph-negative B-cell ALL)

Standard risk



SCT in 0/26 pts

High risk

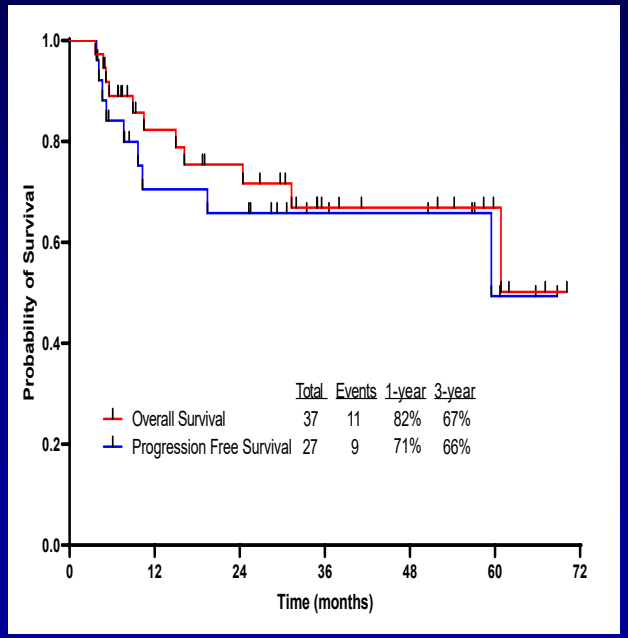


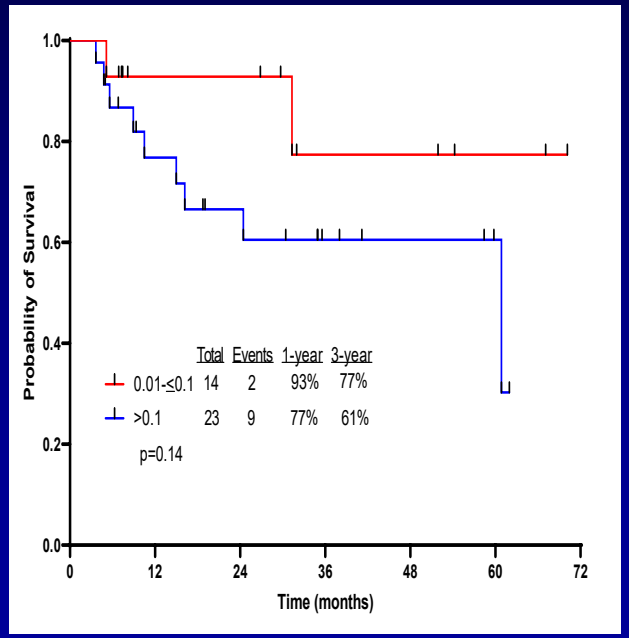
SCT in 7/22 pts (32%)

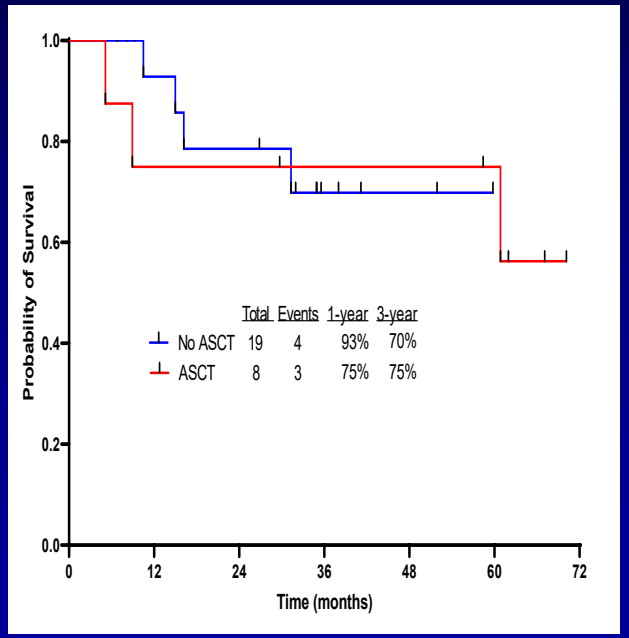
Macaron W, et al. *Blood*. 2024;144:727.

Blinatumomab for MRD-Positive ALL in CR1/CR2+

- 37 pts Rx. Post-blina MRD negative 27/37 = 73%; 83% in Ph-negative ALL
  - 70% after C1
- Median no. cycles 3 (1–9); median F/U 31 mo (5–70+)
- 14 pts 0.01 to <0.1%: 3-yr OS 77%; 23 pts ≥0.1%: 3-yr OS 61%
- 3-yr OS 67%; 3-yr OS if MRD negative 72%



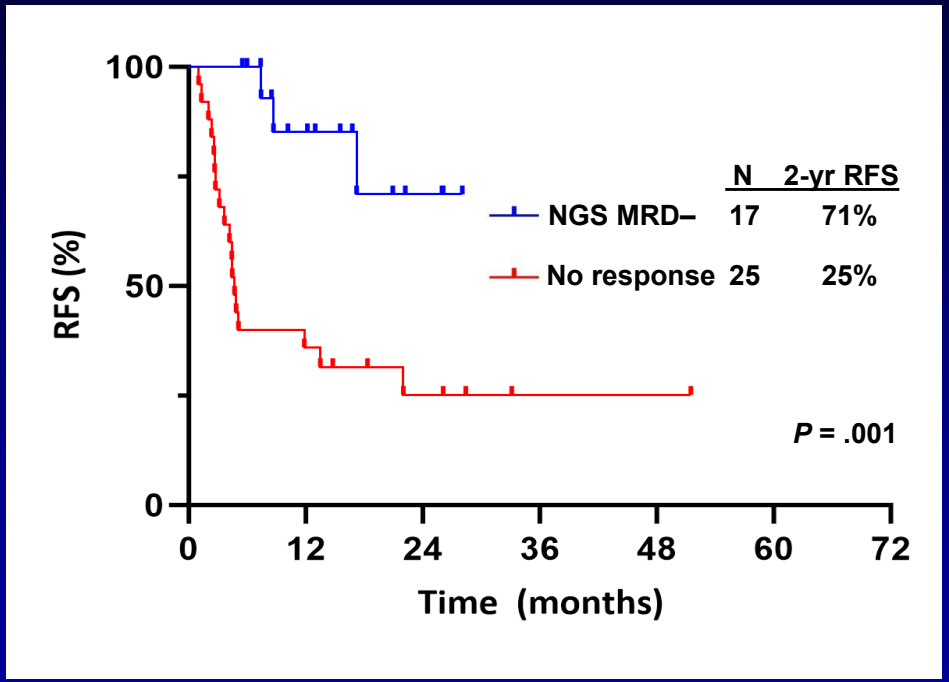


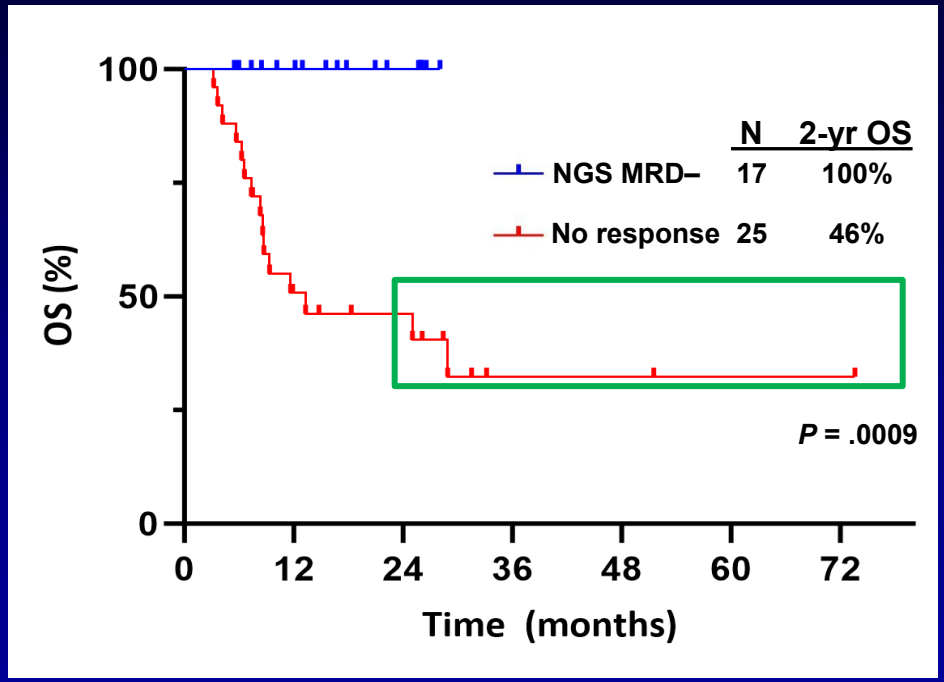


Jabbour E, et al. *Am J Hematol*. 2022;97:1135-1141.

Impact of NGS MRD Response to Blinatumomab on Survival

- 42 pts with B-cell ALL receiving blinatumomab monotherapy (or with TKI, if Ph+)
- 17/42 (41%) demonstrated NGS MRD negativity

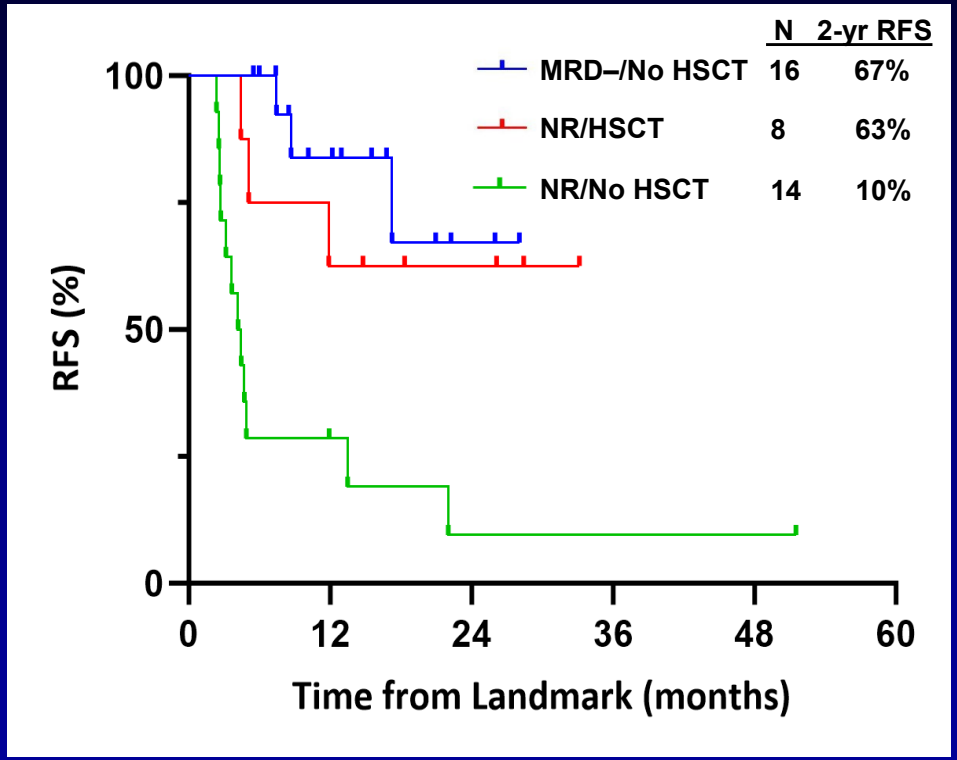


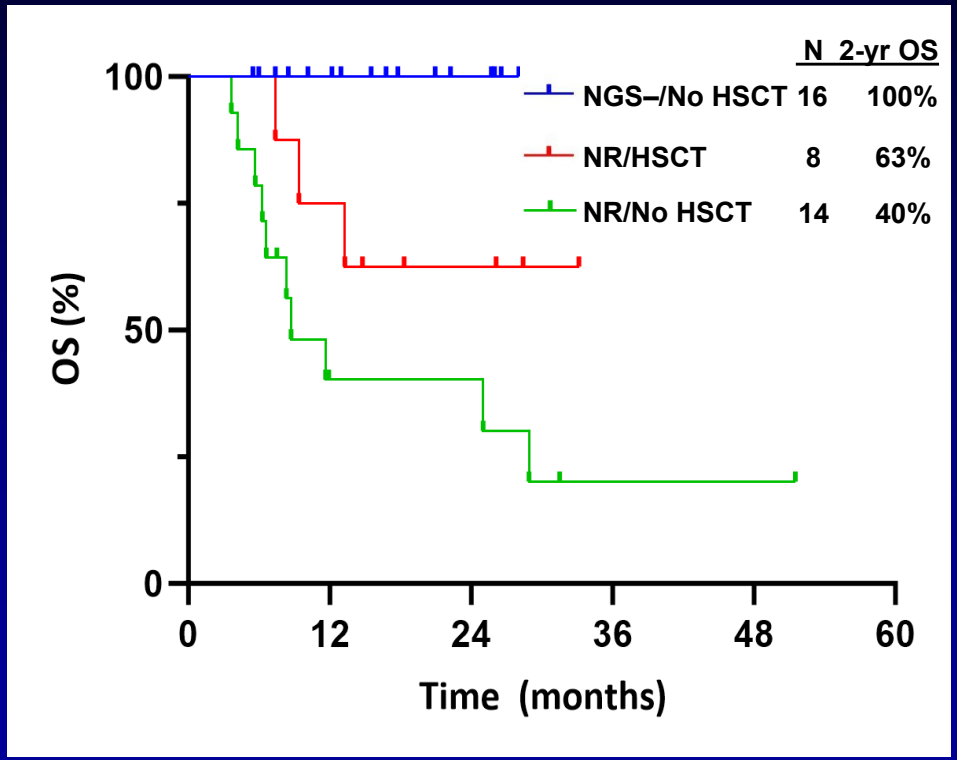


6 patients in NGS MRD nonresponder group with OS of 2+ years → 3 HSCT, 3 CAR T cell

Nguyen D, et al. ASH 2024. Abstract 1465.

Allogeneic SCT May Partially Overcome Poor Prognosis of Blinatumomab Nonresponders





Nguyen D, et al. ASH 2024. Abstract 1465.

Mini-HCVD–InO–Blina in R/R ALL

- 133 pts (median age 37 yr; 17–87) Rx with mini-HCVD–InO (n = 67); same + Blina (n = 44); and DD mini-HCVD–InO–Blina (n = 22). AlloSCT 43%

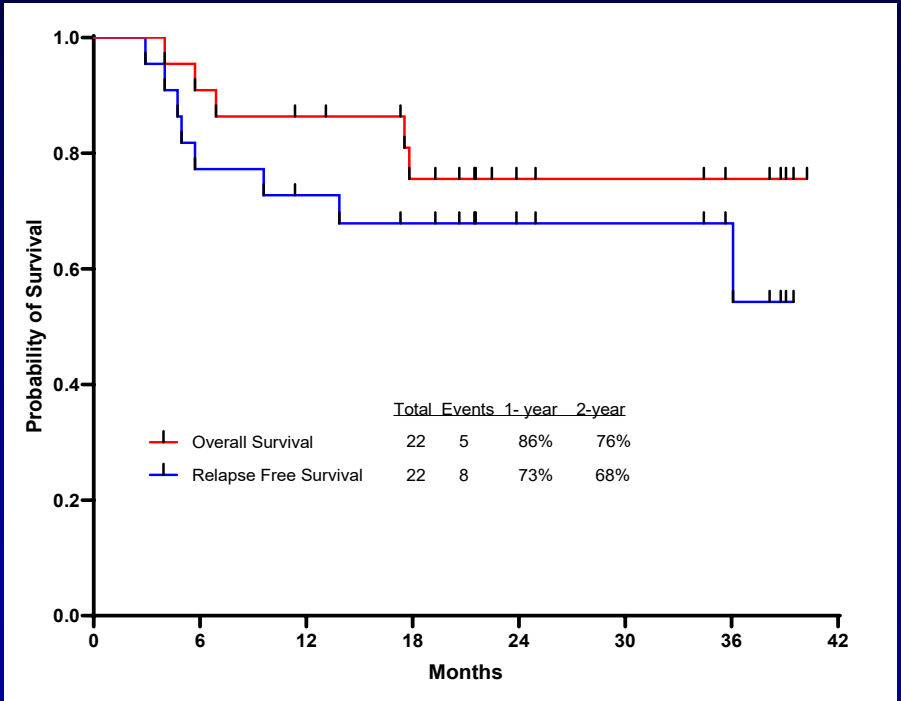
Parameter, %	Total (n = 133)	CT + InO (n = 67)	CT + InO + Blina (n = 44)	DD (n = 22)
ORR	86	76	93	100
CR	65	60	66	81
MRD neg	85	82	85	95
3-yr OS	-	34	50	76
3-yr RFS	-	35	44	68
1-yr OS (S1)	-	51 (63)	66 (66%)	90 (94%)

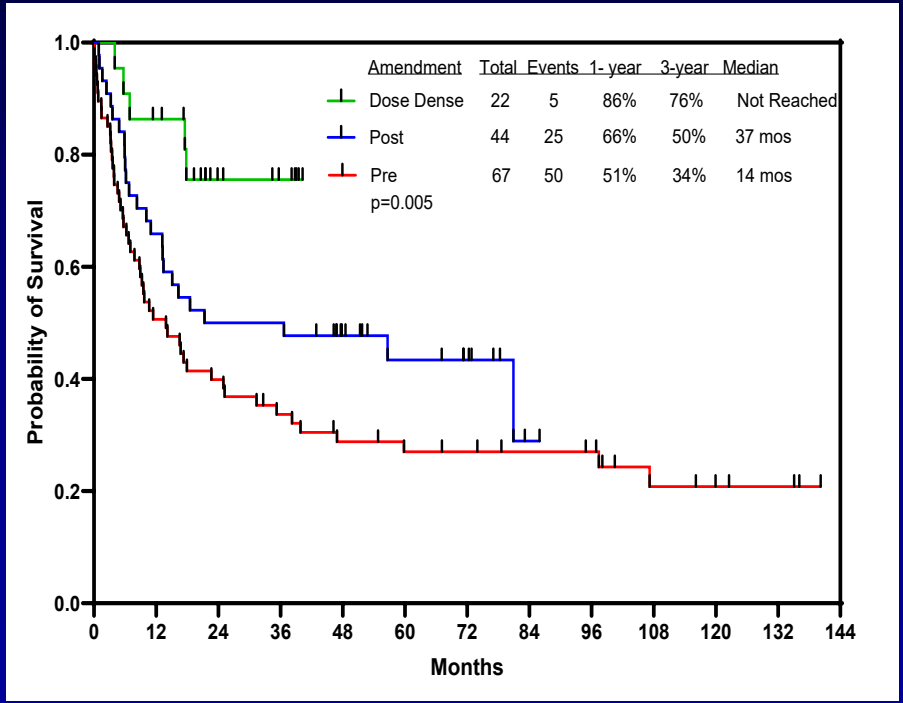
- 3-yr OS 54% in S1, 20% in S2
- 3-yr OS 60% with SCT vs 56% without
- SOS 10 pts: 9 (13%) initial vs (2%) later

Habib D, et al. *Blood*. 2024;144:811.

“Dose-Dense” Mini-HCVD + InO + Blina in R/R B-ALL

- 22 pts median age 41 yr (19-62) Rx; S1 86%
- ORR 100%, CR 81%; MFC MRD negative 95% (74% after C1); NGS MRD negative 94% (43% after C1)
- Median F/U 29 mo: 2-yr OS 76%; 2-yr RFS 68%

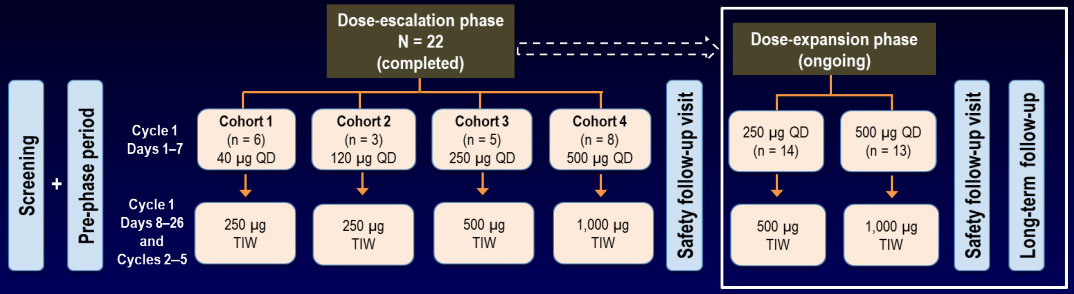




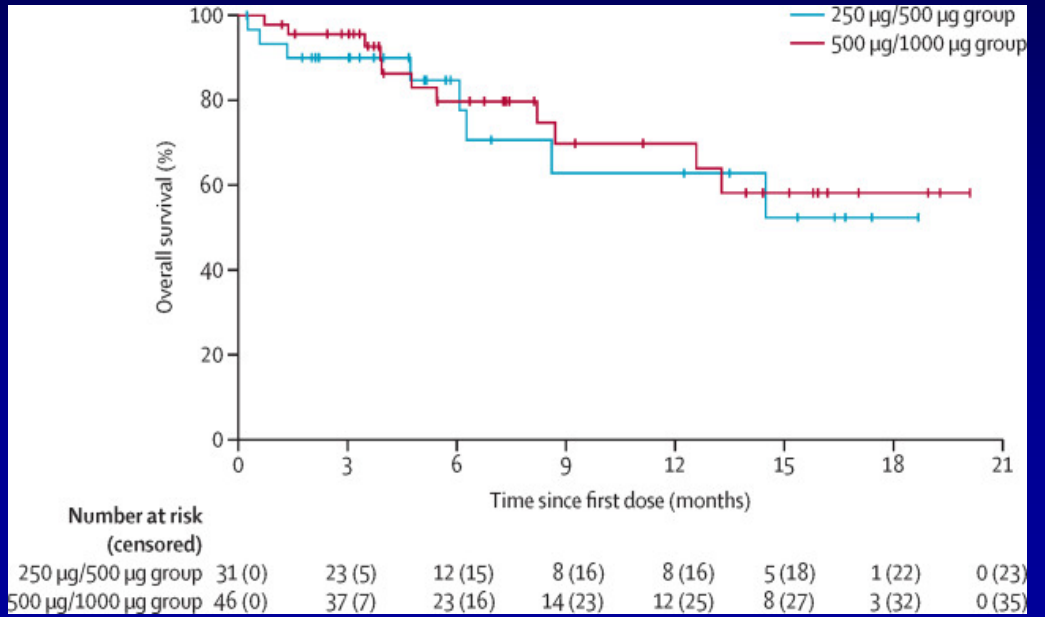
Jabbour E, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24:S153; Jabbour E, et al. SOHO 2024. Abstract ALL-808.

Subcutaneous Blinatumomab in R/R ALL

- 88 pts Rx: 36 at 250/500; 52 at 500/1000
- Rx 250 mcg daily × 7 then 500 mcg TIW; or 500/1000
- Median age 49 yrs (19–78). Median prior Rxs 2 (1–7). Baseline BM blasts 60%
- Prior CAR T 16%, Blina 19%, InO 33%, HSCT 28%



Parameter	250/500	500/1000
%CR-CRh	75	79
% CR-CRh-CRi	89	92
% MRD-neg	89	93
No relapses	0	3
% 12-mos OS	63	70
% G3 CRS	17	23
% G3 ICAN	28	27



Jabbour E, et al. *Lancet Haematol.* 2025;12:e529-e541.

AZD0486 (CD3-CD19 BiTE) in R/R ALL (SYRUS)

- 24 pts Rx in dose escalation. Target doses 2.4 and 7.2 mg

Parameter	DL1	DL2	Total
No Rx	13	9	22
CR-CRi (%)	6/13 (46)	6/9 (67)	12/22 (55)
MRD neg	5/6	6/6	11/12

- BM blasts 50+% – CR 8/10

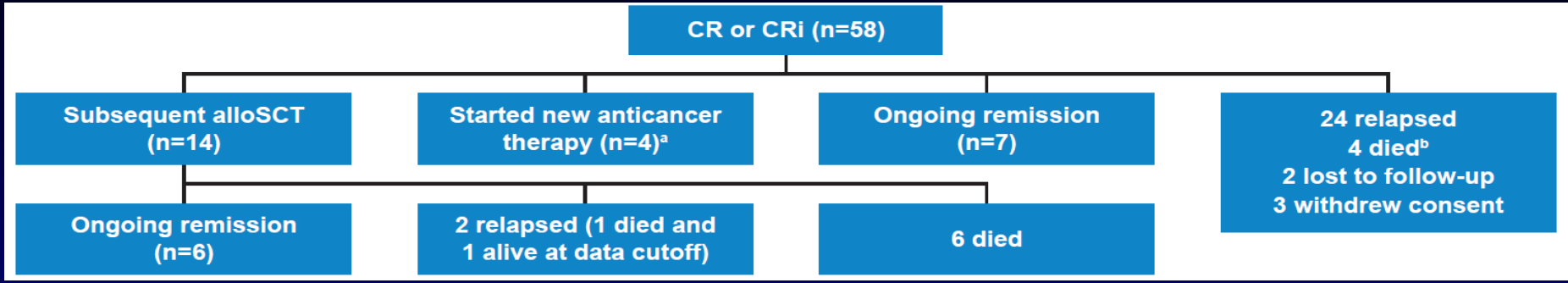
Aldoss I, et al. EHA 2025. Abstract S117

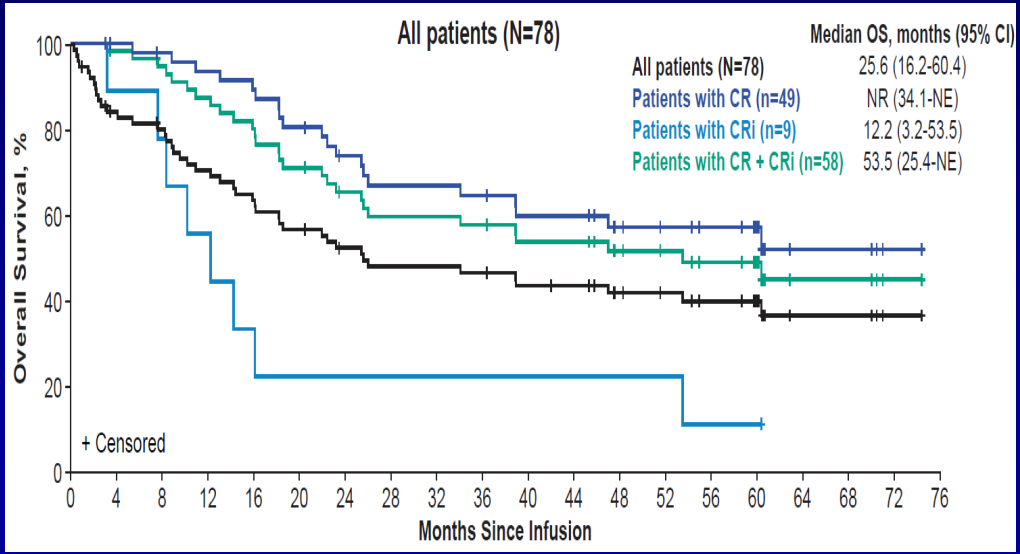
Dose-Dependent Enhanced Efficacy in ITT and CD19-Exposed Populations

Response, n/N (%)	DL1 (SUD: 0.09/0.27/1.0; TD: 2.4 mg) (n = 13)	DL2 (SUD: 0.27/1.0/2.4; TD: 7.2 mg) (n = 12)	DL3 (SUD: 0.27/1.0/2.4; TD: 15 mg) (n = 6)
ORR EoC1 (CR/CRi) (ITT)	**6/13 (46)**	**7/12 (58)**	**5/6 (83)**
CR/CRi MRDneg (local flow [10^{-4}])	5/6 (83)	7/7 (100)	5/5 (100)
Disease relapse	2/6 (33)	0/7	0/5
ORR (CR/CRi) by prior therapy subgroup[a,b]			
Blinatumomab exposed	4/9 (44)	1/4 (25)	3/3 (100)
CAR T exposed	1/3 (33)	2/3 (67)	4/5 (80)
Double exposed	1/3 (33)	1/2 (50)	3/3 (100)
Triple exposed (+ inotuzumab)	0/2 (0)	1/2 (50)	3/3 (100)
ORR (CR/CRi) [in patients with EMD][a]	**2/3 (67)**	**2/2 (100)**	**0/0**

[a]Median follow-up: 97 days (range, 35-401 days); [b]Prior therapy subgroups are not mutually exclusive.
CAR T, chimeric antigen receptor T-cell therapy; CR, complete response; CRi, complete response with incomplete count recovery; DL, dosing level; EMD, extramedullary disease; ITT, intent-to-treat; MRDneg, minimal residual disease negative; ORR, overall response rate; SUD, step-up dosing; TD, target dose.

ZUMA-3: 5-Year Follow-Up

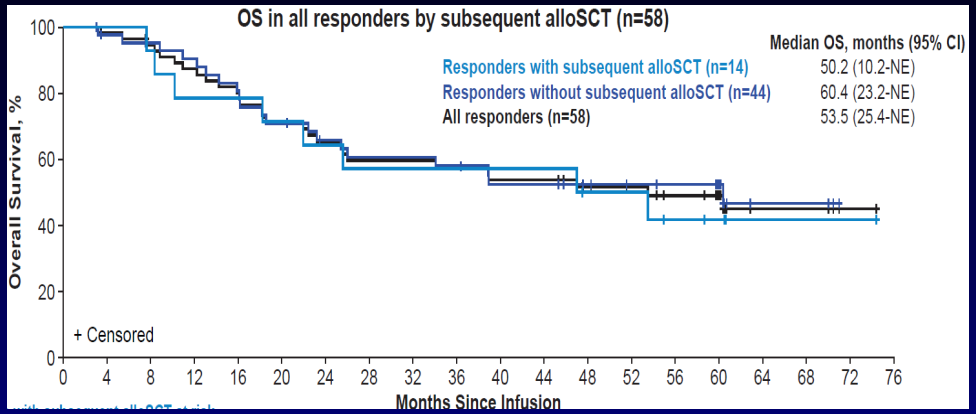


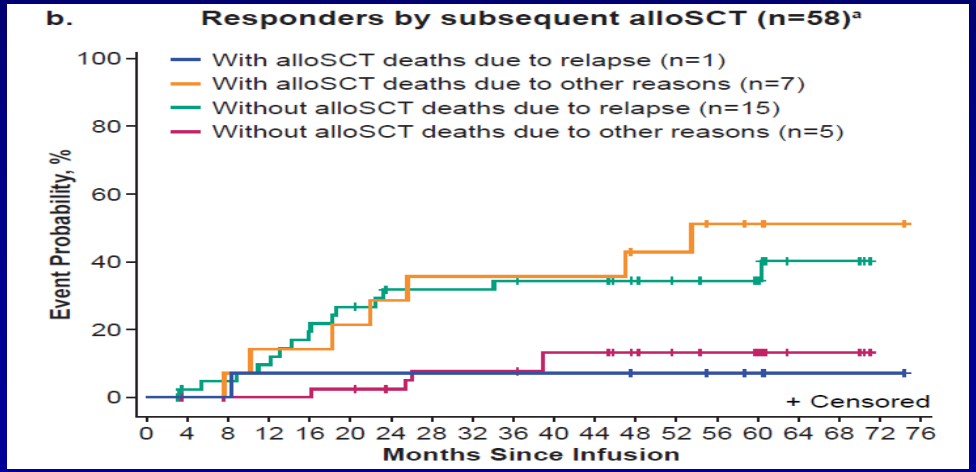


- 7 out of 58 (12%) patients are in ongoing remission at 5 yr of follow-up
- No additional relapses noted between yr 4 and 5 of extended follow-up
- OS remains unchanged at 40%, at 5 yr

Oluwole O, et al. EHA 2025. Abstract PF374.

ZUMA-3: Role of AlloSCT Post-CAR T



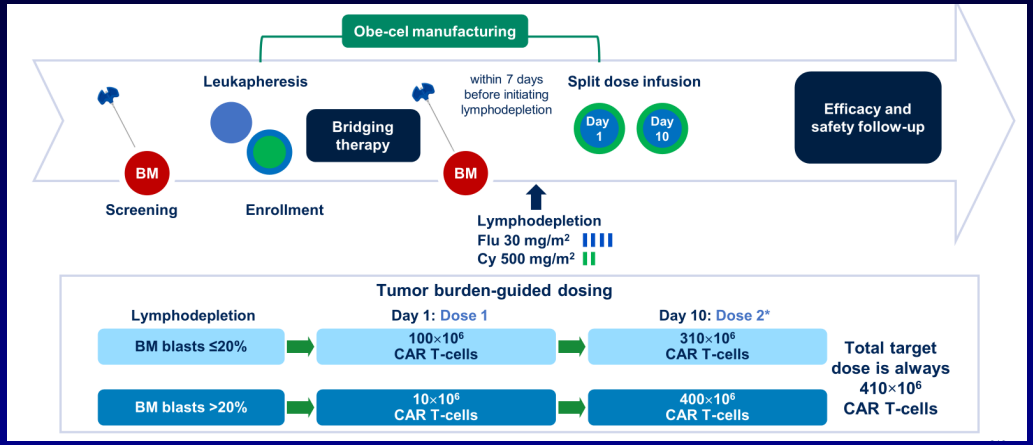


- Nonrelapse mortality high in patients undergoing subsequent alloSCT, with a 5-yr rate of 26%
- Death due to relapse post-alloSCT low compared with patients without alloSCT
- Without alloSCT, the main reason for death was relapse

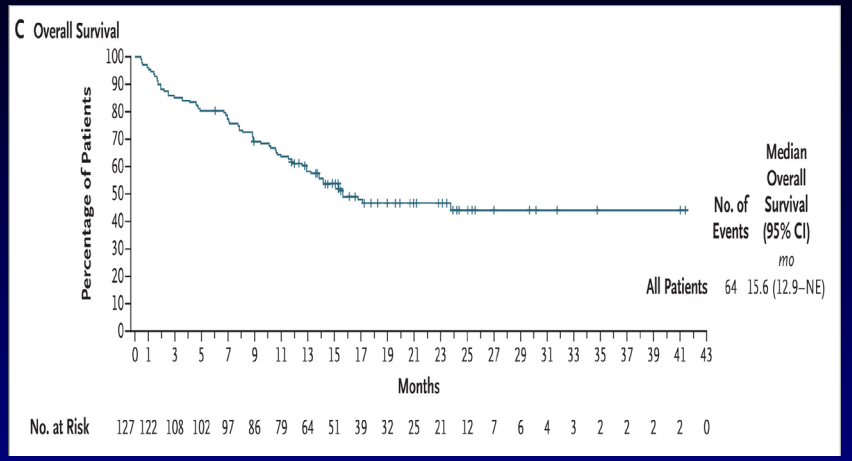
Oluwole O, et al. EHA 2025. Abstract PF374.

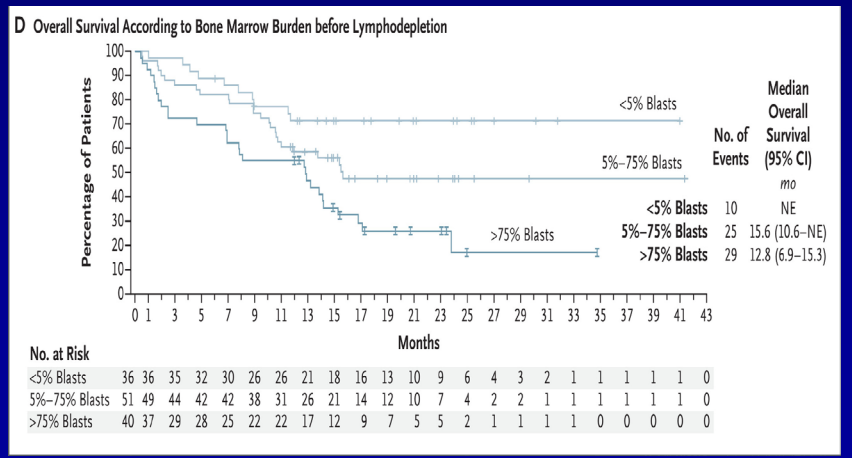
Obecabtagene Autoleucel (obe-cel) in Adult R/R ALL: FELIX

- AUTO 1 fast off-rate CD19 binder CAR T
- 153 enrolled, 127 (83%) infused; median age 47 yr



- G3 CRS 2.5%; G3 ICANS 7.5%
- Prior blina 42%, InO 31%, alloSCT 44%
- cCR-CRi 99/127 = 78% (99/153 = 65%); 19/77 alloSCT
- Loss of CAR T = HR 2.9
- 12-mo EFS 49%, 12-mo OS 61%





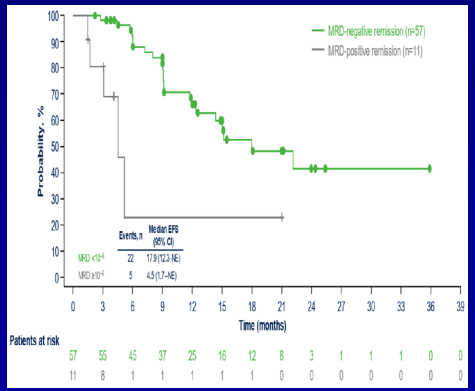
Jabbour E, et al. *J Clin Oncol.* 2024;24:S6504; Roddie C, et al. *N Engl J Med.* 2024;391:2219-2230.

Obe-cel in Adult R/R ALL: FELIX – Impact of MRD

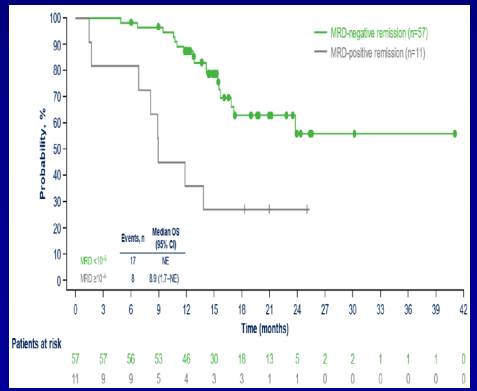
- 96/127 (76%) NGS calibration by NGS; 73/96 (76%) CR/CRi; 68/73 (93%) MRD assessment
- MRD neg 68/73 (84%); median to MRD neg 1 mo
- F/U 21.5 mo; 70% MRD-neg CR alive

Parameter, %	MRD Pos	MRD Neg	MRD Neg if <5% BL@ LD	MRD Neg if ≥5% to ≤75% BL@ LD	MRD Neg if >75% BL@ LD
	16	84	90	87	72
Median EFS, mo	4.5	18	NR	18	12
Median OS, mo	9	NR	NR	NR	17

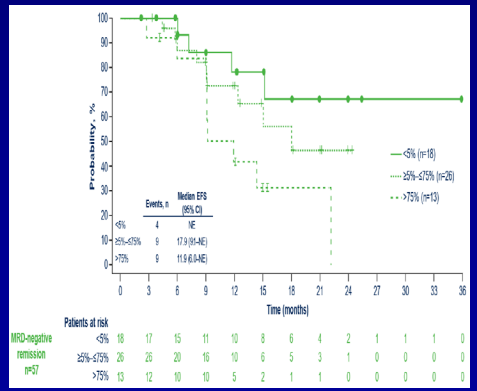
EFS by MRD status



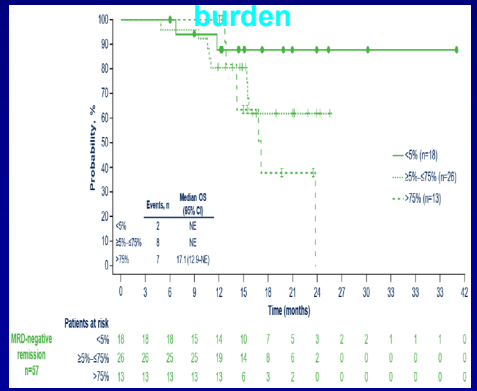
OS by MRD status



EFS in MRD neg by tumor burden



OS in MRD neg by tumor burden

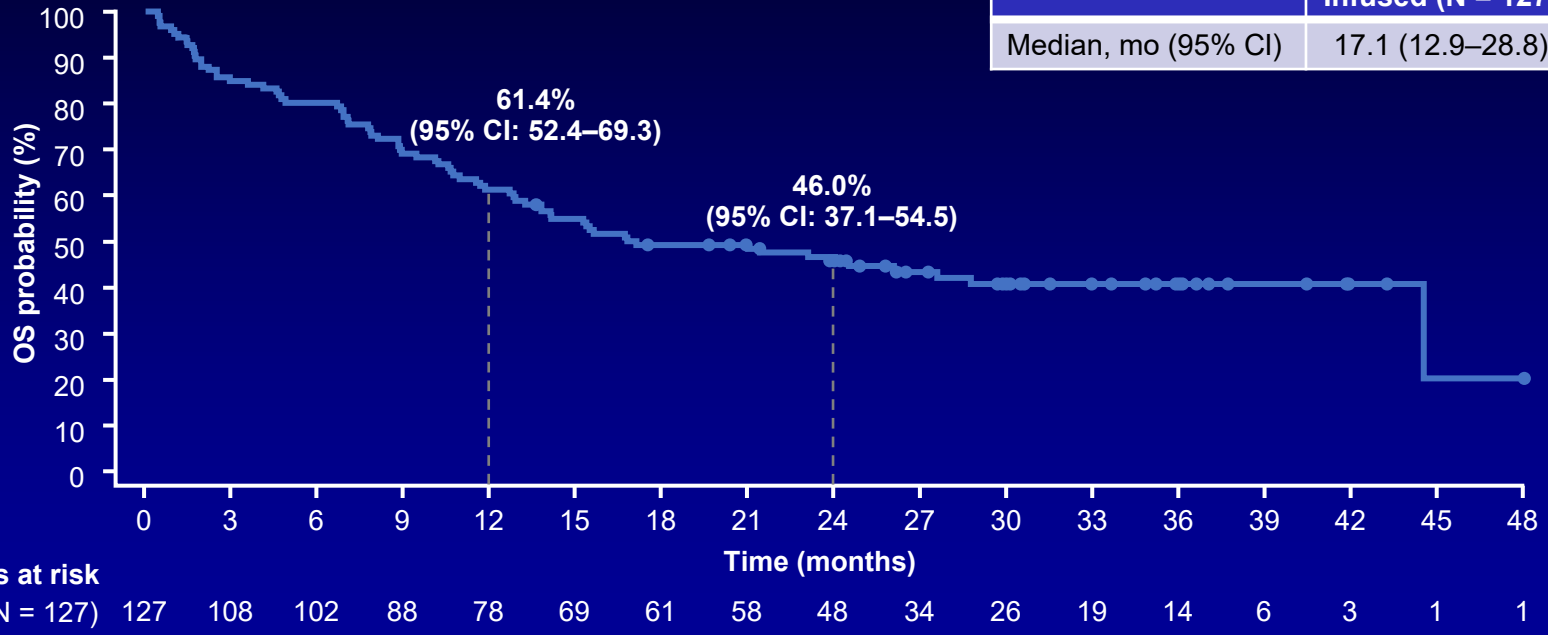


Jabbour E, et al. *Blood*. 2024;144:963.

Overall Survival, Without Censoring for Consolidative SCT

At 24 months, overall survival probability was 46.0%

	Infused (N = 127)
Median, mo (95% CI)	17.1 (12.9–28.8)

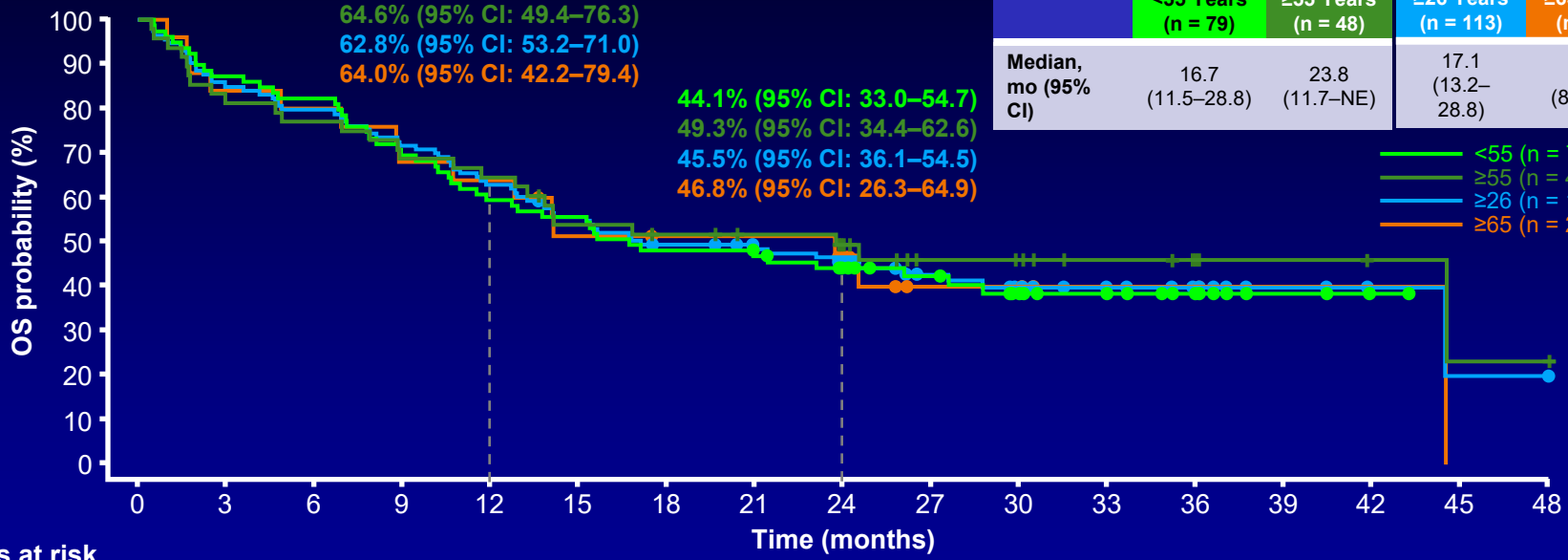


Current data cut: 18 Jan 2025; median follow-up: 32.8 months (range: 19.9–52.8).
OS without censoring for consolidative SCT.
CR, complete remission; CRi, complete remission with incomplete hematologic recovery; OS, overall survival; SCT, stem cell transplant.

Overall Survival, Without Censoring for Consolidative SCT

OS was comparable in all investigated age groups

OS	Patients Aged <55 Years (n = 79)	Patients Aged ≥55 Years (n = 48)	Patients Aged ≥26 Years (n = 113)	Patients Aged ≥65 Years (n = 25)
Median, mo (95% CI)	16.7 (11.5–28.8)	23.8 (11.7–NE)	17.1 (13.2–28.8)	23.8 (8.9–NE)



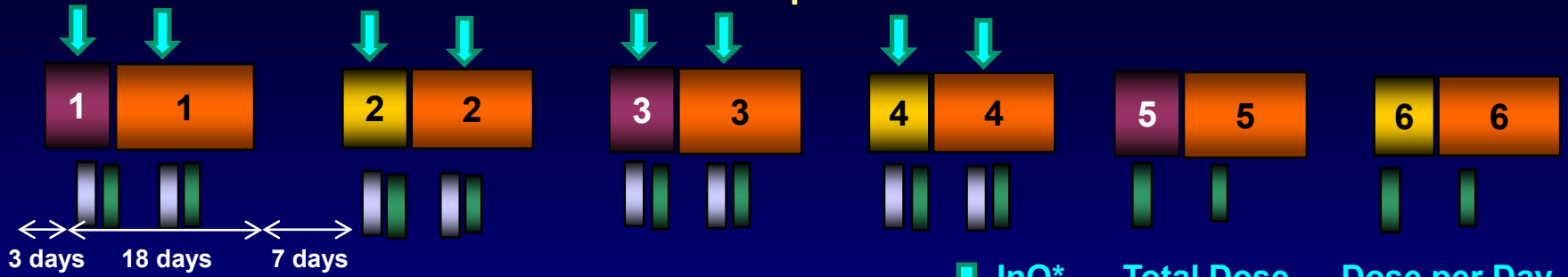
Patients at risk

<55 (n = 79)	79	69	65	55	47	44	38	37	30	23	16	12	9	3	1	0	0
≥55 (n = 48)	48	39	37	33	31	25	23	21	18	11	10	7	5	3	2	1	1
≥26 (n = 113)	113	96	90	81	71	62	54	51	43	29	22	16	12	4	2	1	1
≥65 (n = 25)	25	21	20	17	16	12	11	11	9	4	4	2	2	1	1	0	0

Current data cut: 18 Jan 2025; median follow-up: 32.8 months (range: 19.9–52.8).
OS without censoring for consolidative SCT.
NE, not estimable; OS, overall survival; SCT, stem cell transplant.

Dose-Dense Mini-HCVD + InO + Blina + CAR T Cells in ALL: The CURE

Induction phase: C1–C6



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.

Consolidation phase

CAR T consolidation

Mini–Hyper-CVD

Mini-MTX–Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

ALL 2025 and Beyond: Conclusions

- Significant improvements across all ALL categories
- Ph-positive ALL
  - Ponatinib > imatinib – evaluating newer TKI (olverembatinib, asciminib)
  - Blina-ponatinib: 4-year OS 89%, rarely alloSCT
  - CNS relapses: 15 IT vs systemic chemotherapy in WBC >70K
- Incorporation of Blina-InO in FL therapy highly effective and improves survival
  - HCVAD-blina-InO: 5-year OS 90%
  - Mini-HCVD–InO in older ALL: 5-year OS 50%
  - Exploring chemotherapy-free approach to reduce death in CR in older ALL
- Early eradication of MRD predicts best overall survival
  - NGS > FCM in Ph-negative ALL, NGS > PCR in Ph positive
- Antibody-based Rxs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather, complementary
  - CAR T as consolidation post–blina/InO (BRICK)-based regimen
- Future of ALL Rx
  - Less chemotherapy and shorter durations
  - Combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22, CD79
  - SQ blinatumomab
  - CAR Ts CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT

Thank You

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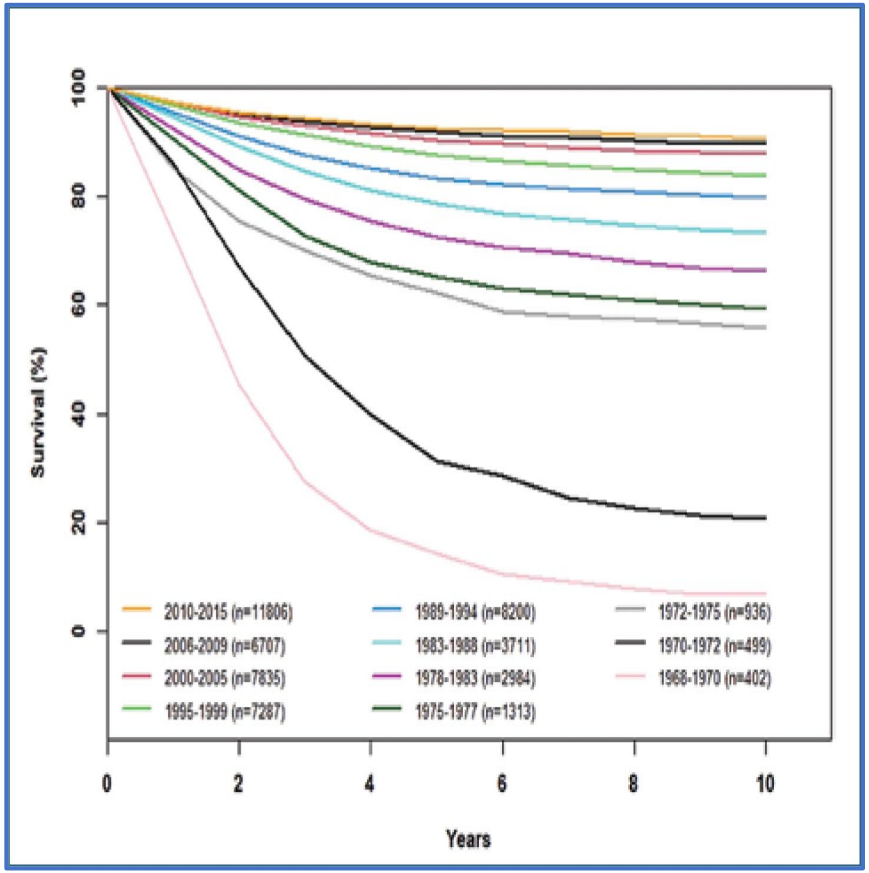
Global Leukemia Academy

Review of prognostic and predictive markers in ALL

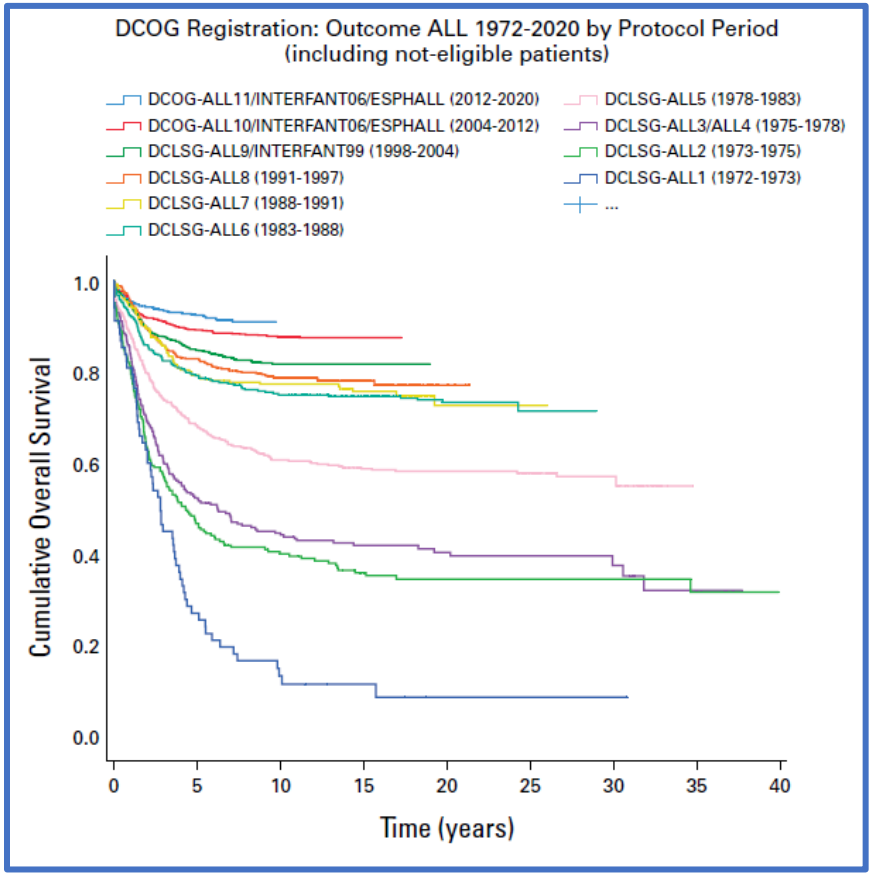
Josep-Maria Ribera

APTITUDE HEALTH

COG and DCOG trials for ALL in children



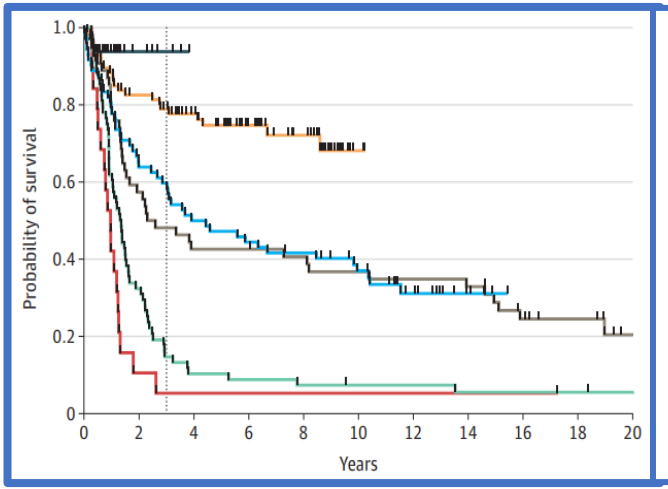
Raetz EA, et al. *Pediatr Blood Cancer*. 2023;70:e30585.



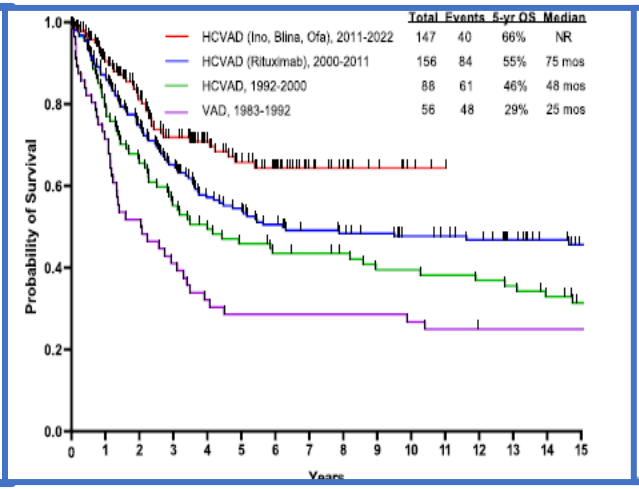
Pieters R, et al. *J Clin Oncol*. 2023;41:5579-5591.

Improvements in adult ALL: MDACC

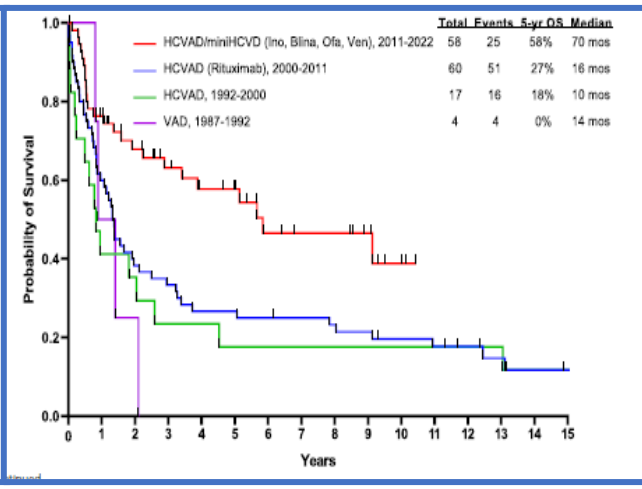
Ph+ ALL



Ph– ALL <60 yr



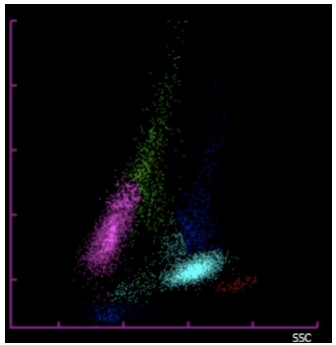
Ph– ALL ≥60 yr

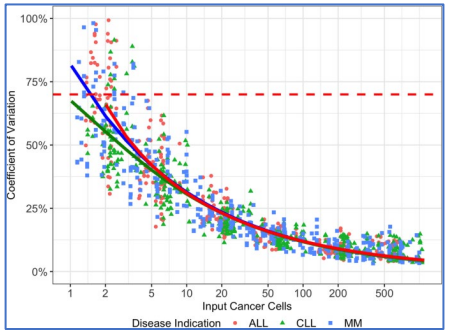


Jabbour E, et al. *J Hematol Oncol*. 2023;16:22.

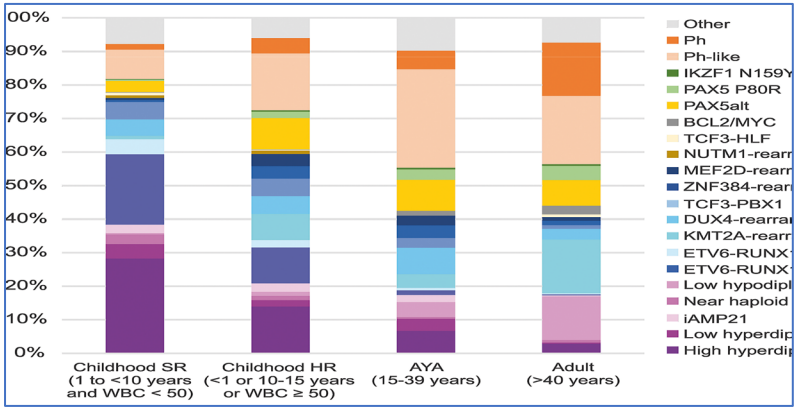
Factors contributing to improved outcomes in ALL

MRD assessment

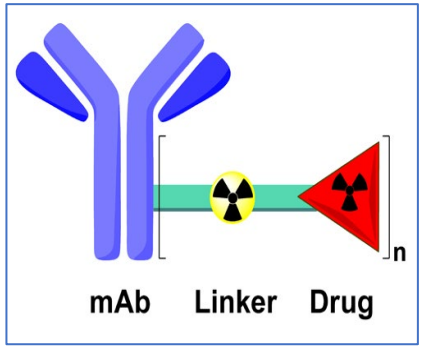


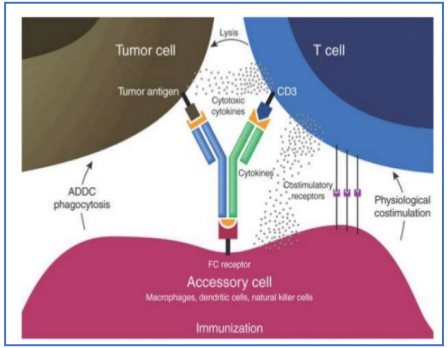


Disease genetics

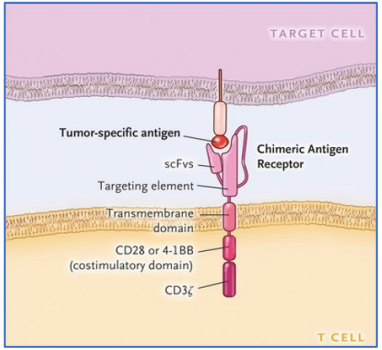


Immunotherapy (frontline and relapse)

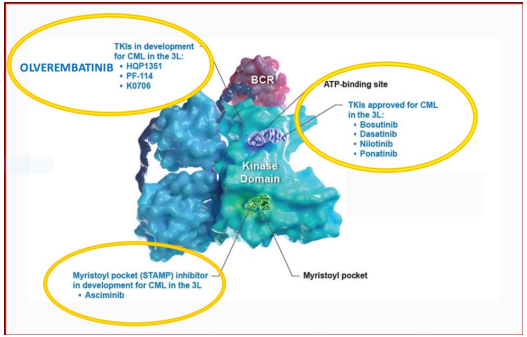




CAR T-cell therapy



Targeted therapy



Prognostic and predictive factors in ALL

	Risk factor	Comment
Patient related	• Age (continuous, <60 yr vs ≥60 yr) • General status, comorbidities	Young adults, older adults, elderly Fit vs unfit
Disease related	• WBC count (>30K [B], >100K [T])	Maintained with modern therapies for BCP-ALL, not for T-ALL
	• Immunophenotype (pro-B, pro-T, ETP)	
	• Cytogenetics (low hypodiploid, t[4;11], CK, iAMP21, t[17;19])	
	Molecular genetics • KMT2Ar, Ph-like, IKZF1plus, IgHr, HLFr, ZNF384r, MEF2Dr, MYCr • NOTCH1 unmut and/or RAS/PTEN mut, other	BCP-ALL T-ALL
Response dynamics	• No CR demonstration after induction • End-induction/consolidation MRD+ (≥0.01%)	Different time points in Ph+ and Ph– ALL

Modified from Gökbuget N, et al. *Blood*. 2024;143:1891-1902.

Most relevant prognostic factors (before frontline immunotherapy)

- Age
- WBC count
- Genetics/genomics
- MRD

Should be reassessed in the era of frontline immunotherapy

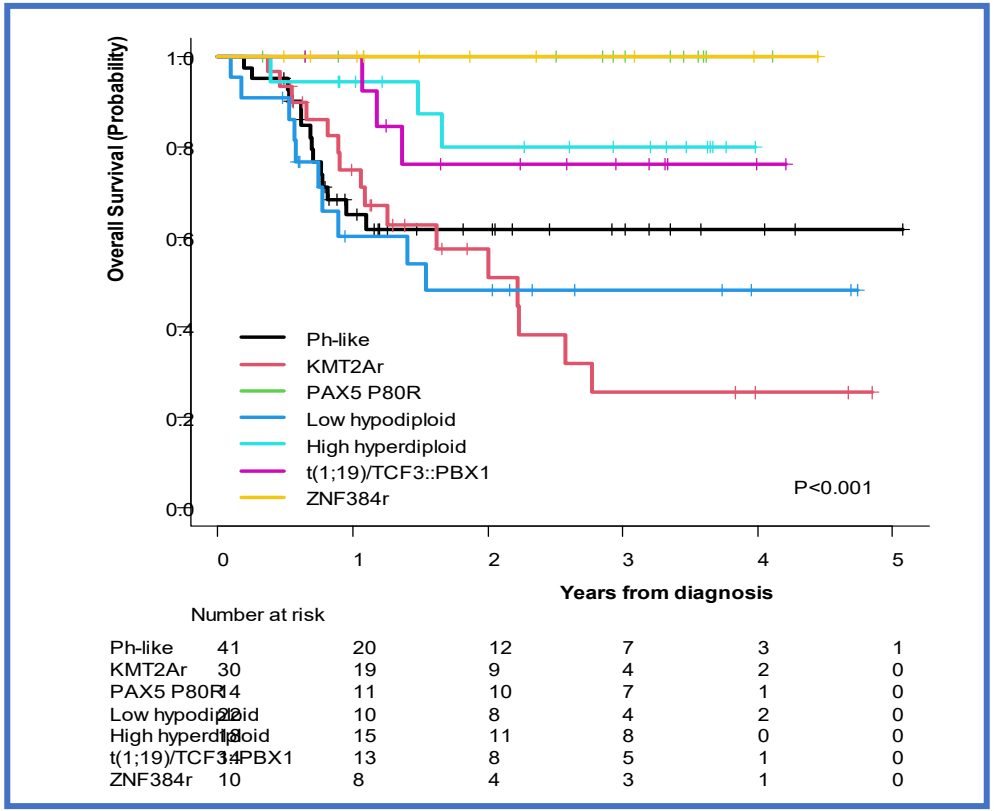
Prognostic factors in the PETHEMA ALL-HR11 trial

Variable	N	OS HR (95% CI)	*P*	CIR HR (95% CI)	*P*
WBC count (continuous variable)	289	1.003 (1.001–1.005)	.002	1.003 (1.001–1.004)	<.001
HR cytogenetics*	30/209	1.995 (1.109–3.587)	.021		—
MRD ≥0.01% after induction 1	103/282	1.641 (1.002–2.706)	.049		

***HR cytogenetics**: t(v;11q23), hypodiploidy, and complex karyotype.

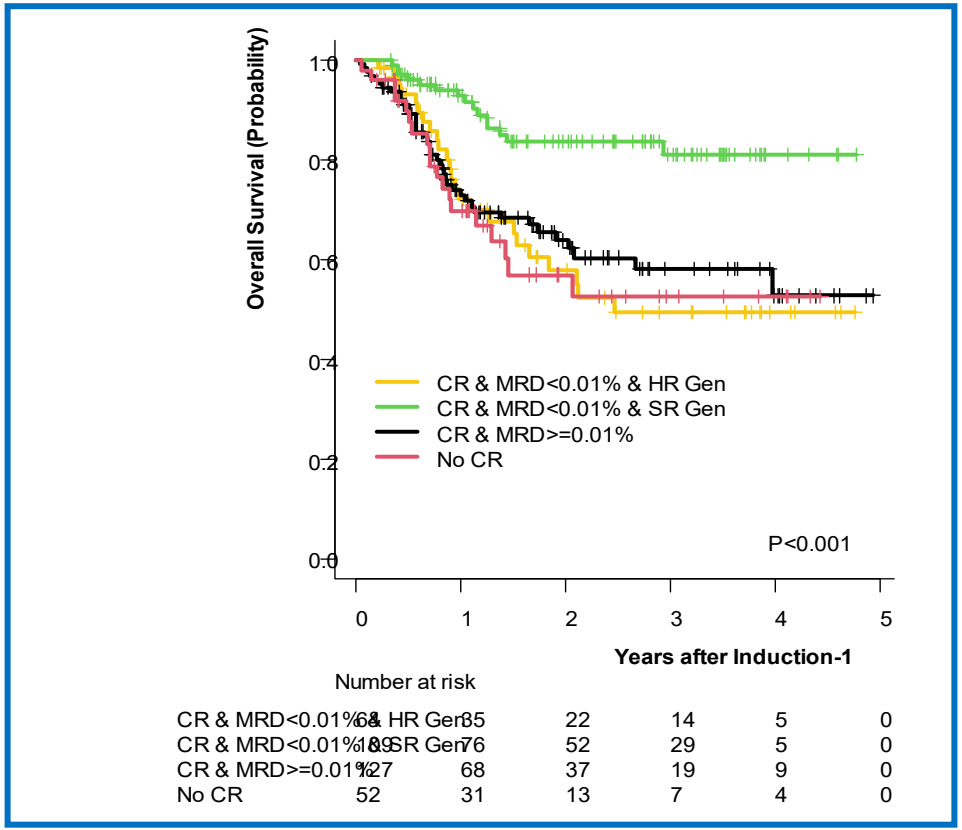
Ribera JM, et al. *Blood*. 2021;137:1879-1894.

Different outcome according to genetic BCP-ALL subtypes (PETHEMA ALL19 trial)



Ribera JM, et al. Manuscript in preparation.

Impact of combined MRD and genetics on outcome in Ph– ALL (PETHEMA ALL2019 trial)



Ribera JM, et al. Manuscript in preparation.

Actionability in genetic aberrations in ALL is still poor

Abnormality	Prognostic	Actionable
BCR-ABL	Poor → Favorable	Yes (TKI + blin)
Ph-like	Poor, esp CRLF2r	Not currently (allo in CR1) Ruxolitinib for JAK2? Dasatinib for ABL-class kinase mut?
*KMT2A*r/MLL	Poor	No (allo in CR1) Menin inhibitor?
TP53	Poor	No (allo in CR1)
Hypodiploidy (low)	Poor	No (allo in CR1)
Complex karyotype	Poor	No (allo in CR1)
IKZF1	Unclear	No

Under research

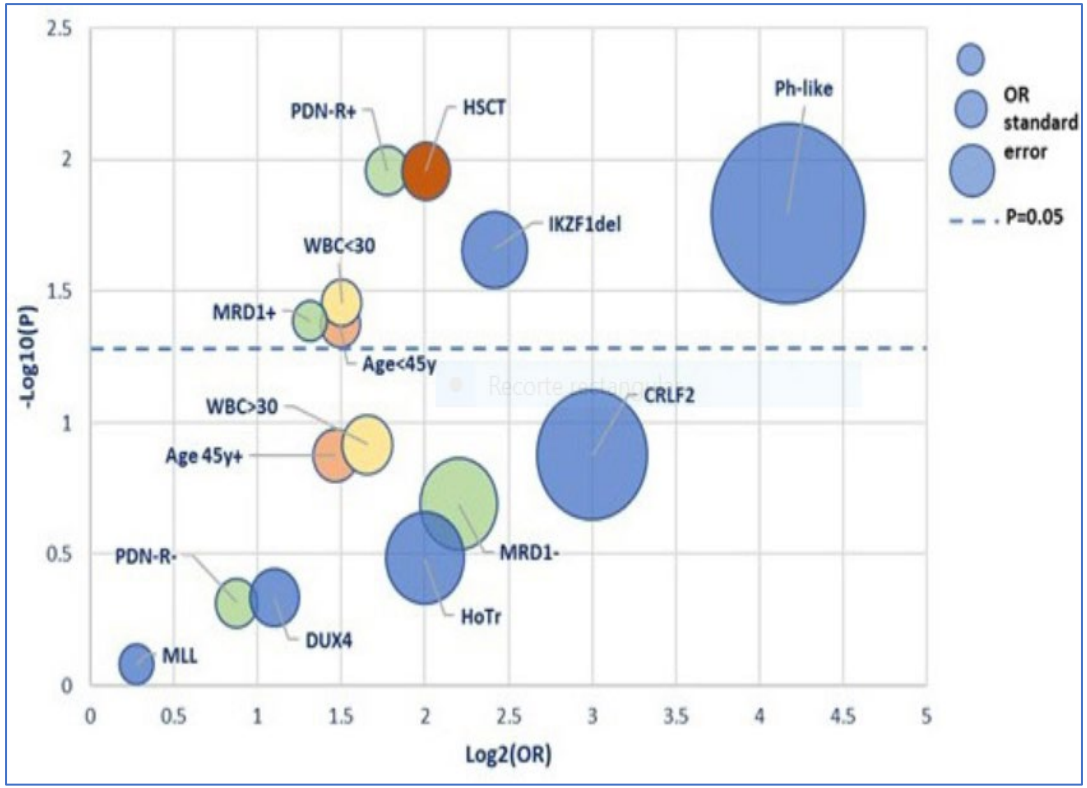
- ***KMT2A*r:** menin inhibitors
- ***ZNF384*r:** FLT3 inhibitors
- ***DUX4*r:** PI3K inhibitors
- **Hypodiploidy:** BCL2 inh
- **Ph-like:** TKI, JAK inhibitors
- **ETP-ALL:** BCL2 inhibitors

Effect of blinatumomab in 1L on prognostic and predictive factors

Ph– ALL

Ph+ ALL

GRAALL-2014/B QUEST substudy: Heterogeneous landscape of response to blin among genetic entities

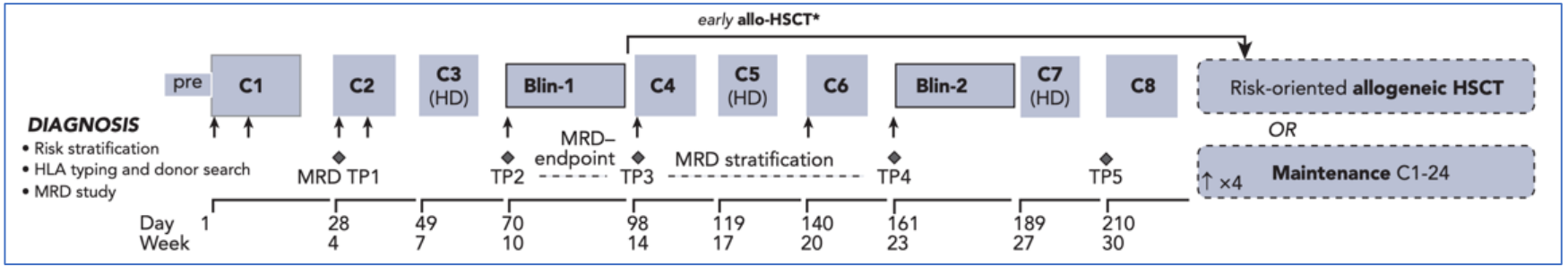


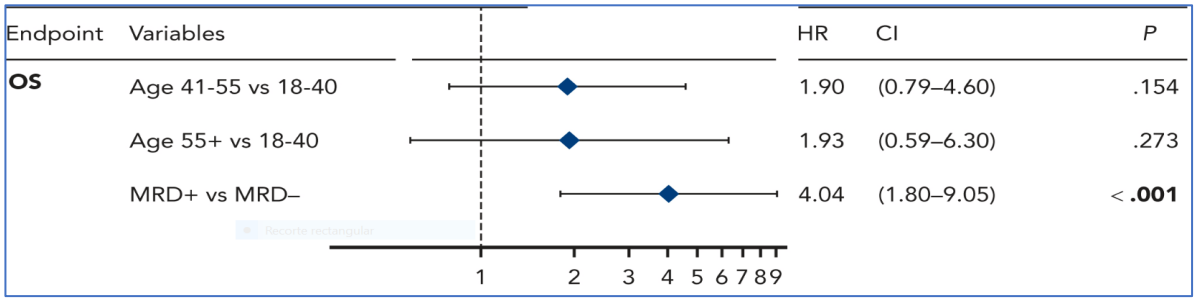
Higher chance to be MRD3-negative ($<10^{-4}$)
After blin (vs controls)

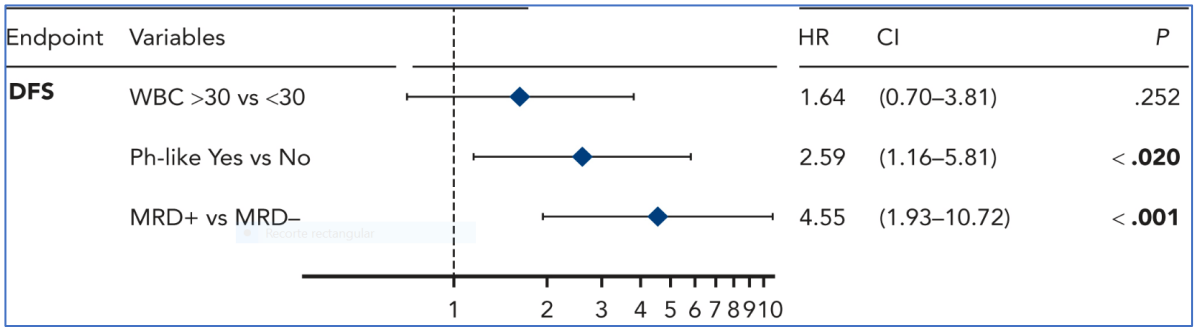
- Younger age (<45 yr)
- WBC <30 G/L
- Poor prednisone response
- *IKZF1* deletion
- Ph-like

Boissel N, et al. ASH 2023. Abstract 4349.

Phase II GIMEMA LAL2317 trial with 1L blinatumomab



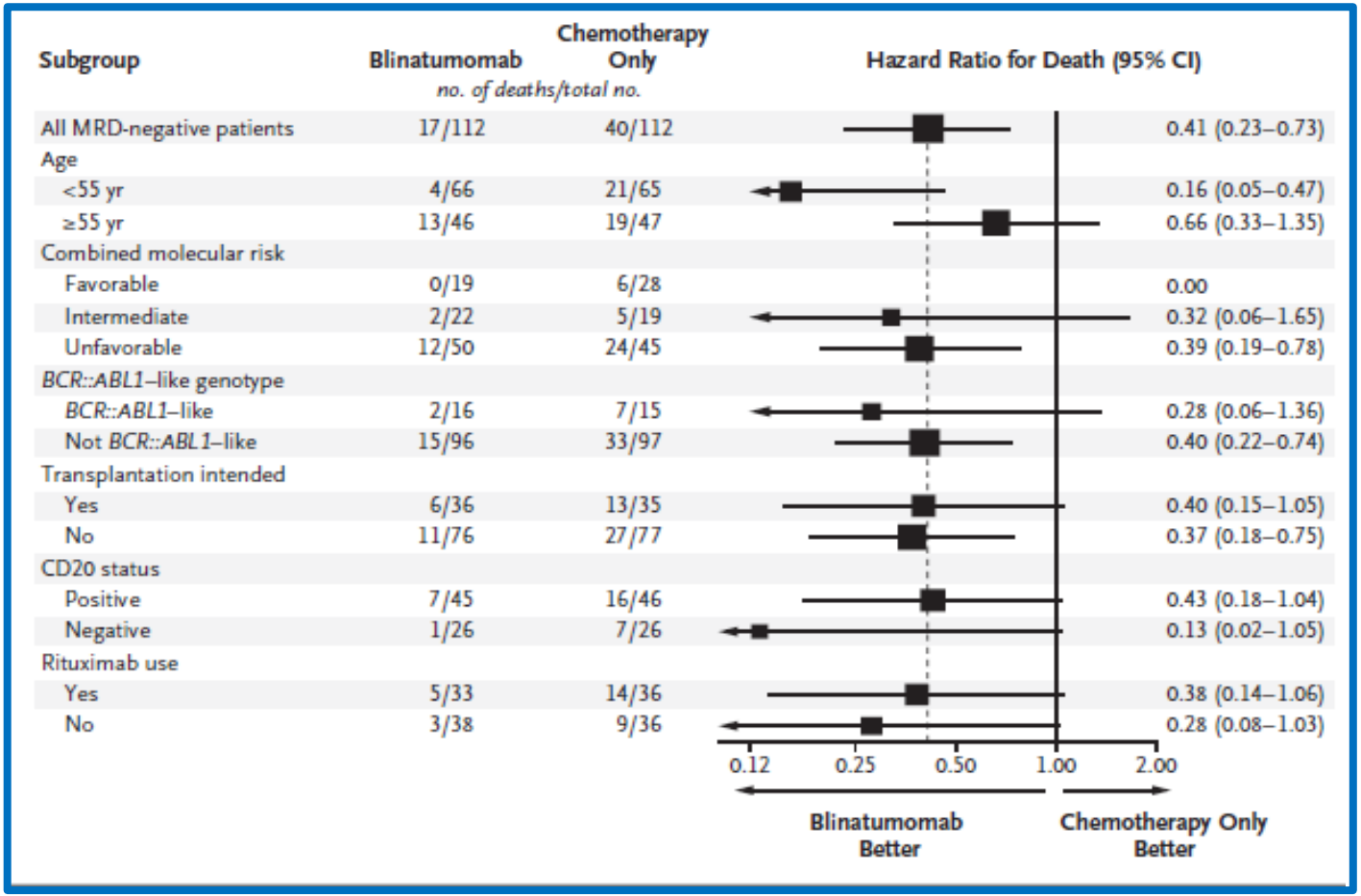




Age and WBC count lost their prognostic significance

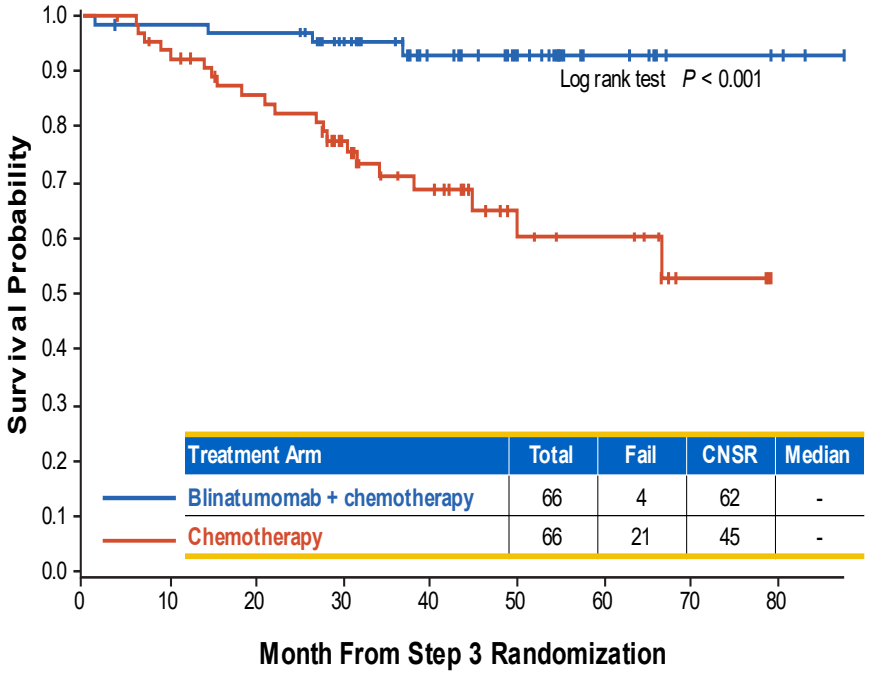
Bassan R, et al. *Blood*. 2025;145:2447-2459.

E1910: Subgroup analyses for OS



E1910: Outcomes by age

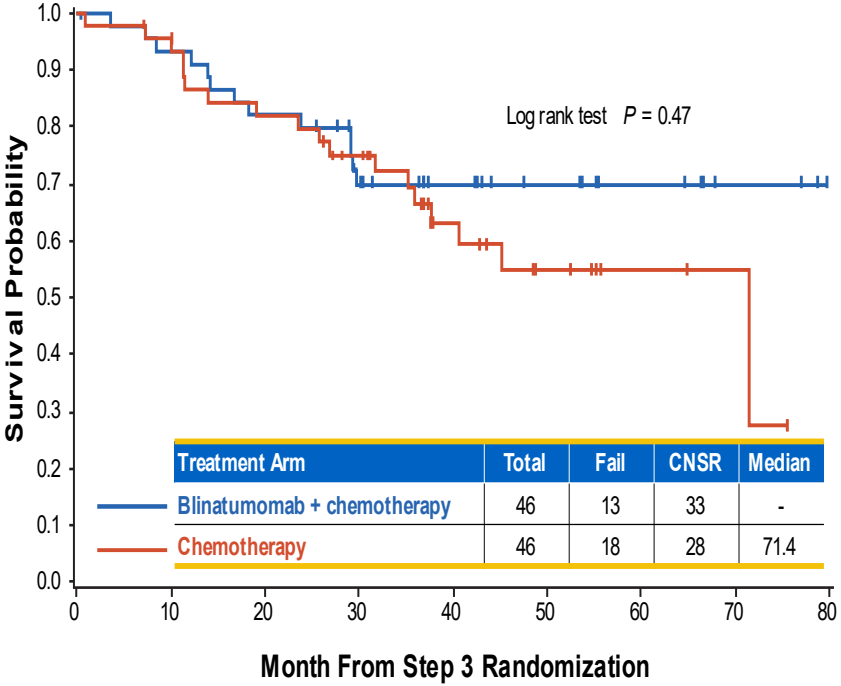
OS Comparison: MRD– Age < 55 Years



Treatment Arm	Total	Fail	CNSR	Median
Blinatumomab + chemotherapy	66	4	62	-
Chemotherapy	66	21	45	-

Median OS: NR in both arms; HR: 0.18; 95% CI: 0.06–0.52; $P < 0.001$

OS Comparison: MRD– Age ≥ 55 Years



Treatment Arm	Total	Fail	CNSR	Median
Blinatumomab + chemotherapy	46	13	33	-
Chemotherapy	46	18	28	71.4

Median OS: NR vs 71.4 months; HR: 0.77; 95% CI: 0.37–1.58; $P = 0.47$

E1910: MRD– molecular subgroup analysis

Molecular risk n (%)	Blina + Chemo, n=66	Chemotherapy, n=65
Favorable	14 (21)	22 (33)
Intermediate	17 (26)	12 (18)
Unfavorable	20 (30)	23 (35)
Not assigned	15 (23)	8 (14)

Favorable: *DUX4*r; high hyperdiploid; *TCF3::PBX1*; *PAX5* P80R

Intermediate: *PAX5*alt; *PAX5::ETV6*; *MEF2D*r; *ZNF384*r

Unfavorable: *KMT2A*r; low hypodiploid/near haploid; *BCR::ABL1*-like; *BCL2/MYC*r; *ETV6::RUNX1*-like and *IGH::CRLF2*

Favorable

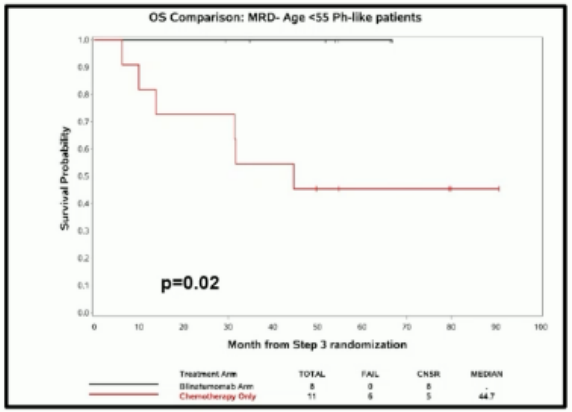
Intermediate

Unfavorable

Litzow M, et al. *N Engl J Med*. 2024;391:320-333.

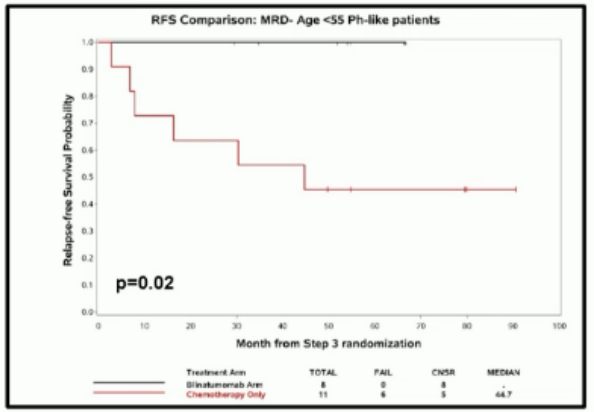
E1910: Outcomes ≤55yo subgroup analysis

MRD Negative *BCR::ABL1*-like Patients



(8)
(11)

	3 Year Overall Survival
Blinatumomab	100%
Chemotherapy	45%



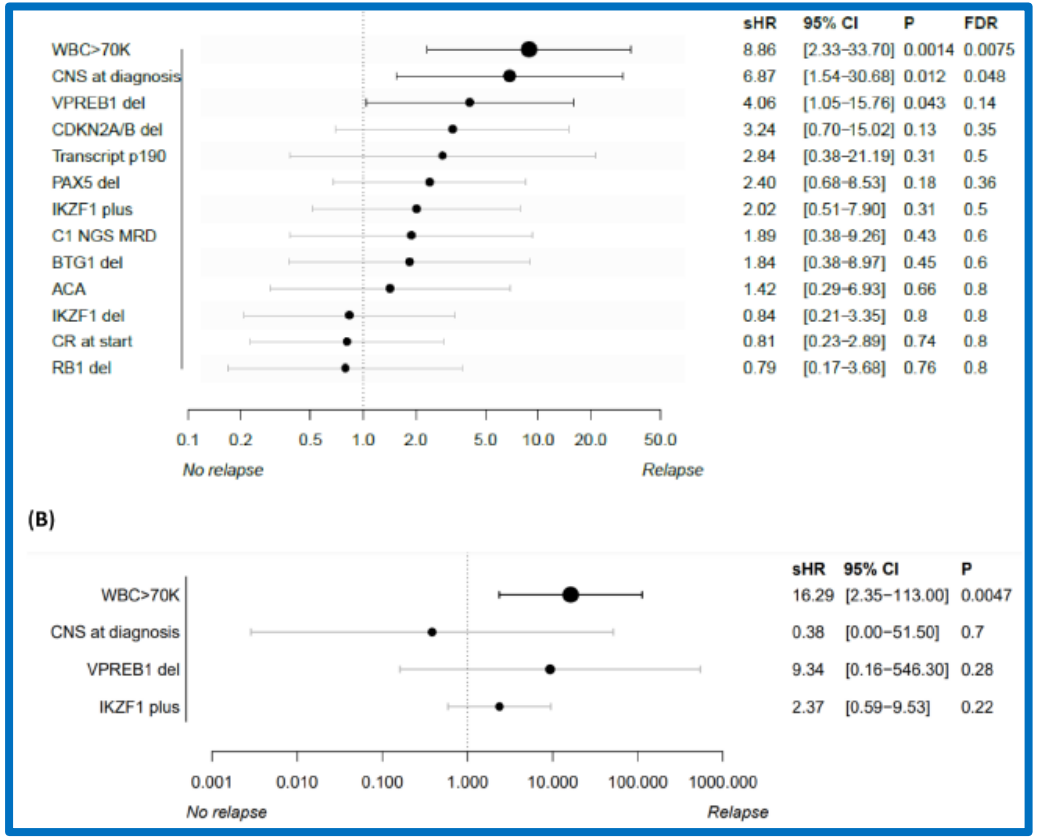
	3 Year Relapse Free Survival
Blinatumomab	100%
Chemotherapy	45%

- 7/19 (37%) patients received HCT.

*NB: This is **19** of the **66** Ph-like patients in this age group who started on study.

Dinner S, et al. EHA 2015. Abstract S110.

Indicators of high relapse risk in Ph+ ALL under blina-ponatinib



Short NJ, et al. *J Hematol Oncol*. 2025;18:55.

Concluding remarks

- The most relevant prognostic factors before frontline immunotherapy are consistent according to studies – MRD and genetics are the most important

- Larger prospective studies under frontline immunotherapy should further explore the prognostic/predictive factors

Global Leukemia Academy

Best practices for first-line treatment in ALL, including Ph+

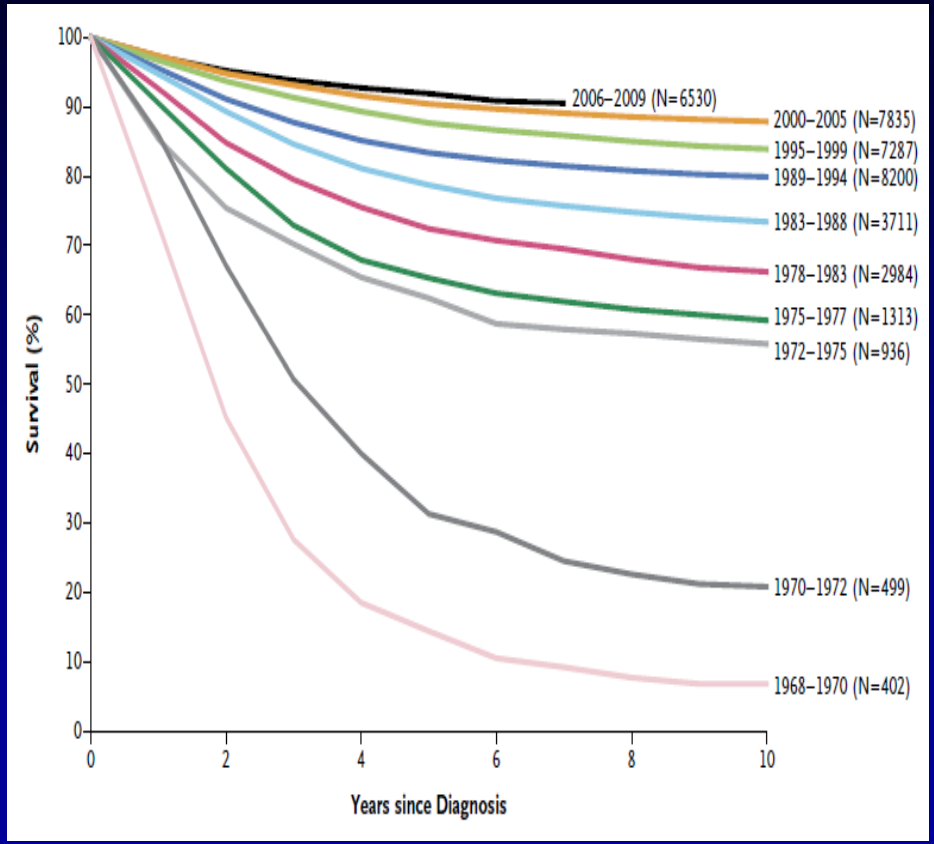
Elias Jabbour

APTITUDE HEALTH®

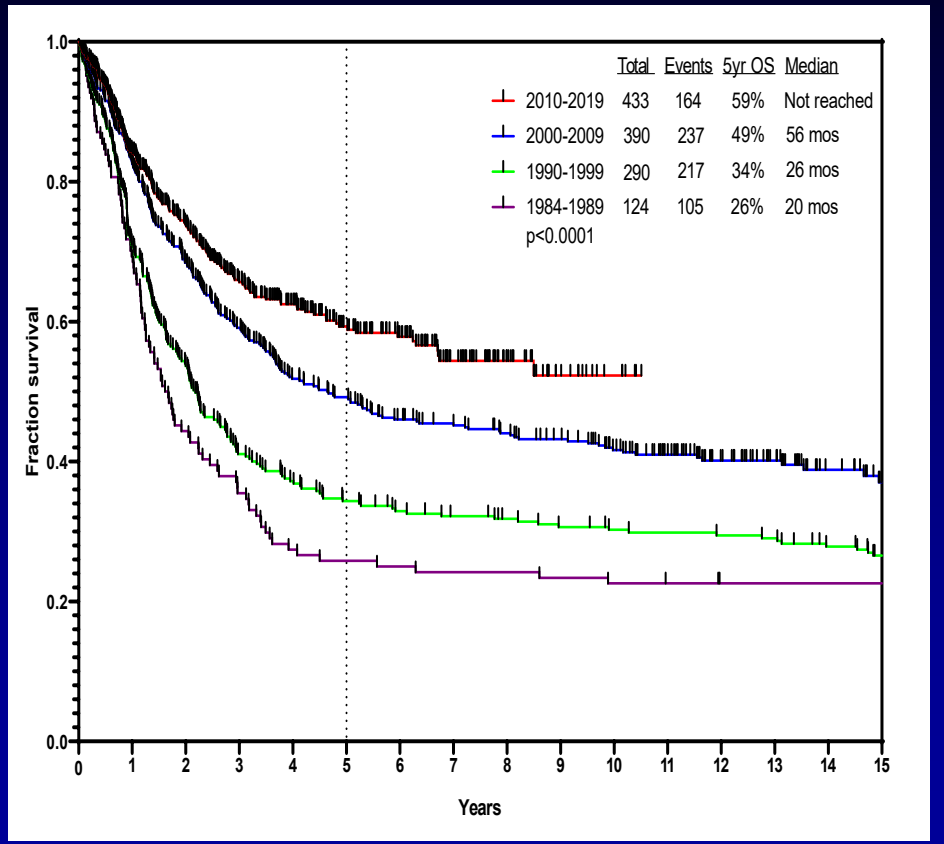
Frontline Therapies in ALL in 2025

Elias Jabbour, MD

Survival in Pediatric and Adult ALL With Classical Intensive ChemoRx Regimens



Hunger SP, et al. *N Engl J Med*. 2015;373:1541-1552.



Kantarjian HM, et al. *Cancer*. 2022;128:240-259.

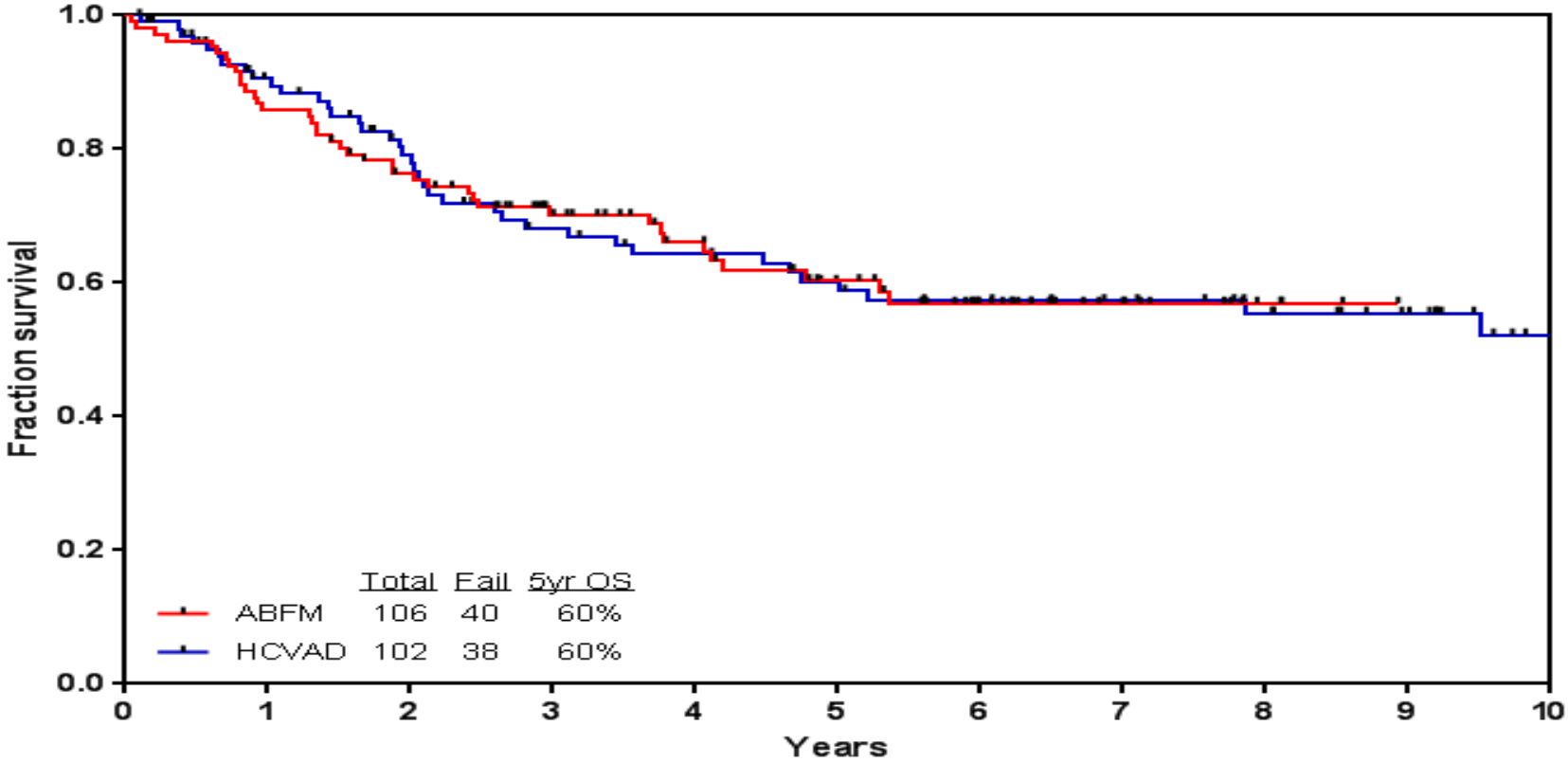
Why Pediatric ALL Does Better Than Adult ALL

Entity	Prognosis	Pediatric, %	Adult, %
Hyperdiploid	Favorable	25–30	5
t(12;21), *ETV::RUNX1*	Favorable	20–25	2
Ph+ ALL	Unfavorable (not anymore)	5	25
Ph-like ALL	Unfavorable (not in 2022+)	10	25

Reasons for Recent Success in Adult ALL

- Addition of TKIs (ponatinib) ± blinatumomab to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Addition of CD19 bispecific T-cell engager (BiTE) antibody blinatumomab, and of CD22 monoclonal antibody-drug conjugate (ADC) inotuzumab, to chemoRx in salvage and frontline ALL Rx
- CAR T therapy
- Importance of MRD in CR (at CR vs 3 mo; NGS)

Hyper-CVAD vs ABFM: Overall Survival



Rytting ME, et al. *Cancer.* 2014;120:3660-3668; Rytting ME, et al. *Am J Hematol.* 2016;91:819-823.

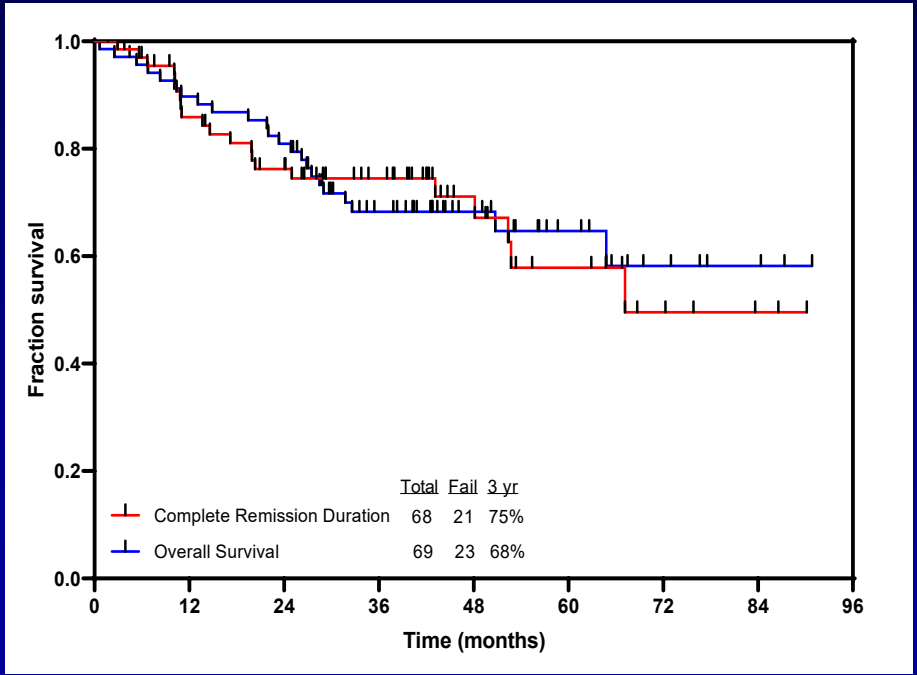
What Should We Incorporate?

- Ph-positive ALL: ponatinib, blinatumomab; novel BCR::ABL1 TKIs (asciminib; olverembatinib)
- Pre-B ALL: antibodies targeting CD19 (blinatumomab), CD22 (inotuzumab), and CD20 (rituximab, CD20 BiTEs)
- CAR T consolidation instead of alloSCT??
- MRD tracking by NGS clonoSEQ for IgHV (analyzes >1 million cells) to decide on changes in Rx, and duration of Rx
- Dose-dense mini-CVD–inotuzumab–blinatumomab ± CAR T regimen – 7 months of Rx
- T-ALL: need CD7 CAR Ts

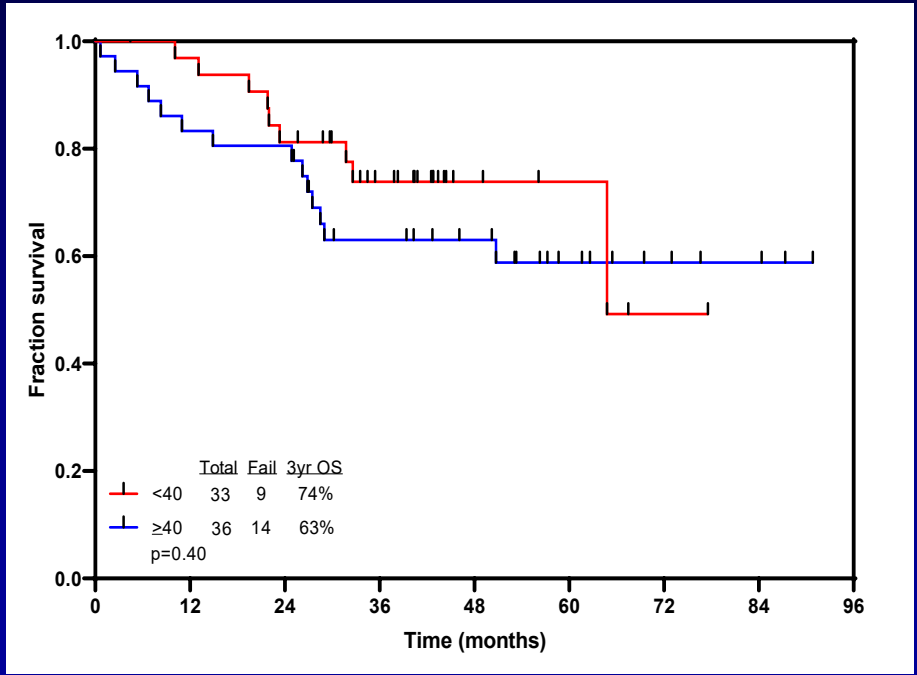
HCVAD + Ofatumumab: Outcome (N = 69)

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

CRD and OS overall

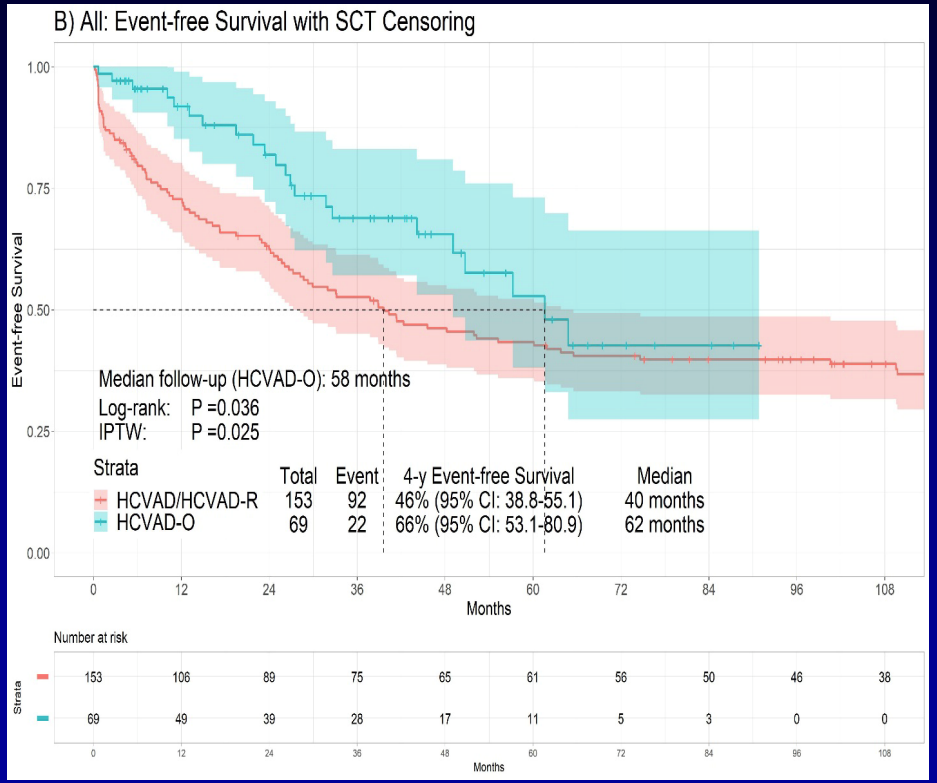


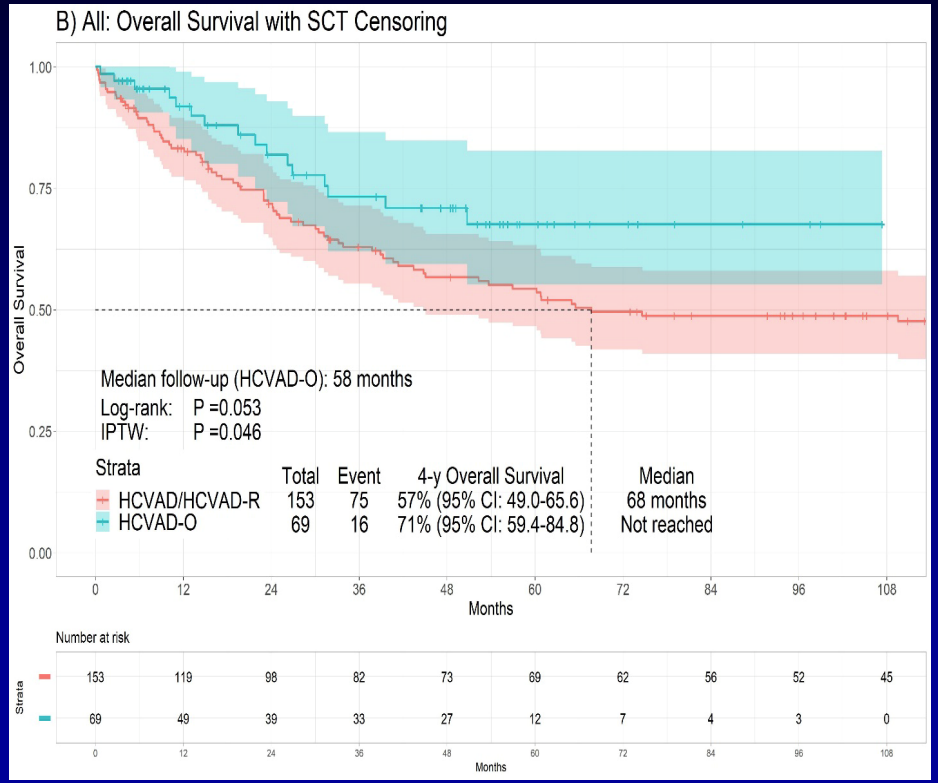
OS by age



Jabbour E, et al. *Lancet Haematol*. 2020;7:e523-e533.

HCVAD-Rituximab vs HCVAD-Ofatumumab: Propensity Score Matching



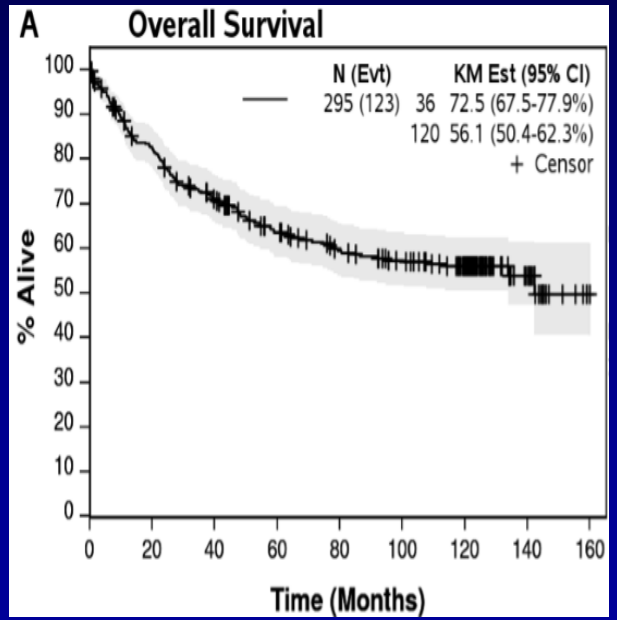


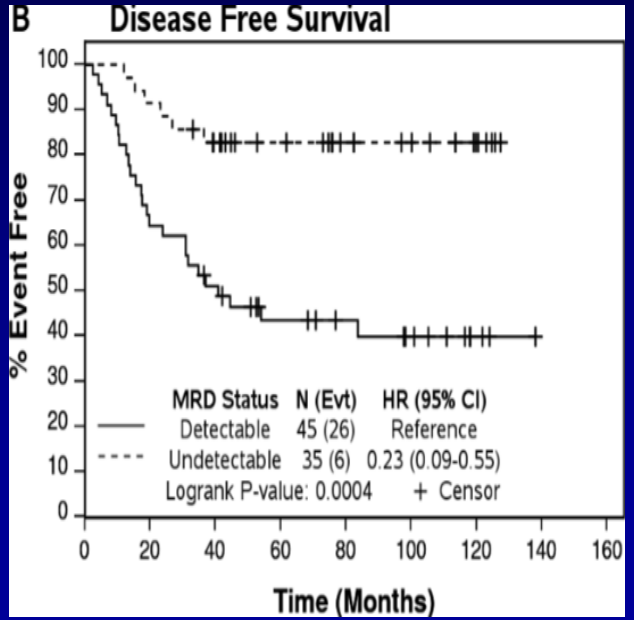
Sasaki K, et al. *Cancer*. 2021;127:3381-3389.

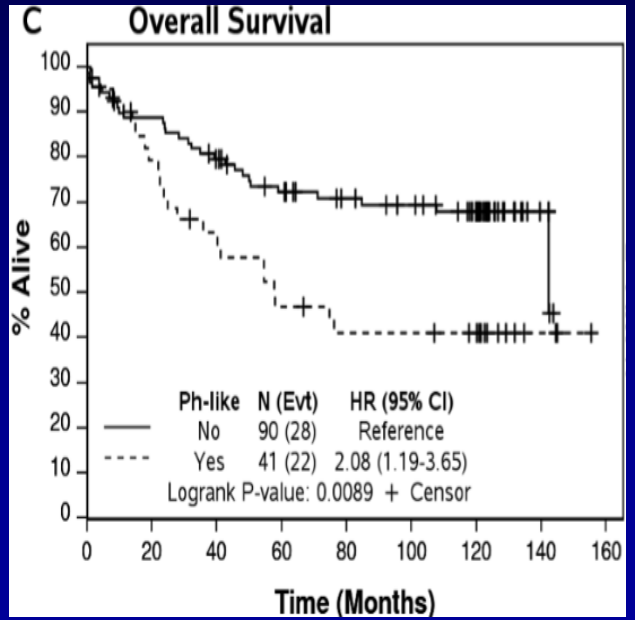
Pediatric Regimen CALGB 10403 in AYA ALL

- 295 evaluable pts; median age 24 yr (17–39)
- 28 SCT in CR1; Ph-like and MRD prognostic

Parameter	
10-yr EFS	44%
10-yr OS	56%

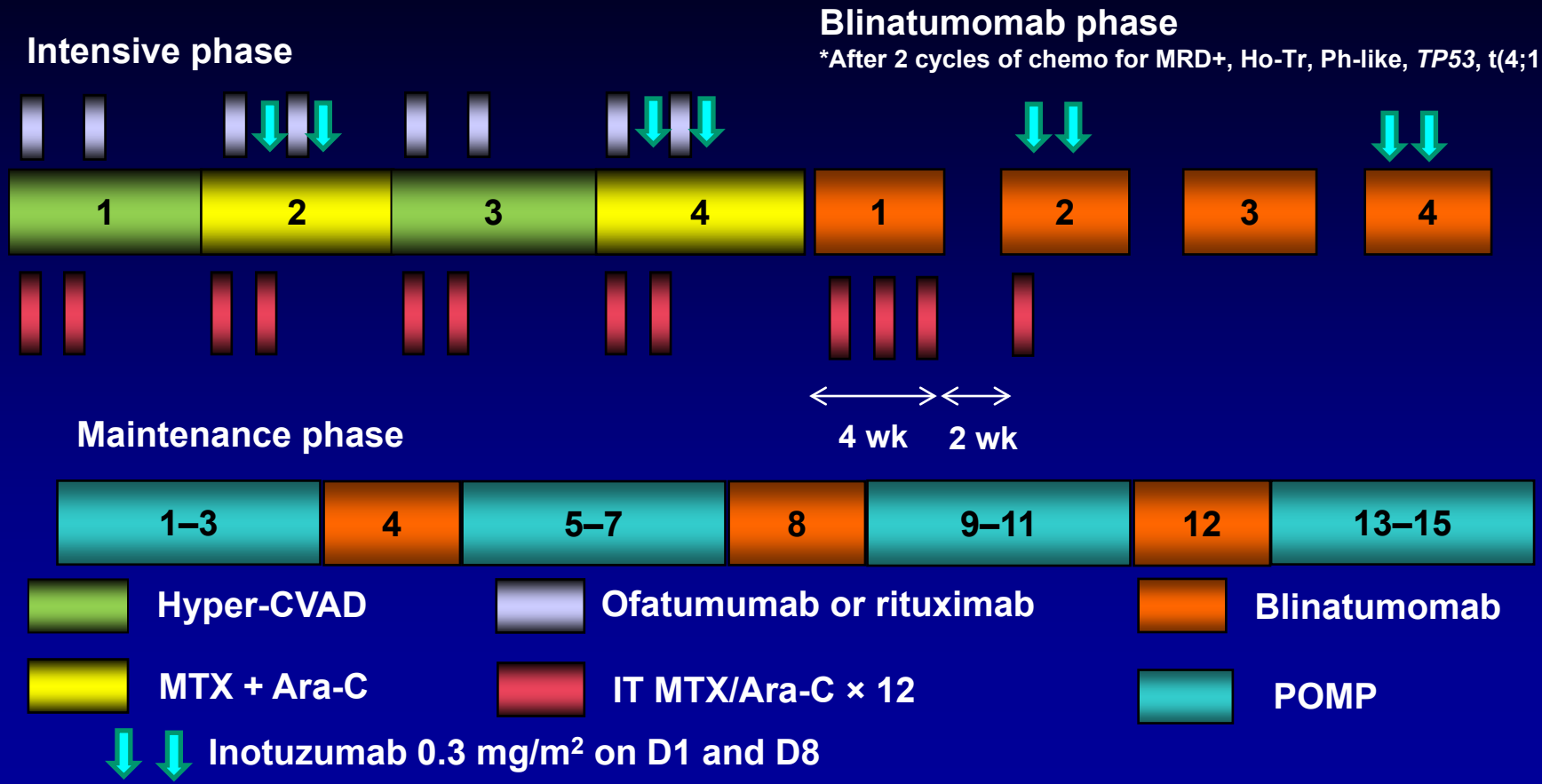






Stock W, et al. EHA 2025. Abstract S118.

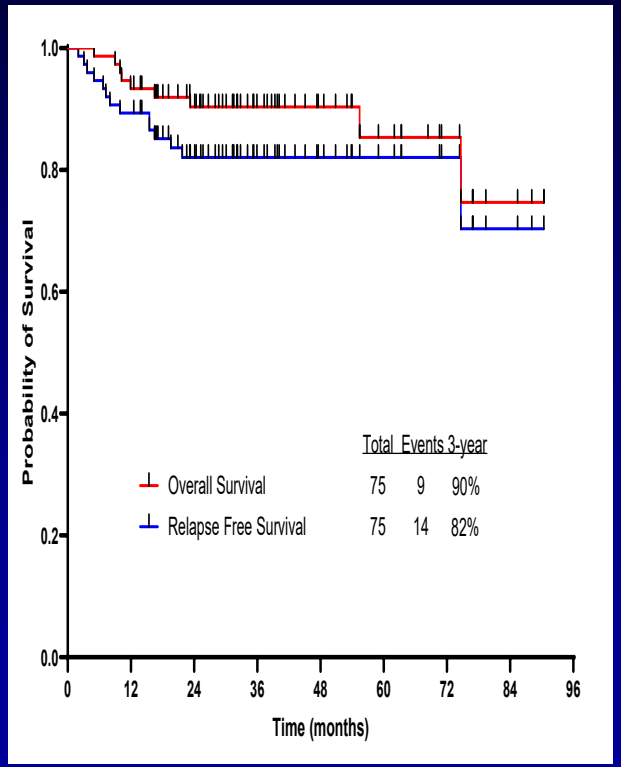
Hyper-CVAD + Blinatumomab in B-ALL: Regimen



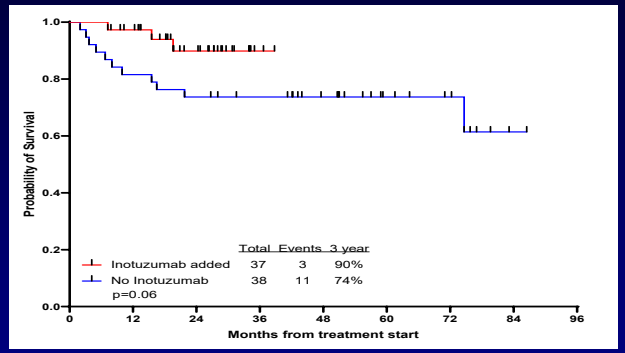
Jabbour E, et al. *Lancet Haematol.* 2022;9:e878-e885; Kantarjian H, et al. *Am J Hematol.* 2025;100:402-407.

Hyper-CVAD–Ino → Blina in Newly Dx Adult ALL

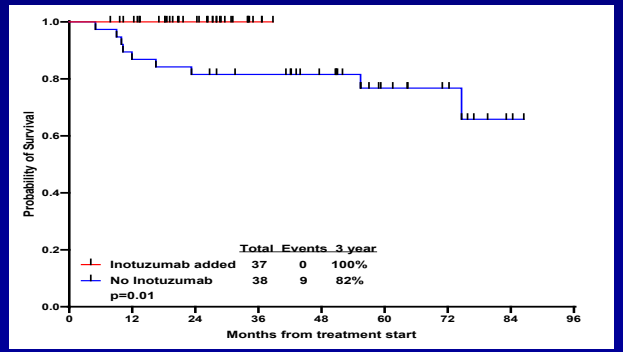
- 75 pts; median age 33 yr (18-59); median F/U 44 mo (13-90)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 76%; 60-day mortality 0%; 24 (32%) alloSCT



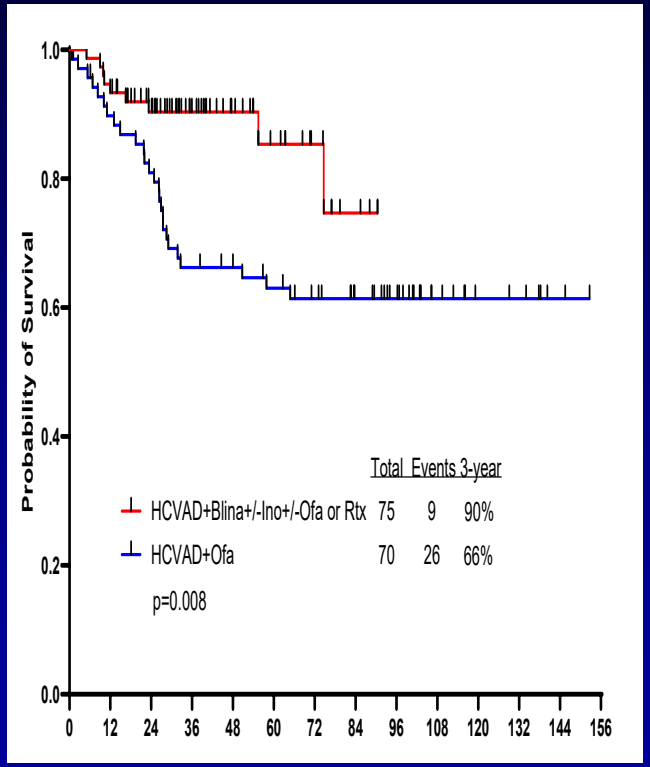
Relapse-free survival



Overall survival

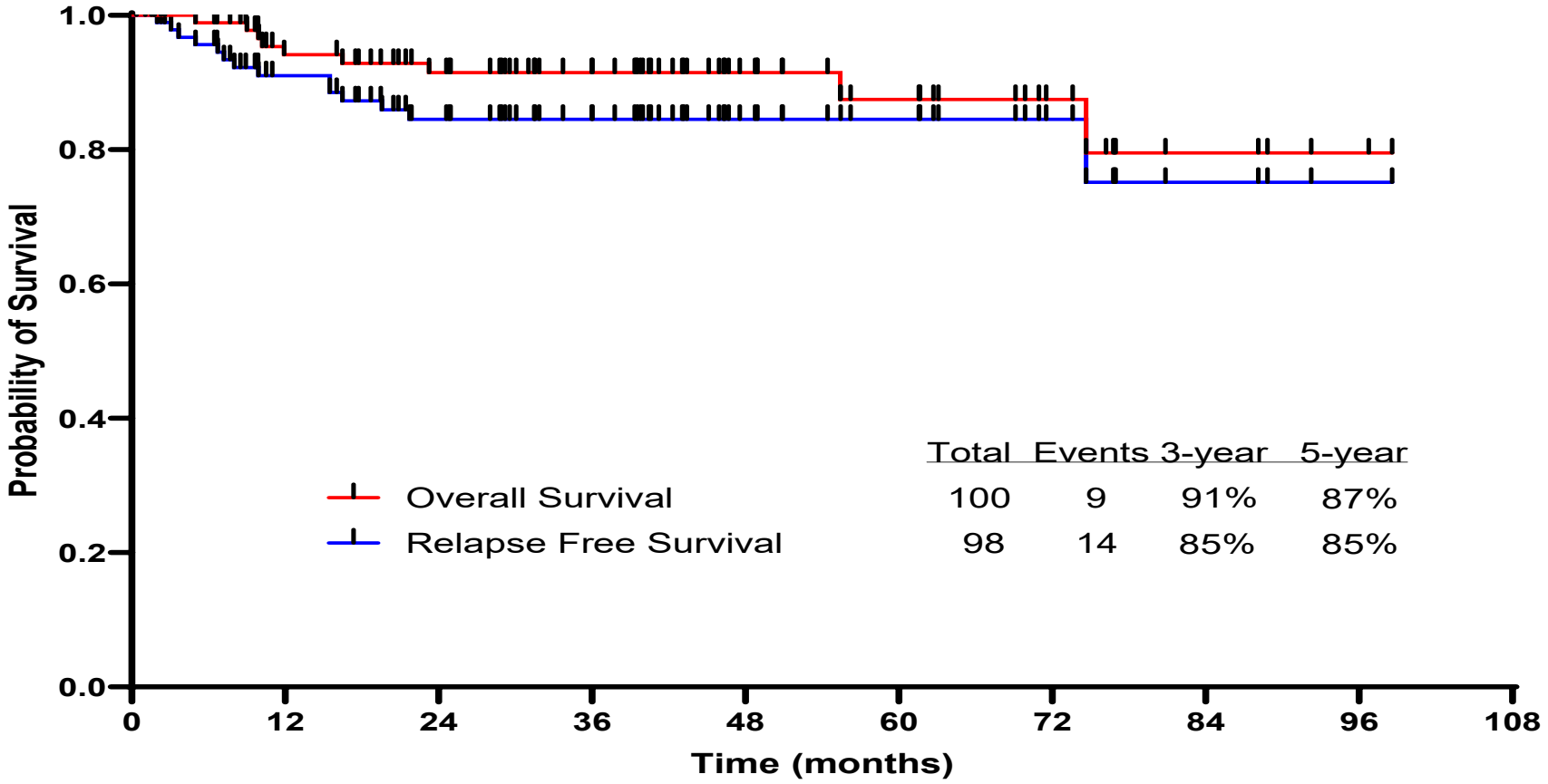


Overall survival



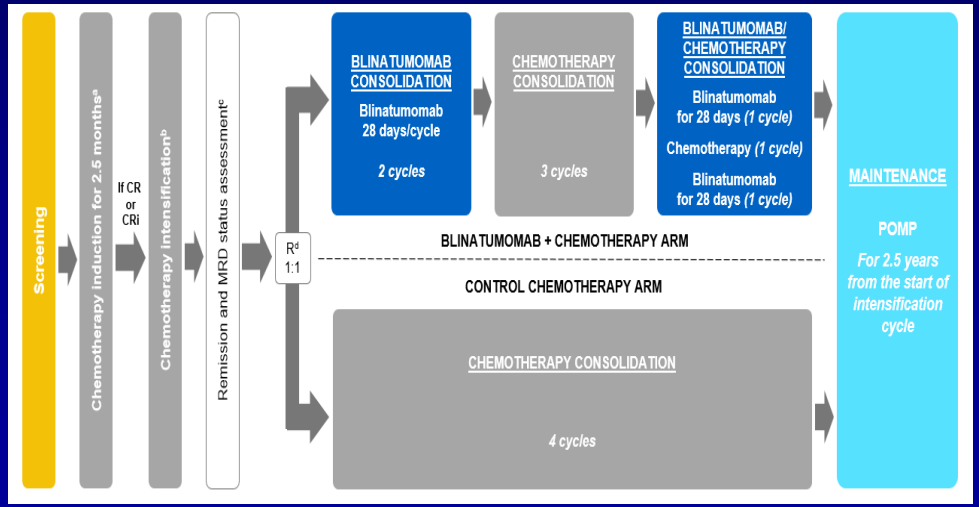
Jabbour E, et al. *Lancet Haematol.* 2022;9:e878-e885; Kantarjian H, et al. *Am J Hematol.* 2025;100:402-407.

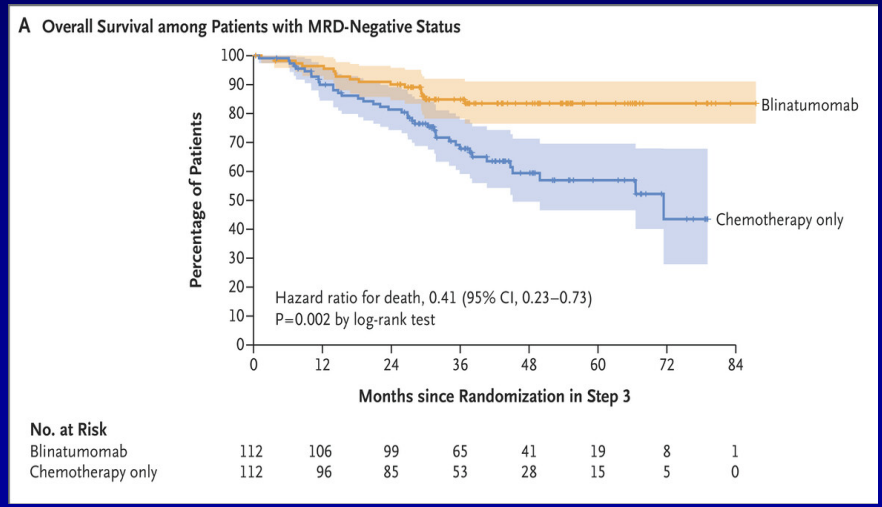
Hyper-CVAD + Blina + InO in B-ALL: Outcome



E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD-Negative CR

- 488 pts median age 51 yr (30–70)
- 224 MRD-negative CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median F/U 43 mo; median OS NR vs 71.4 mo (HR 0.42; *P* = .003)
- No difference in OS if 1–2 cycles of blina vs control (HR 0.62; *P* = .22)
- OS: 1–2 cycles vs 4 cycles (HR 0.39; *P* = .07)

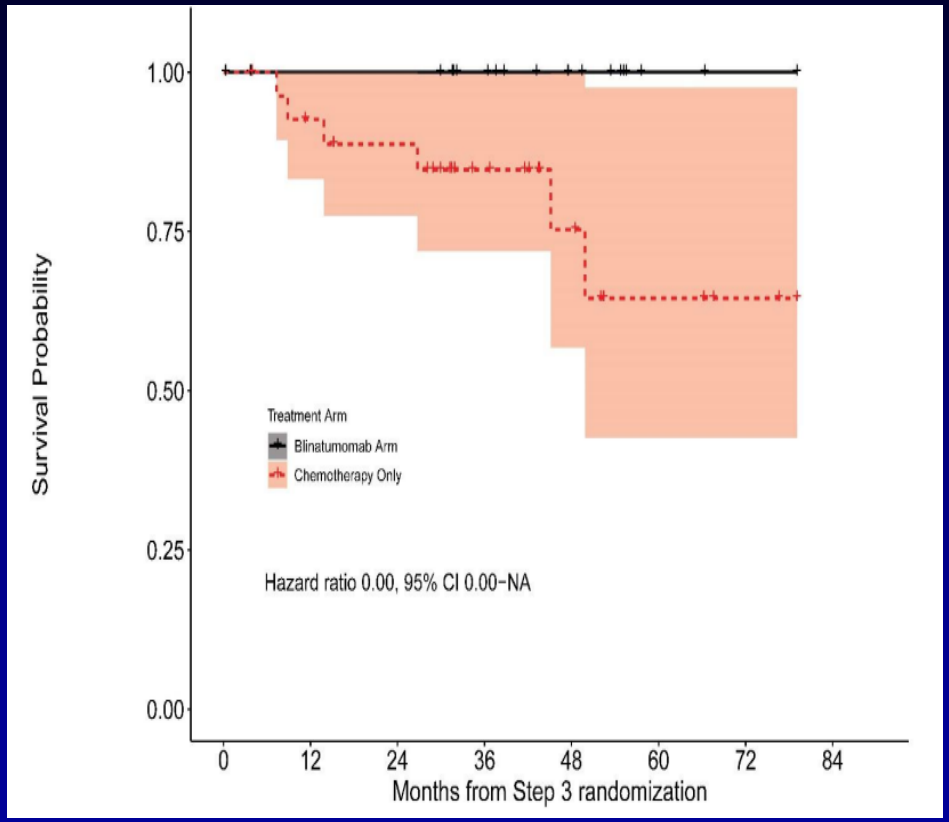




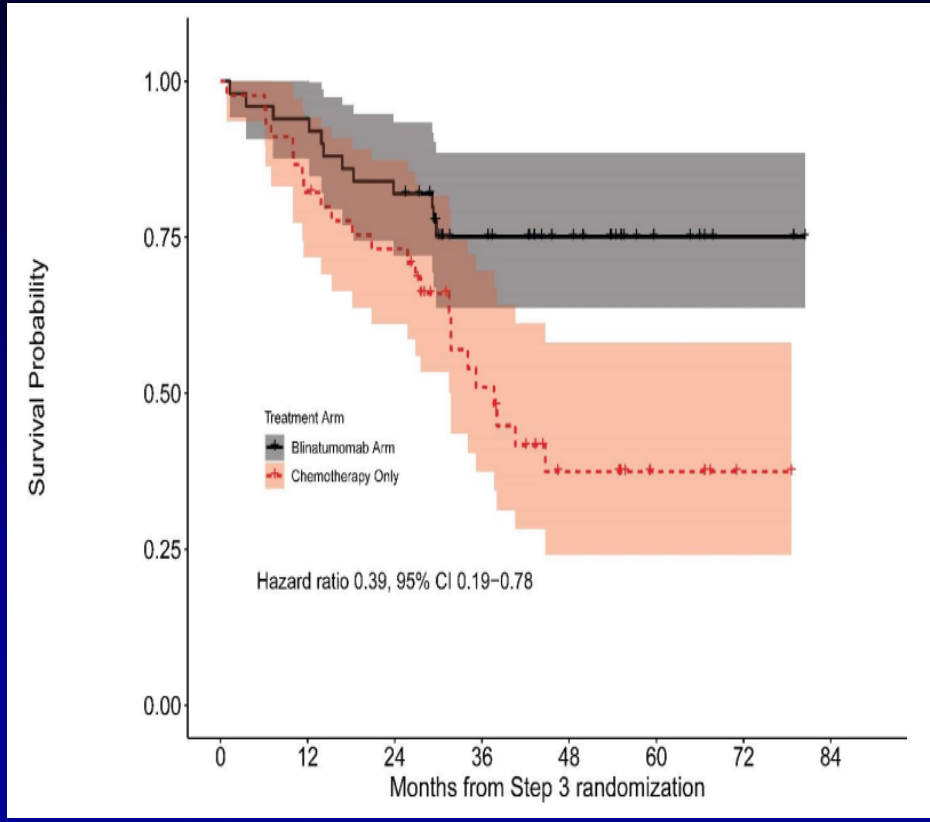
Litzow MR, et al. *N Engl J Med.* 2024;391:320-333.

E1910: Outcomes by ALL Risk

Favorable Risk



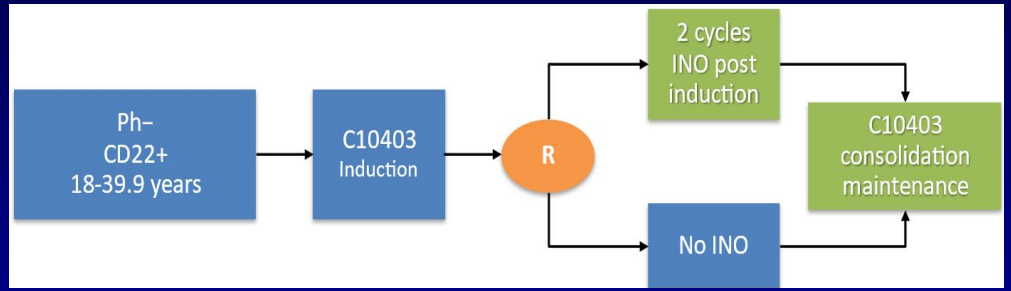
Adverse Risk



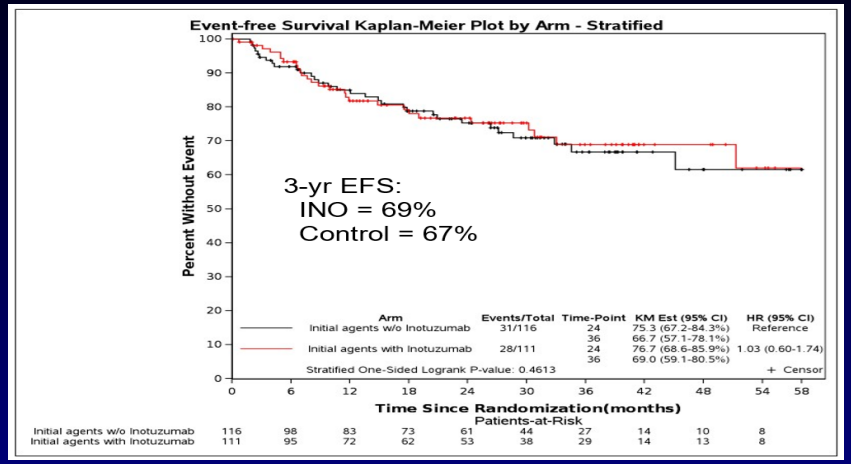
Litzow MR, et al. *N Engl J Med.* 2024;391:320-333.

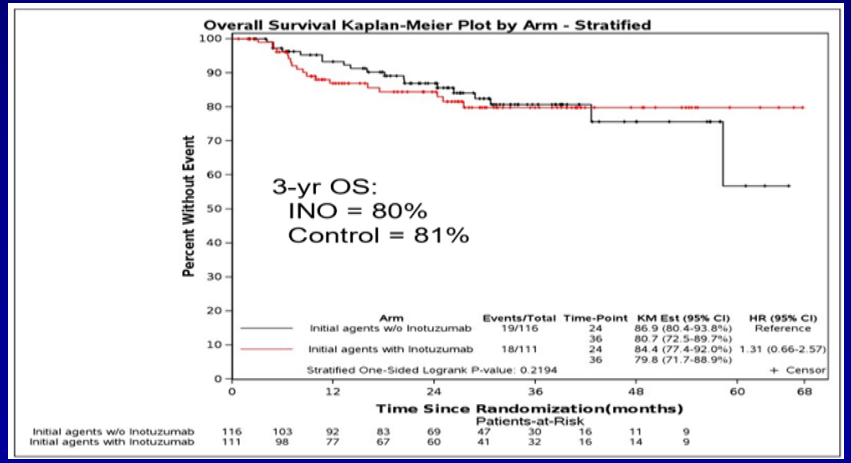
CALGB 10403 ± InO in AYA ALL: A041501 Phase III Study

- 227/273 pts enrolled in CR/CRi/PR post-induction Rx (341 planned)
- Randomization 1:1 to chemoRx ± InO 2 cycles (1.5 mg/m^2/course)
- Median age 27 yr (18-39); 14% CNS 2/3; 49% Ph-like
- CR 86.8%; median F/U 28.3 mo; 13% alloSCT
- 12 G5 post-InO during consolidation: 8 myelosuppression/2 hepatobiliary



Parameter	ChemoRx (n = 116)	ChemoRx + InO (n = 111)	HR
3-yr EFS, %	67	69	1.03
3-yr OS, %	81	80	1.31
D56 MRD negative, %	74	80.6	
Grade 5	3	12	





DeAngelo DJ, et al. *Blood*. 2024;144:308.

Frontline Blinatumomab and Inotuzumab Combinations in Newly Dx Older ALL

	Agent	N	Median Age, yr (range)	CR, %	MRD Negativity, %	OS, % (x-yr)
HCVAD-Blina	Blina	47	33 (18–59)	100	93	82 (3-yr)
HCVAD-Blina-InO	Blina + InO	53	27 (18–58)	96	93	100 (3-yr)
GIMEMA LAL1913	Blina	149	41 (18–65)	88	93	71 (3-yr)
HOVON-146	Blina	70	53 (18–70)	95	91	76 (4-yr)
GRAALL-2014-QUEST	Blina	94	34 (18–59)	100	72	79 (2.5-yr)
ECOG 1910	Blina	112	51 (30–70)	--	100	85 (3-yr)
CALGB 10403 + InO	InO	111	27 (18–39)	--	74	80 (3-yr)

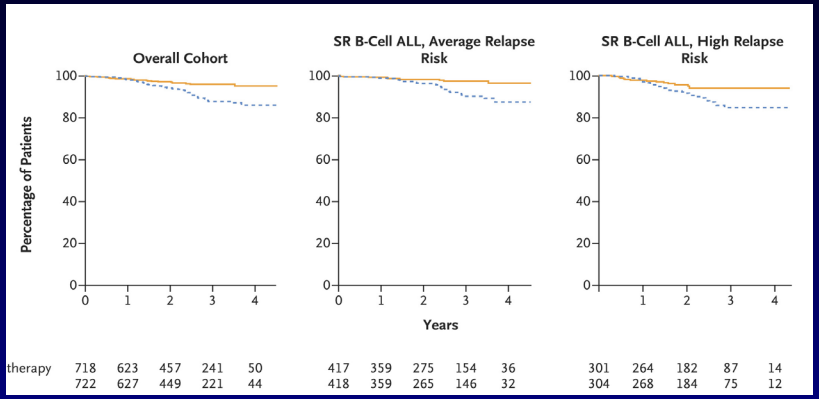
Jabbour E, et al. *Lancet Haematol.* 2023;9:e878-e885; Kantarjian HM, et al. *Am J Hematol.* 2025;100:402-407; Chiaretti S, et al. *Blood.* 2023;142:826; Van Baalen E, et al. EHA 2024. Abstract S113; Boissel N, et al. *Blood.* 2023;142:4349; 2023. Litzow MR, et al. *N Engl J Med.* 2024;391:320-333; DeAngelo DJ, et al. *Blood.* 2024;144:308.

Blinatumomab + ChemoRx Improves DFS in Childhood ALL (AALL1731)

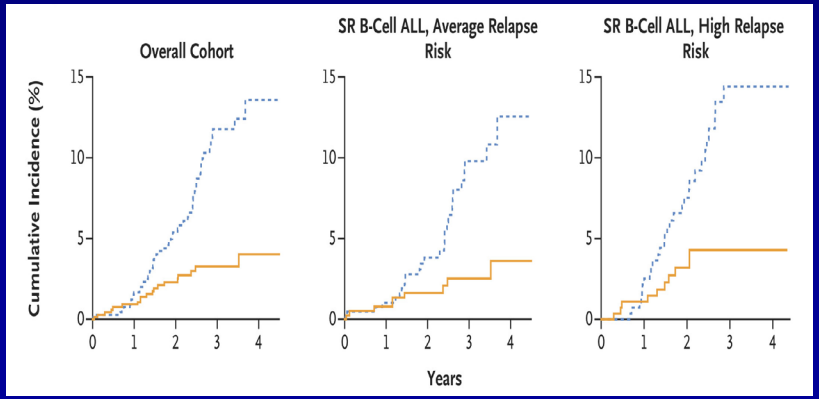
- 1440/2245 SR; median age 4.3 yr (1–10)
- Median F/U 2.5 yr; Rx chemoRx ± 2 Blina

Parameter	ChemoRx (n = 722)	ChemoRx + Blina (n = 718)	HR/*P* Value
3-yr DFS, %	88	96	0.39/<.0001
--SR avg	90	97.5	0.33/
--SR high	84.8	94	.045/
3-yr CIR, %	11.8	3.3	

DFS



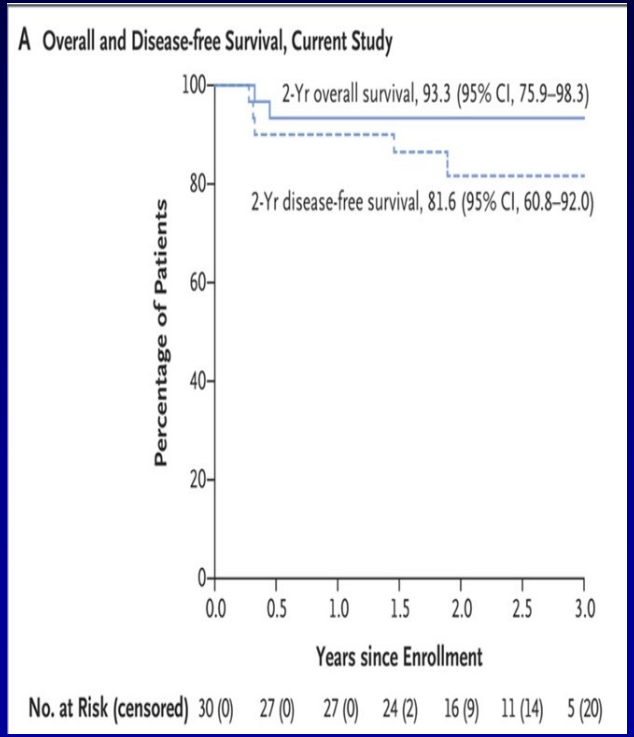
CIR

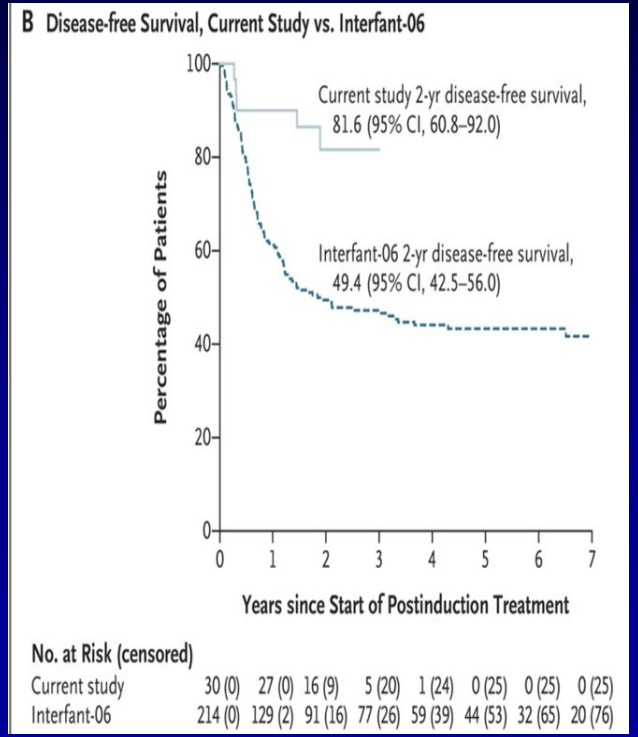


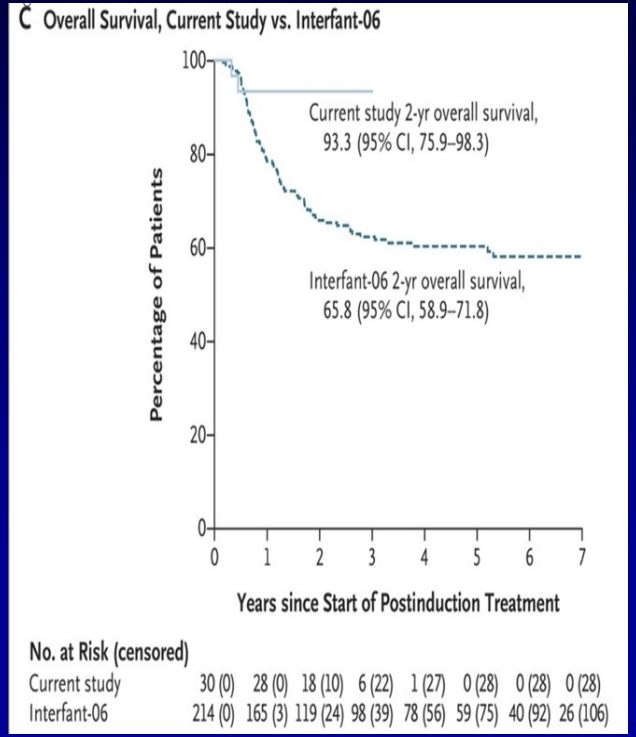
Rau RE, et al. *Blood*. 2024;144:1; Gupta S, et al. *N Engl J Med*. 2025;392:875-891.

ChemoRx + Blinatumomab in Newly Dx *KMT2A*-Rearranged ALL

- 30 infants age <1 yr Rx with chemoRx induction, then 1 course Blina consolidation (15 µg/m² × 28), then chemoRx continuation



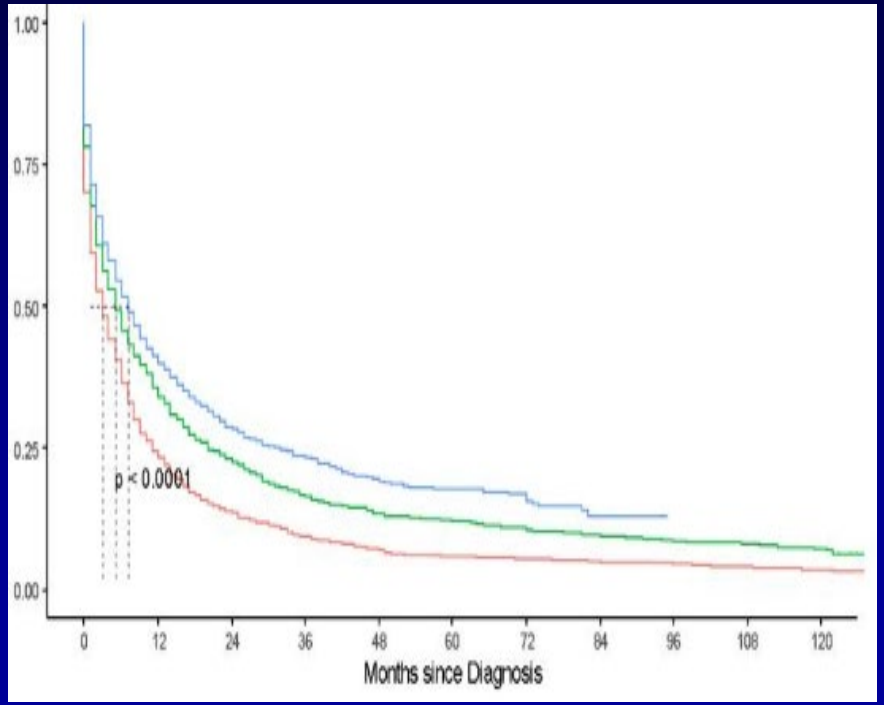


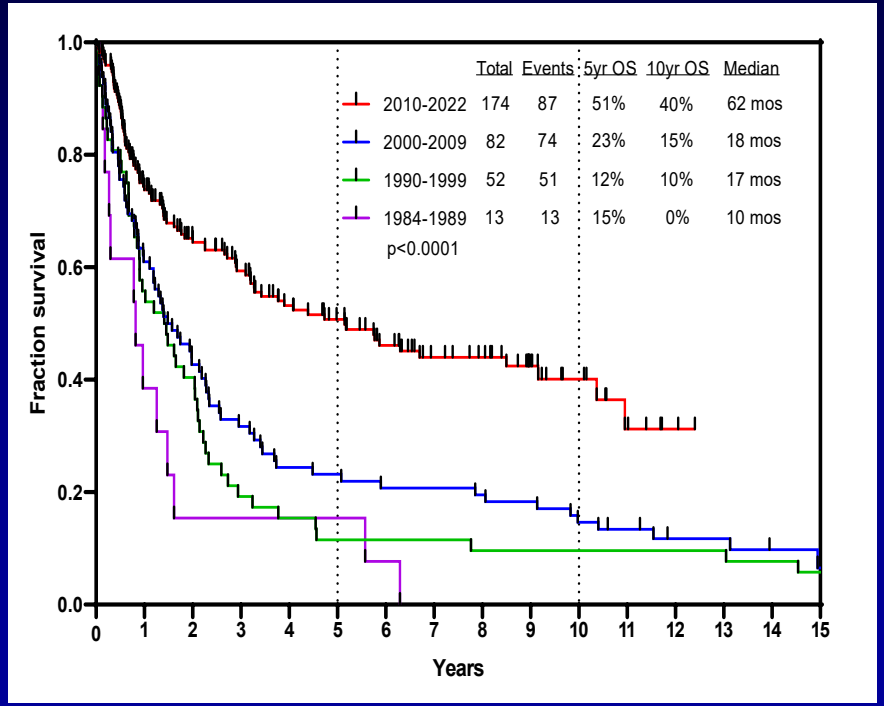


van der Sluis IM, et al. *N Engl J Med*. 2023;388:1572-1581.

MDACC vs SEER ALL: Survival by Decades for ≥60 Years

- 26,801 pts age 65+ yr; B-ALL 91%
- OS better in Ph+ (HR 0.68) and 2012-2018 (HR 0.64); worse in secondary ALL (HR: 1.15), AA (HR: 1.19), and Hispanic (HR 1.1)
- 5-yr OS <20%

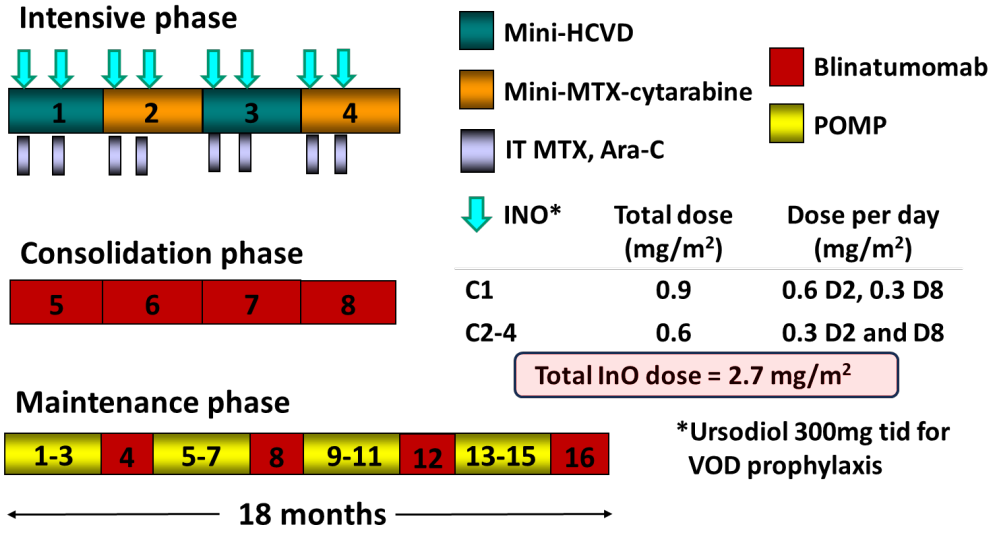




Gupta S, et al. *Blood.* 2022;140:1379.

Mini-HyperCVD–InO ± Blina in Newly Dx Older Ph-Negative B-Cell ALL: 10-Year Follow-Up

Study regimen: Post-amendment



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 300mg tid for VOD prophylaxis

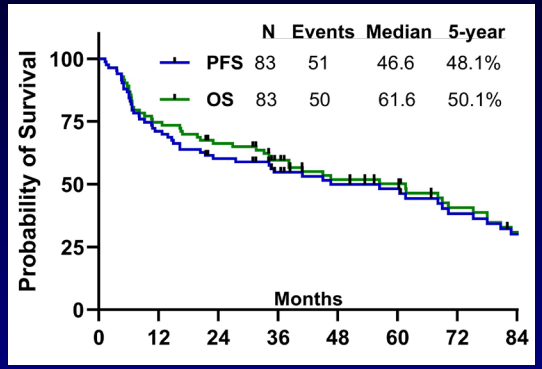
Characteristics		N (%), median [range]
Age	≥70 years	67 [60–88] 28 (34)
ECOG PS ≥2		11 (13)
WBC ($\times 10^9$/L)		3.1 [0.3–111.0]
CG (n = 67) [excludes pts in CR at enrollment and inadequate metaphases]	Diploid Adverse • Ho-Tr • Complex • Tetraploidy • KMT2Ar	27 (40) 19 (28) 12 (18) 4 (6) 2 (4) 1 (1)
CNS disease at diagnosis		4 (5)
CRLF2 positive		6/48 (13)
TP53 mutation		25/64 (39)

		N (%)
Response evaluable		77
CRc (CR + CRi)	CR CRi	76 (99) 69 (90) 7 (9)
MRD evaluable		
MRD-negative response by MFC	Best Post-C1	76/82 (94) 63/80 (79)
MRD negative by NGS (1 in 10^6 sensitivity)	Best response	16/17 (94)

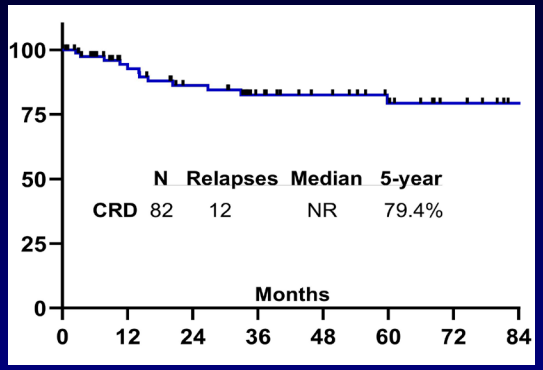
Jabbour E, et al. *Lancet Haematol*. 2023;10:e433-e444; Senapati J, et al. *Blood*. 2024;144:1441.

Mini-HyperCVD–InO ± Blina in Newly Dx Older Ph-Negative B-Cell ALL: 10-Year Follow-Up

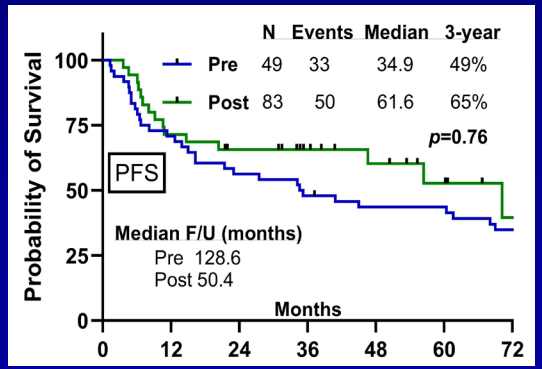
PFS and OS of the full cohort



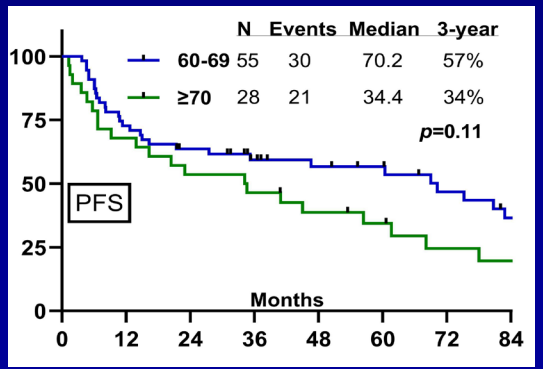
Continuous remission duration



PFS pre- and post-amendment



PFS stratified by age



Patient disposition

- HSCT = 5 (6%; 4 adverse genomics, 1 persistent MRD positive)
- 33 (39.8%) patients alive
- 50 (60.2%) died: 1 nonresponder; 11 post-relapse, 38 nonrelapse mortality (NRM)
- **Causes of NRM: secondary MDS/AML = 8**; infections = 9 (6 on study, 3 off study), **SOS = 4**; other (noninfection/nonleukemia related) = 16
- **Age-wise NRM**: 60–69 years = 20/55 (36.4%); ≥70 years = 18/28 (64.3%)

Safety analysis

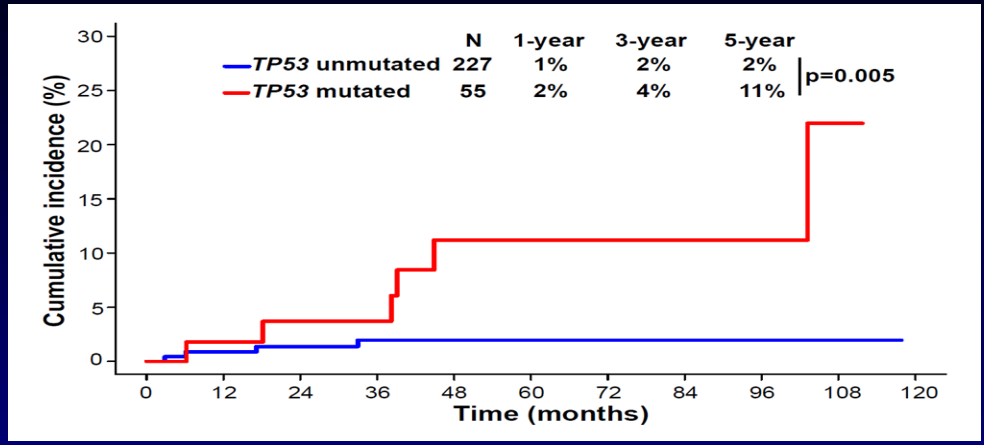
- Secondary MDS/AML = 8 (9.6%)
  - 6 on Rx, 2 off Rx **– 5 *TP53* at ALL Dx and MDS/AML Dx**
  - **Hepatic SOS = 6 (7.2%) –** 4 pre-amendment, 1 post-amendment; 1 after HSCT, 4 without HSCT
- Blina neurotoxicity (grade 3) = 7 (8.4%); no seizures

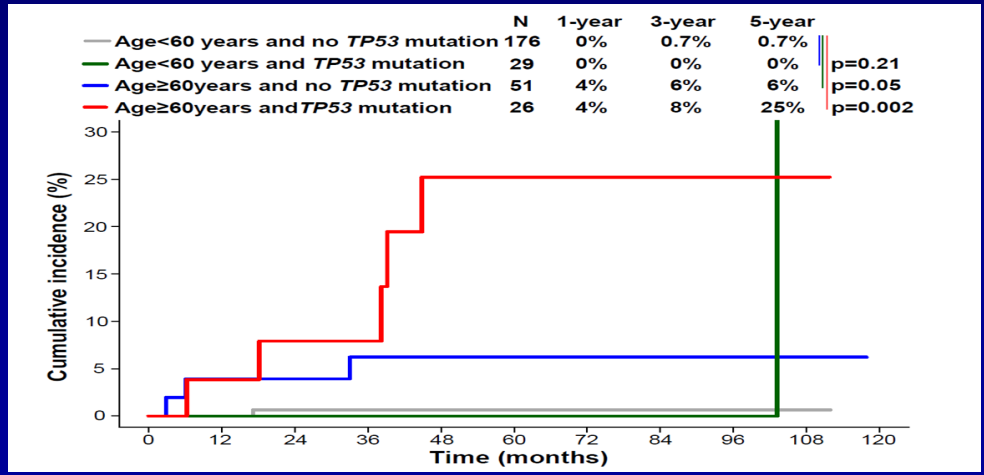
Jabbour E, et al. *Lancet Haematol*. 2023;10:e433-e444; Senapati J, et al. *Blood*. 2024;144:1441.

TP53-Mutated ALL and Therapy-Related AML/MDS

- 816 pts; median age 45 yr (18-87); Rx with HCVAD regimens
- *TP53* mutation at ALL Dx 55/282 (20%)
- 36 pts developed T-MN (median 38 mo): 24 MDS, 10 AML, 1 CMML
- T-MN Rx: ORR 45%; median OS 9.8 mo, 2-yr OS 19%
- 5/6 pts with *TP53* tested had it at ALL and T-MN

Parameter	T-MN, %	*P* Value
Age <60	3	.009
Age ≥60	7	-
TP53 negative	1	.008
TP53 positive	9	

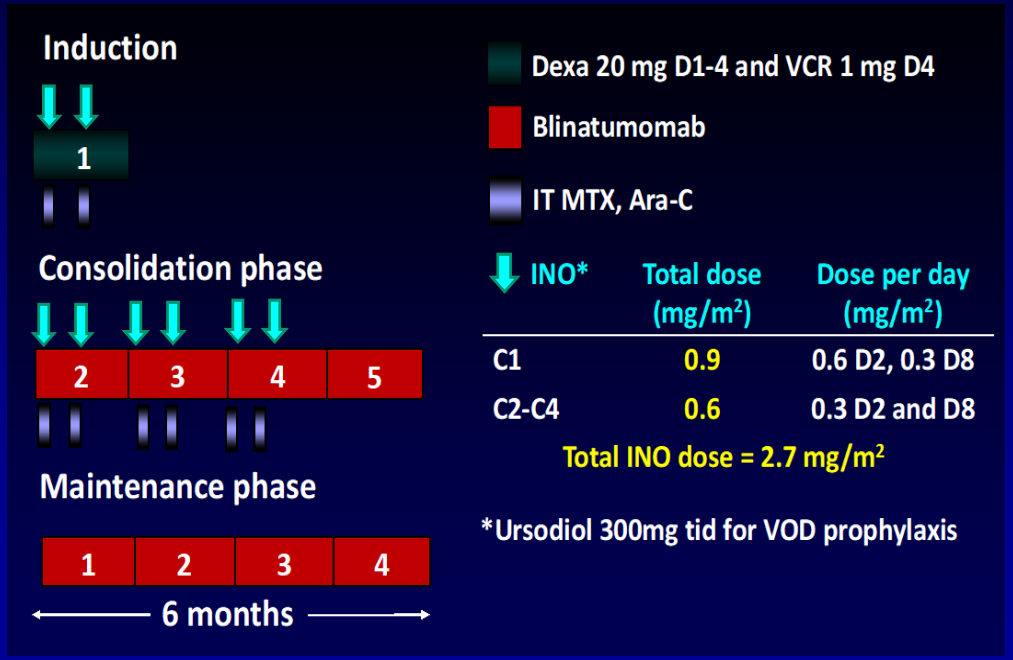




Santos-Azevedo R, et al. *Blood*. 2024;144:728.

ChemoRx-Free Regimen of InO and Blina in Newly Dx Older (≥70 years) Ph-Negative B-Cell ALL (n = 14)

Study regimen



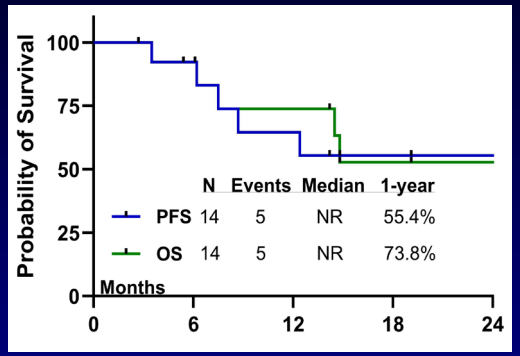
Characteristics		N (%), Median [range]
Age	≥70 years ≥75 years	76 [65-84] 13 (93) 8 (57)
ECOG PS	0–1	14 (100)
Karyotype (n = 13)	Diploid Adverse • Ho-Tr • Complex • *KMT2Ar*	2 (15) 6 (46) 3 (23) 1 (6) 2 (4)
***CRLF2* positive**		1 (8)
***TP53* mutations**		7 (50)

Characteristics		N (%), Median [range]
Response evaluable		14
CRc (CR + CRi)	**CR** **CRi**	**13 (93)** **12 (86)** **1 (7)**
MRD-negative response (MFC)	Best response Post-C1	13 (100) 12 (86)
MRD negative by NGS (1 in 10^6)	**Best** **Post-C1**	**11/12 (92)** **6/8 (75)**

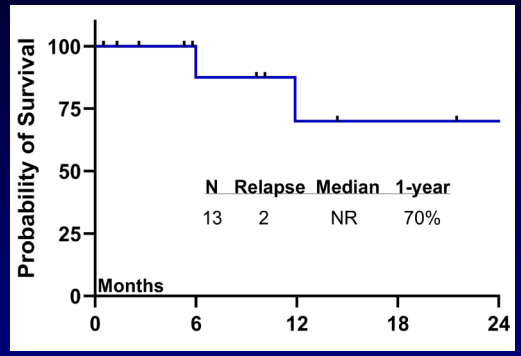
Senapati J, et al. *Blood*. 2024;144:1442.

ChemoRx-Free Regimen of InO and Blina in Older (≥70 years) Ph-Negative B-Cell ALL

PFS and OS of the full cohort

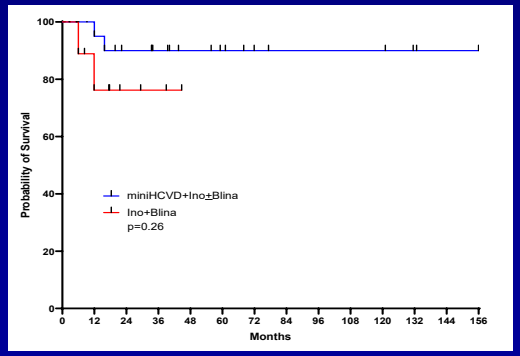


Continuous remission

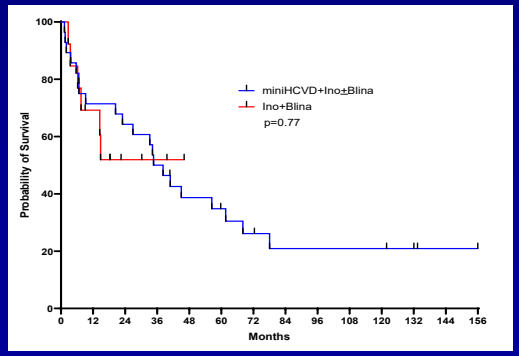


InO-Blina vs mini-HCVD–InO–Blina

CRD



OS



Patient disposition

At data cutoff: Oct 31, 2024

- HSCT = 1 (Pt #8); CAR T-cell therapy = 1 (Pt #10; *KMT2A*r)
- Relapses = 2 (Pt #10, *KMT2A*r; Pt #14, hypoploidy with *TP53* mutation; both patients had NGS MRD-negative response)
- Died = 6 (1 nonresponder, 2 post-relapse; 3 NRM)
- Causes of NRM: pneumonia = 1, myocardial infarction = 1, noninfectious respiratory failure = 1

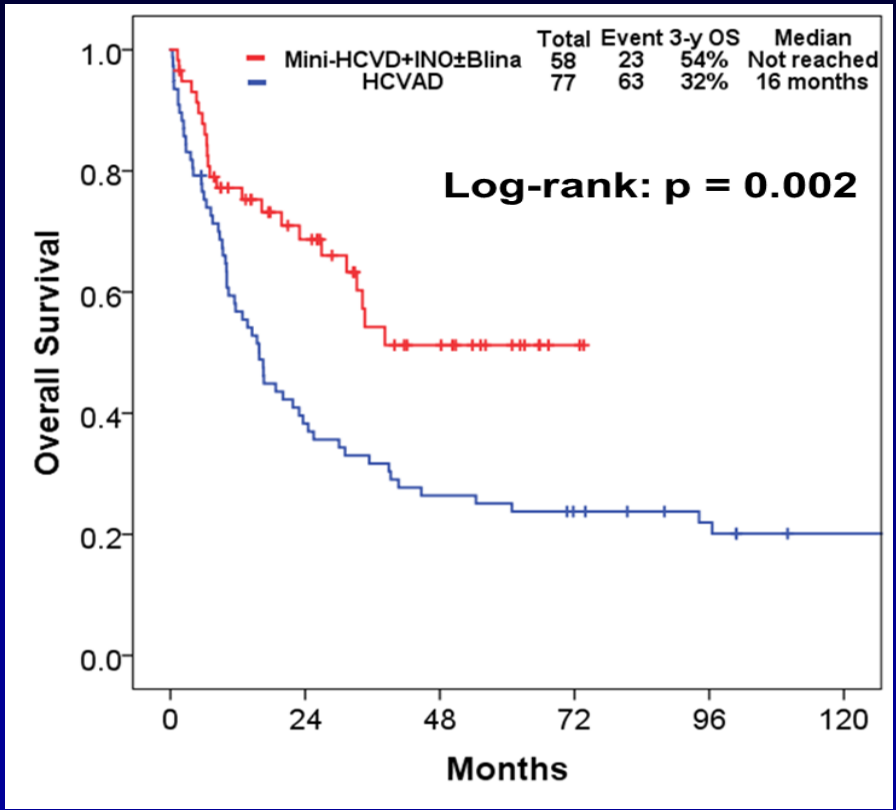
Safety

- Median time on study = 20 mo (range, 8.6-46)
- Hepatic SOS = 0; grade 3 ALT elevation = 1 (7%)
- Blina-related neurotoxicity
  - Grade 3 encephalopathy = 1 (7%)
  - Grade 1–2 confusion = 5 (36%)
  - Grade 1–2 tremors = 3 (21%)
- Blina-related CRS = 1 (7%, grade 2)
- Secondary myeloid neoplasm = 0

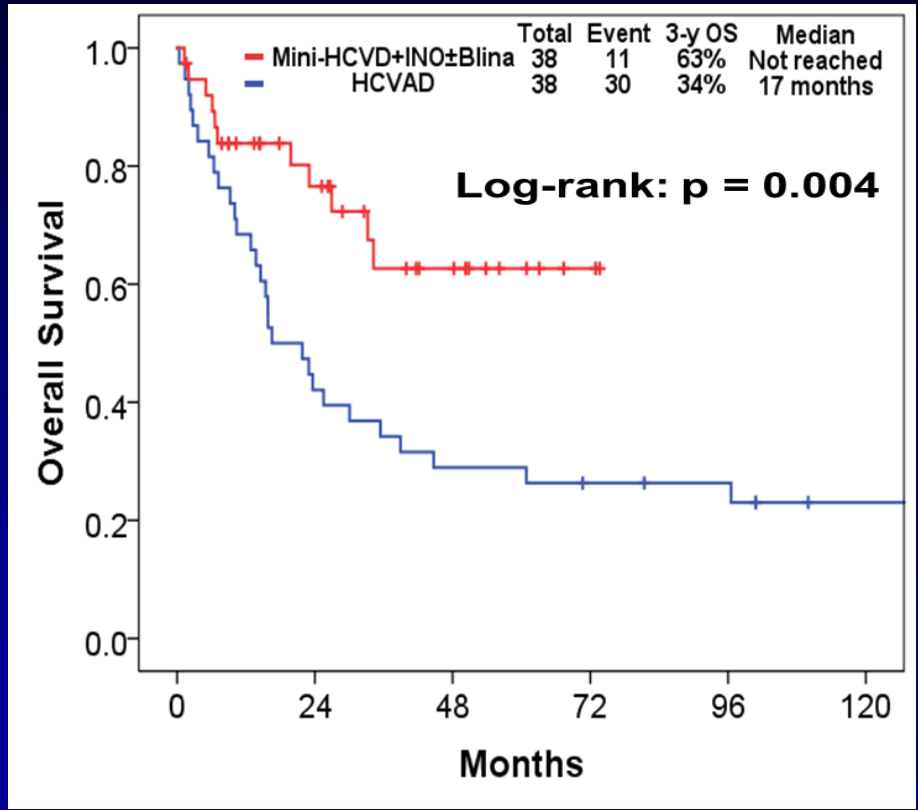
Senapati J, et al. *Blood*. 2024;144:1442.

Mini-HyperCVD + InO ± Blina vs HCVAD in Older ALL: Overall Survival

Prematched



Matched



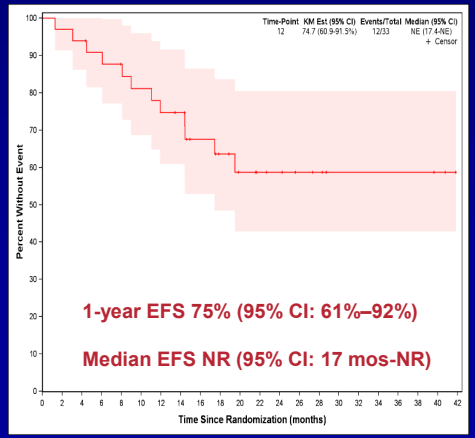
Jabbour E, et al. *Cancer.* 2019;125:2579-2586.

ChemoRx-Free InO + Blina in Pre–B-ALL (Alliance A041703)

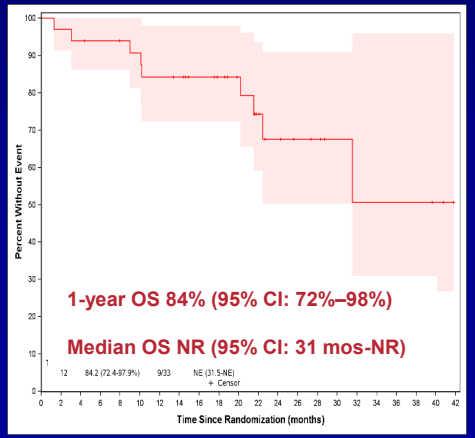
- 33 pts; median age 71 yr (60–84); median CD22 92%; F/U 22 mo
- Induction: InO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 and 15 (1.8 mg/m^2)
- Maintenance: if CR-CRi, InO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) × 2 then Blina × 2
- If no CR-CRi, Blina 28 µg/D × 21 then × 28 × 3
- IT × 8
- CR 85% post-InO × 3; cumulative CR 97%
- 1-yr EFS 75%; 1-yr OS 84%
- 9 relapses; 2 deaths in CR; 9 deaths, 6 post-relapse; ?1 SOS

	Induction With Inotuzumab (IA/B/C)	Consolidation With Blinatumomab
Cumulative CR (CR + CRh + CRi)	28/33 (85%)	32/33 (9%)
CR	15/33 (45%)	19/33 (58%)
CRh	11/33 (33%)	12/33 (36%)
CRi	2/33 (6%)	1/33 (3%)
Refractory	3/33 (9%)	-

EFS



OS



Wieduwilt M, et al. *HemaSphere.* 2023;7:S117.

CD19 CAR T-Cell Rx in Older ALL in CR1

- 20 pts ≥55 yr consented; minimal bridging followed by CAR T cells
- 14 evaluable (200 million CAR Ts)
- Median age 68 yr (55–79); 4 Ph positive; 2 hypodiploidy/*TP53* mutations
- 11 Rx Blina; 13/14 MRD-neg CR at LD
- No ICANS or G≥2 CRS
- Median F/U 244 days: 13/14 MRD-neg CR; 1 pt Ph positive ALL molecular relapse (alive in MRD-neg CR post-ASCT)
- No deaths
- CAR T cells expanded (peak 7–4 days; 14%)
- D28 10 pts LP CAR T cells expanded in CSF (median 0.28 × 10^3/mL)
- Baseline and D100 walk speed and cognitive function similar

Aldoss I, et al. *Blood.* 2024;144:966.

Frontline Blinatumomab and Inotuzumab Combinations in Newly Dx Older ALL

	Agent	N	Median Age, yr (range)	CR, %	MRD Negativity, %	OS, % (x-yr)
Mini-HCVD–InO–Blina	Blina + InO	83	67 (60–88)	99	93	50 (5-yr)
InO-Blina	InO + Blina	14	76 (65–84)	92	100	74 (2-yr)
SWOG 1318	Blina	31	73 (66–86)	66	92	37 (3-yr)
EWALL-INO	InO	131	68 (55–84)	90	80	55 (2-yr)
GMALL BOLD	Blina	50	66 (56–76)	85	82	67 (3-yr)
INITIAL-1	InO	45	64 (56–80)	100	74	81 (2-yr)
A041703	InO + Blina	33	71 (60–84)	97	NA	84 (1-yr)

Senapati J, et al. *Blood*. 2024;144:1441; Senapati J, et al. *Blood*. 2024;144:1442; Advani AS, et al. *J Clin Oncol*. 2022;40:1574-1582; Chevallier P, et al. *J Clin Oncol*. 2024;42:4327-4341; Goekbuget N, et al. *Blood*. 2023;142:964; Stelljes M, et al. *J Clin Oncol*. 2024;42:273-282; Wieduwilt M, et al. *HemaSphere*. 2023;7:S117.

Hyper-CVAD, Venetoclax, Nelarabine–Peg-Asp in T-ALL/LL

- 145 pts (8/2007–12/2024) on 5 cohorts; median age 35.4 yr
- 46 pts (34%) with VEN
- 60% T-ALL; 18% ETP; median F/U 62 mo
- ORR 95%; CR 89%; 5-yr OS 64%. Cohorts 3–5: 3-yr OS 76%–88%
- OS shorter ETP/near-ETP vs non-ETP phenotype (71 mo vs NR; *P* = .08)
- VEN vs no VEN: 2-yr PFS 89% vs 64% (*P* = .03); 3-yr OS 88% vs 74% (*P* = .16)

Figure 1C: Overall survival (OS)

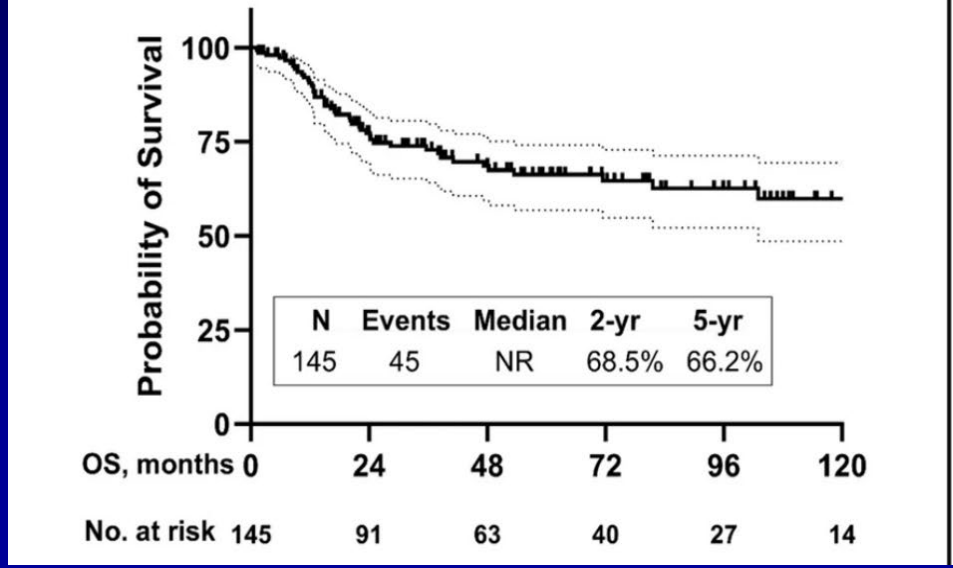
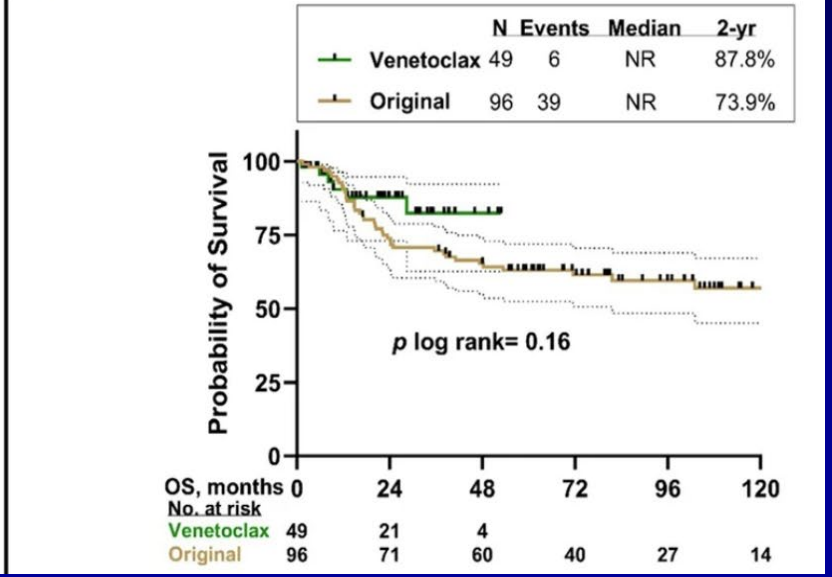


Figure 1F: Overall survival (OS)



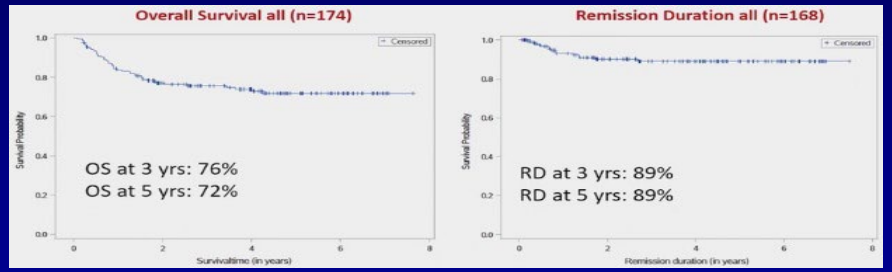
Ravandi F, et al. *Leukemia*. 2024;38:2717-2721.

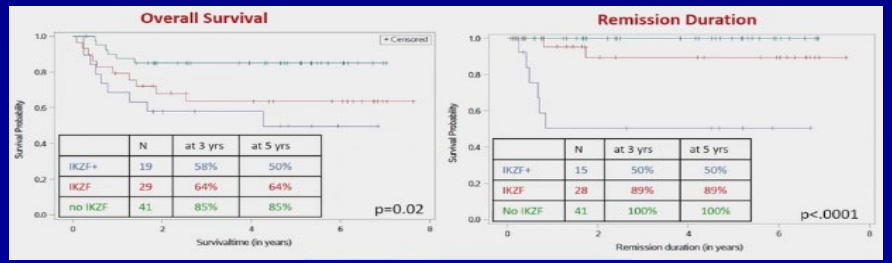
Ph-Positive ALL on GMALL

- 174 pts; median age 42 yr (18-55)
- Imatinib 600 mg/D + LI chemoRx; then alloHSCT 160/174 (92%; 98% of CRs; median time to SCT 4 mo)
- CR 85% post-induction; CR 96% overall
- Molecular CR 9% post-induction, 42% after C3
- 3-yr OS 76%; 3-yr OS post-HSCT 81%; Rx mortality 16%

	after Induction I	pre Consolidation I	after Consolidation I
Evaluable cytology	165	**174**	174
CR/CRu	**85%**	**96%**	**94%**
PR	9%	2%	0%
Failure	4%	1%	2%
Early Death	**1%**	**1%**	**3%****

	After Induction I		Pre Consolidation I		After Consolidation I	
MRD Total	174		150		144	
MRD Evaluable	139	(80 %)	150	(87%)	144	(87%)
Mol CR	9 %		24 %		42%	
Mol Fail	81%		58%		38%	
$\geq 10^{-2}$					17%	
$<10^{-2} \geq 10^{-3}$					41%	
$<10^{-3} \geq 10^{-4}$					43%	
Mol IMR	25%		18%		21 %	

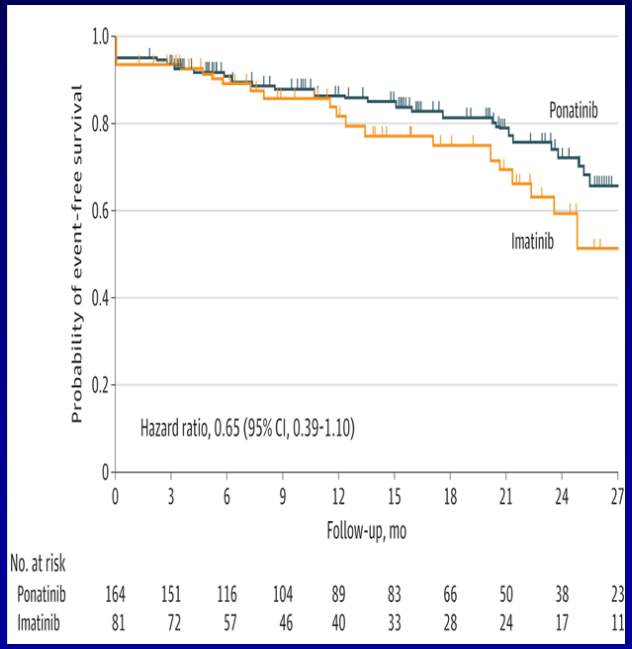


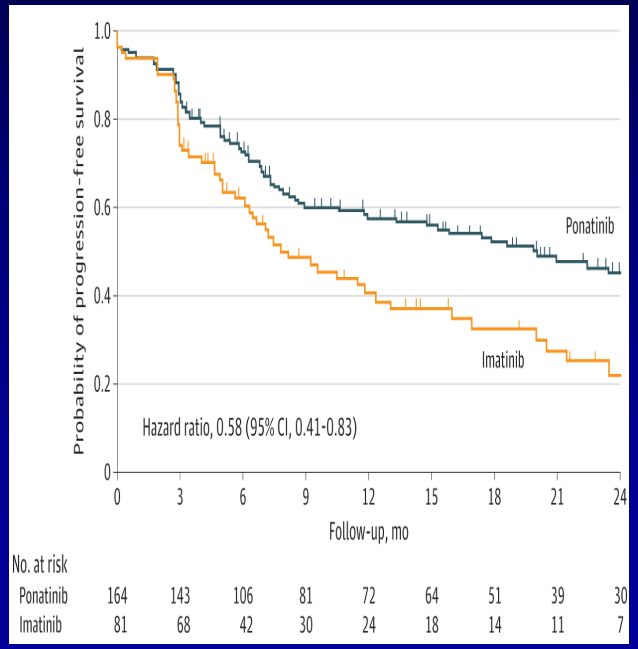


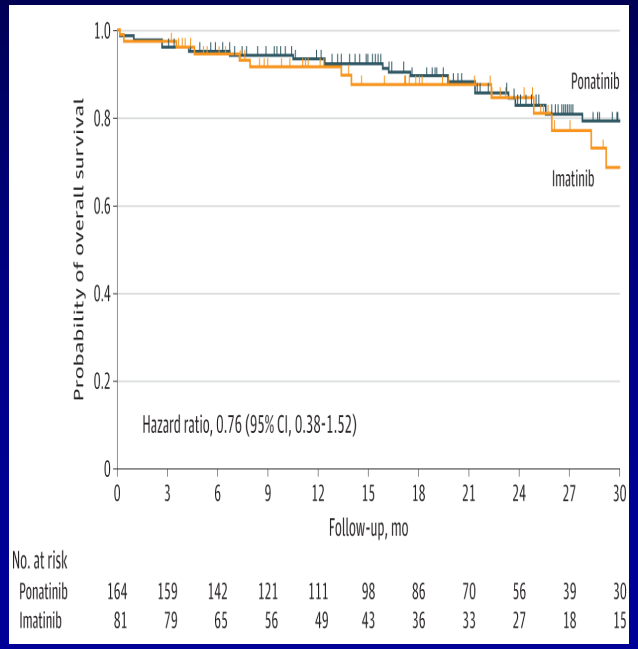
Pfeifer H, et al. *Blood*. 2024;144:840.

Ponatinib vs Imatinib in Newly Dx Ph-Positive ALL: PhALLCON Phase III Trial

- 245 pts randomized (2:1) to ponatinib 30 mg/D (n = 164) or imatinib (n = 81), both with VCR-Dex for 90 days; then continuation of TKIs and chemoRx
- Primary endpoint MR4 CR at 90 days: 34.4% vs 16.7% (*P* = .002)
- Subsequent ASCT 30% vs 37%

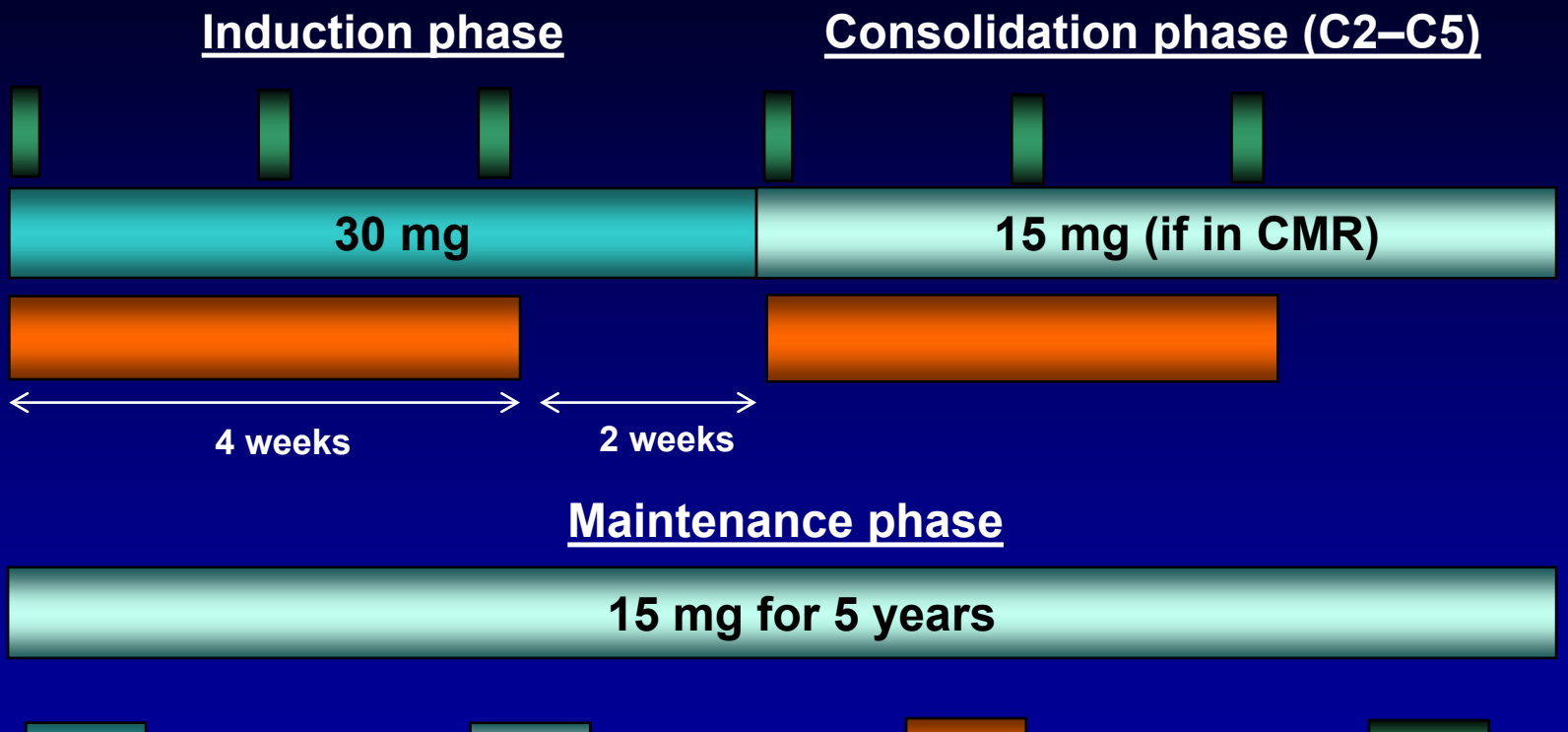






Jabbour E, et al. *JAMA*. 2024;331:1814-1823.

Ponatinib + Blinatumomab in Ph-Positive ALL: Regimen

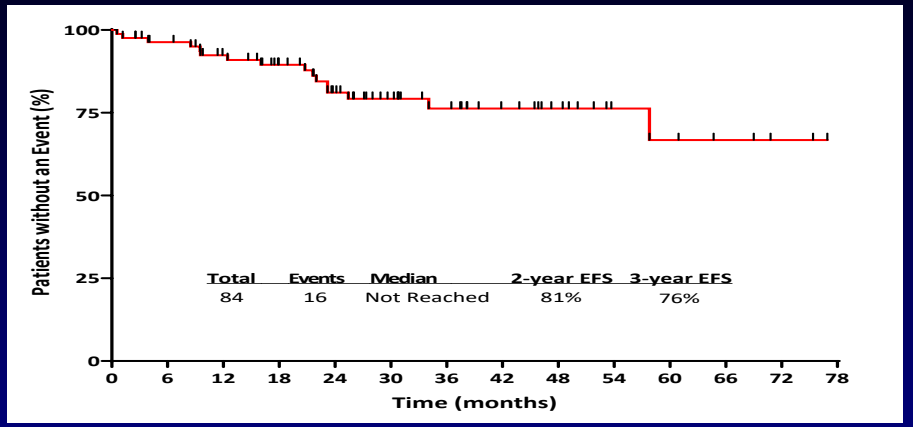


Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

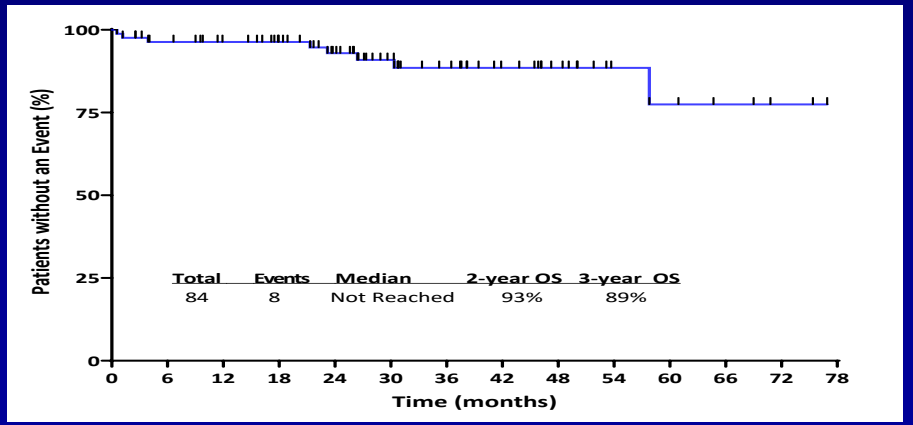
- 84 pts Rx with simultaneous ponatinib 30–15 mg/D and blinatumomab × 5 courses; 12–15 ITs. Median F/U 29 mo
- Only 2 pts had SCT (2%)
- Median F/U 29 mo; 3-yr EFS 76%, OS 89%
- 10 relapses (9 p190): 5 CNS, 4 BM, 1 *CRLF2*+ (Ph–); 3-yr cumulative relapse 12%

Parameter	%
CR-CRi	97
CMR	78
NGS-MRD negative	95
3-yr OS	89

Event-free survival

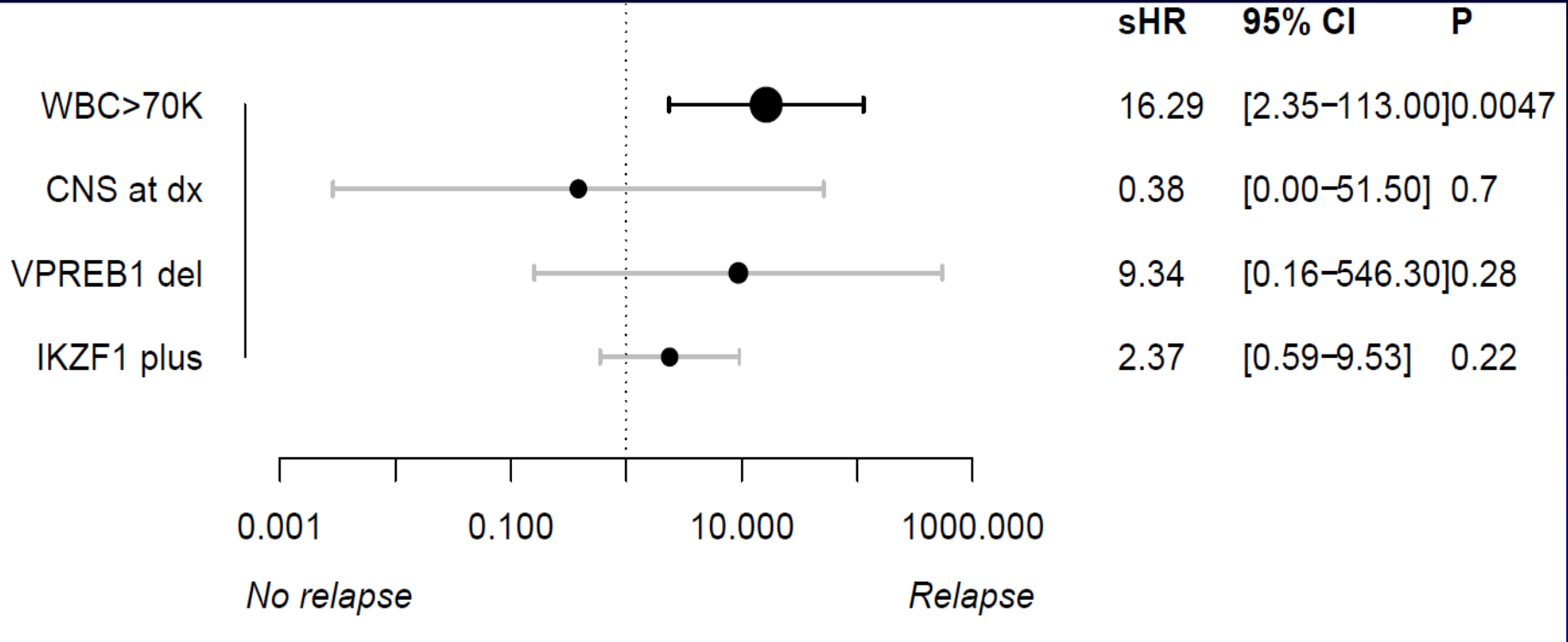


Overall survival



Jabbour E, et al. *Lancet Haematol*. 2023;10:e24-e34;
Kantarjian H, et al. *J Clin Oncol*. 2024;42:4246-4251.

Ponatinib + Blinatumomab in Ph-Positive ALL: MVA for Relapse Risk



MVA: WBC >70K at Dx was only factor independently predictive of relapse

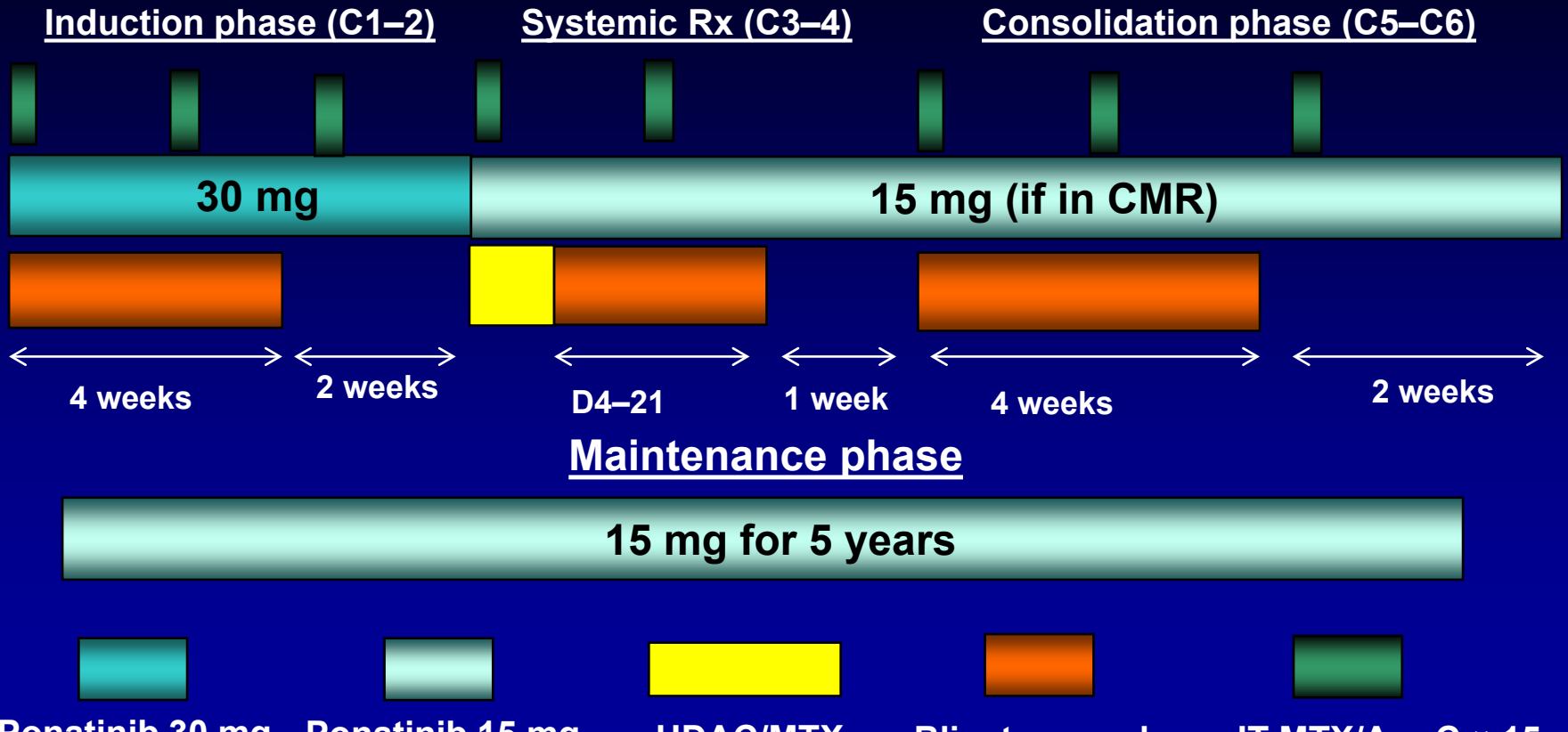
Short N, et al. *Blood.* 2024;144:837.

Ponatinib vs Dasatinib + Blinatumomab in Ph-Positive ALL

Parameter	Pona + Blina (n = 84; 5 blina)	Dasa + Blina (n = 63; 2+ blina)	Dasa + Blina (n = 24; 3 blina)	Pona + Blina (n = 133; 2-5 blina)
Median age, yr	50	54	73	57
PCR neg, % NGS clonoSEQ neg, %	78 95	93 (+ PNQ)	63	73
4-yr OS, %	89	82	75	18-mo OS 92%
AlloSCT, %	2	48	5	12
Relapses (CNS)	10 (5)	9 (4)	8 [3 T315I]	4 (1)

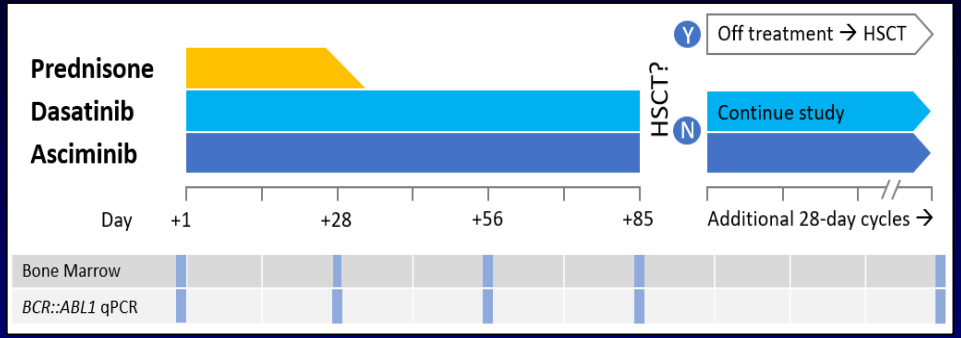
Kantarjian H, et al. *J Clin Oncol*. 2024;42:4246-4251; Foà R, et al. *J Clin Oncol*. 2024;42:881-885; Advani A, et al. *Blood*. 2023;142:1499; Chiaretti S, et al. *Blood*. 2024;144:835.

Ponatinib + Blinatumomab in Ph-Positive ALL: Regimen (WBC ≥70K)



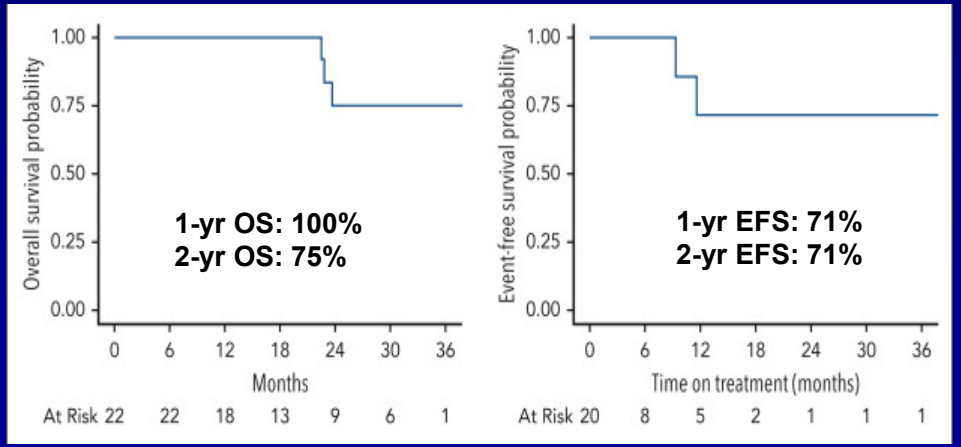
Asciminib + Dasatinib, Prednisone in Ph-Positive ALL and CML-LBP

- 25 pts: 23 Ph+ ALL (73% P190), 2 CML-LBP
- Median age 65 yr (33-85); *IKZF1*^{del} (41%)
- Median F/U 27 mo
- Dasatinib 140 mg/D; prednisone 60 mg/D × 24 ASCi 40–160 mg/D (80 mg RP2D; 14 pts); 8 IT
- 3 of 4 pts Rx ASCi 160 mg/D had amylase and lipase increase meeting DLT (no pancreatitis)
- 8 (36%) alloSCT
- 4 (17%) relapse (1 MRD; 1/3 *T315I*) within 6 mo (range, 4–40)



De Novo ALL Response (n = 22)			
	1 month	2 months	3 months
CR	95%	100%	100%
MRD-neg, flow cytometry (<10^{-4})	65%	89%	89%
Cytogenetic CR	82%	94%	100%
BCR::ABL1 RT-PCR			
MR 1	90%	94%	100%
MR 2	50%	82%	95%
MR 3	25%	41%	74%
MR 4	15%	18%	26%

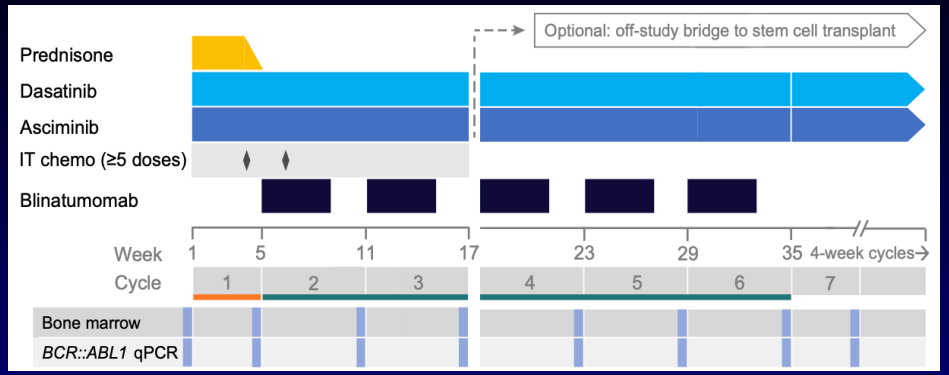
Outcomes



Luskin MR, et al. *Blood.* 2025;145:577-589.

Dasatinib + Asciminib + Blinatumomab in Ph-Positive ALL

- 15 pts: 13 ALL, 2 CML-LBP (73% P190)
- Median age 62 yr (25–83); *IKZF1*^{del} (33%)
- Median F/U 1 yr
- Dasatinib 140 mg/D; prednisone 60 mg/m^2 D × 24; ASCi 80 mg/D; Blina from M2 for 5 C; IT ≥5
- 5 (36%) alloSCT
- **No relapse; 1 died in CR D+119 (81 yr)**

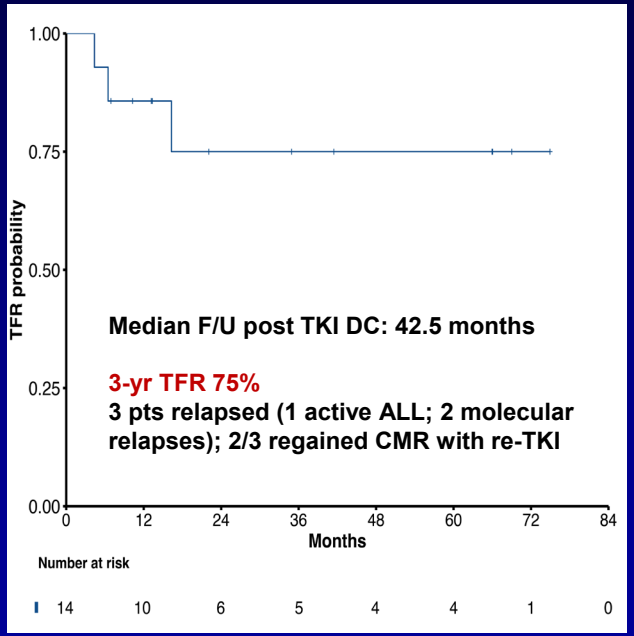


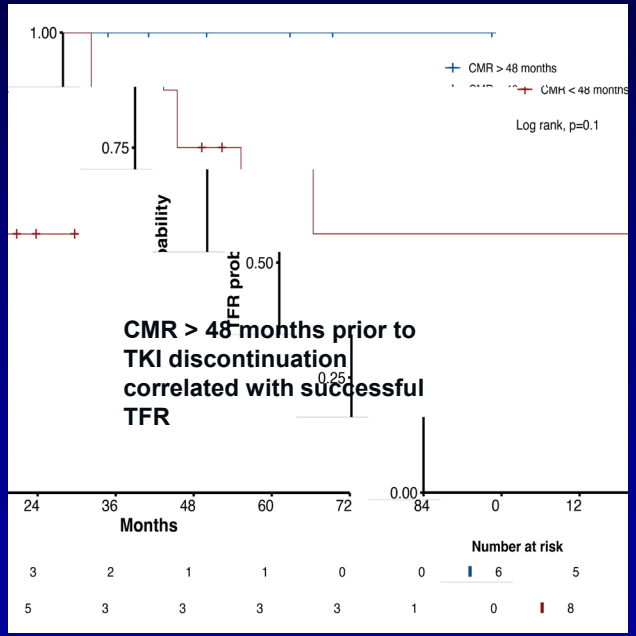
	Induction (asciminib, dasatinib, prednisone)	Blinatumomab Cycle 1 (asciminib, dasatinib, blinatumomab)	Blinatumomab Cycle 2 (asciminib, dasatinib, blinatumomab)
Hematologic CR	**100%** (15/15)	**100%** (15/15)	**100%** (14/14)
Cytogenetic CR	**86%** (12/14)	**100%** (15/15)	**100%** (14/14)
Flow MRD negativity (<10^{-4})	**79%** (11/14)	**100%** (15/15)	**100%** (14/14)
BCR::ABL1 MRD response			
MR1	**87%** (13/15)	**100%** (15/15)	**100%** (14/14)
MR2	**60%** (9/15)	**93%** (14/15)	**93%** (13/14)
MR3	**20%** (3/15)	**53%** (8/15)	**71%** (10/14)
MR4	**7%** (1/15)	**40%** (5/15)	**50%** (7/14)
MR4.5	**7%** (1/15)	**40%** (5/15)	**36%** (5/14)
Not detected	**0%** (0/15)	**13%** (2/15)	**21%** (3/14)
IGH NGS response*			
<10^{-4}	**67%** (6/9)	**92%** (12/13)	**100%** (13/13)
<10^{-6} (0 to <1 transcripts)	**33%** (3/9)	**77%** (10/13)	**85%** (11/13)

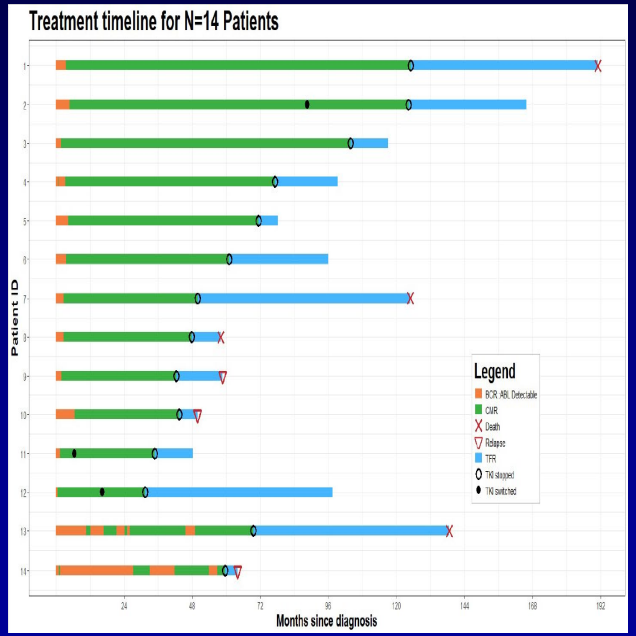
Luskin MR, et al. *J Clin Oncol*. 2025;43:6509.

TKI DC/TFR in Ph+ ALL Without AlloHSCT

- 14/238 pts (6%); median age 61 yr, median time on TKI 60 mo (31–125), median time in CMR 46 mo (2.7–121)
- Rx HCVAD + added TKI: Ima 2, dasa 6, pona 4, blina-pona 2
- Reason for TKI DC: pleural effusions 4, AOE/VOE 4, pulmonary hypertension 2, pancreatitis 1, cytopenia 1, other 2
- 11 pts (79%) remained in TFR; none of 8 in CMR 4+ yr prior to TKI DC had relapse

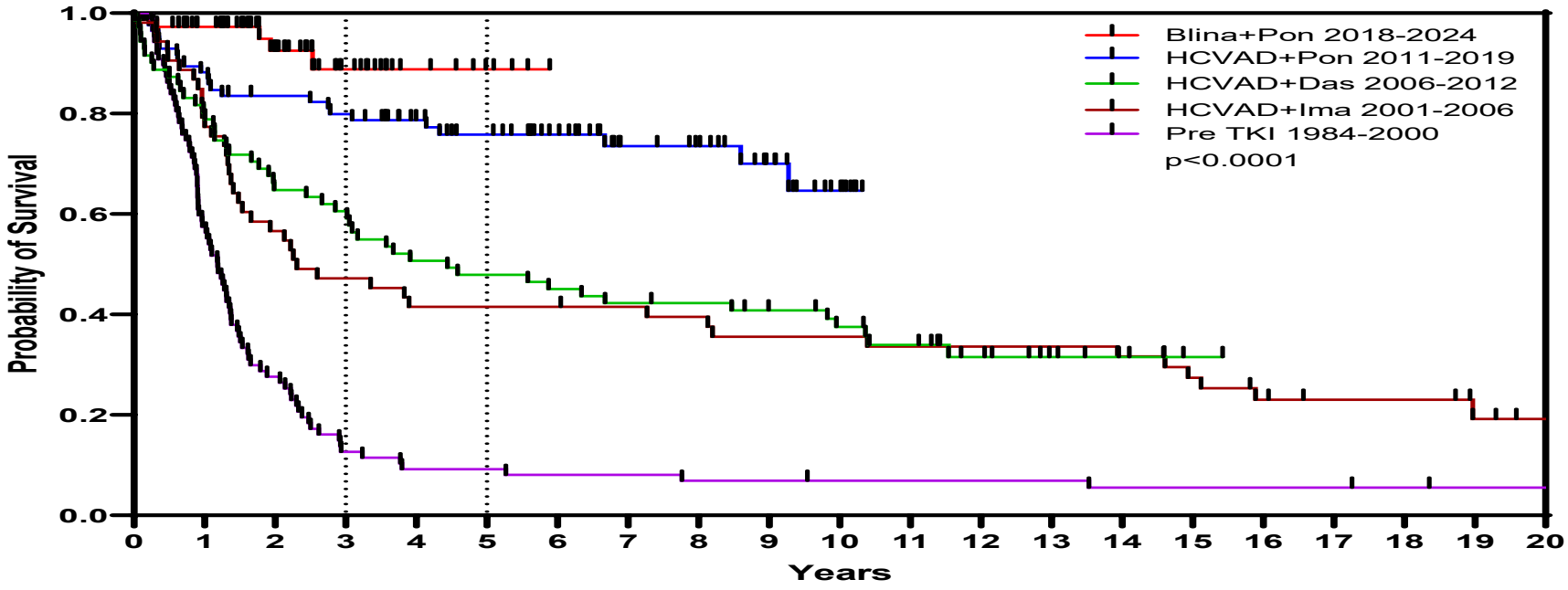






Kugler E, et al. *Cancer.* 2025;131:e35773.

ALL: Survival by Decade (MDACC 1984–2024)

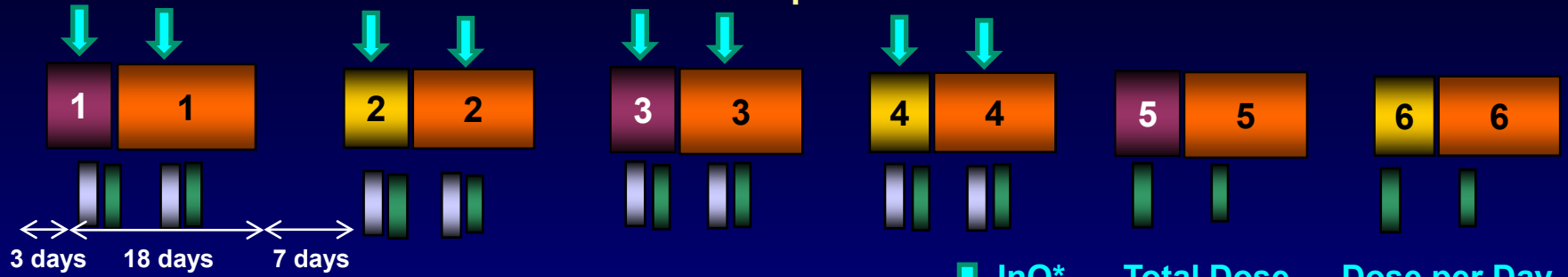


	Total	Events	3yr OS	5yr OS	Median
Blina+Pon 2018-2024	76	5	89%	89%	Not reached
HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
Pre TKI 1984-2000	87	83	13%	9%	14 mos

p<0.0001

Dose-Dense Mini-HCVD + InO + Blina + CAR T Cells in ALL: The CURE

Induction phase: C1–C6



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.

Consolidation phase

CAR T consolidation

Mini–Hyper-CVD

Mini-MTX–Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

ALL 2025 and Beyond: Conclusions

- Significant improvements across all ALL categories
- Future of ALL Rx
  - Less chemotherapy and shorter durations
  - Combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22, CD79
  - SQ blinatumomab
  - CAR Ts CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT

Thank You

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Global Leukemia Academy

AYA patients with ALL:
What is the current treatment approach for this diverse patient population?

Special considerations for adolescents and young adults and how we can use this experience in adult patients

Nicolas Boissel

APTITUDE HEALTH®

Global Leukemia Academy

September 18, 2025

Adolescents and Young Adults With Acute Lymphoblastic Leukemia

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Institut de Recherche Saint-Louis, Université Paris Cité, Paris, France

Group for Research in Acute Lymphoblastic Leukemia

GRAALL
LALA GOELAMS SAKK

Hôpital Saint-Louis AP-HP

INSTITUT DE RECHERCHE SAINT-LOUIS
Hématologie I Immunologie I Oncologie

Université Paris Cité

INSTITUT CARNOT OPALE

Disclosures

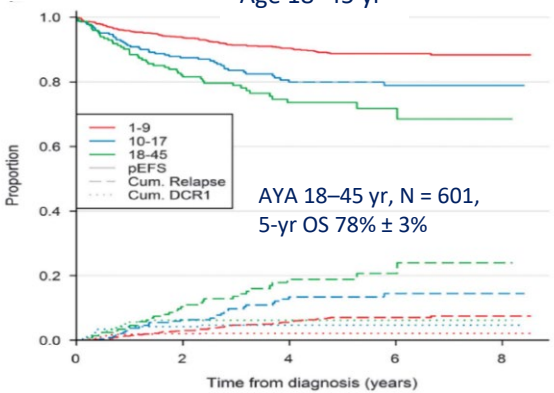
Honoraria (consulting, advisory role)	Amgen Autolus Jazz Pharma Gilead Incyte	medac Novartis Pfizer Sanofi Servier
Research funding	Amgen Incyte	Jazz Pharma Novartis

Intensified strategies in AYA

Pediatric and pediatric-inspired protocols

NOPHO-2008[1]
(children and AYA)

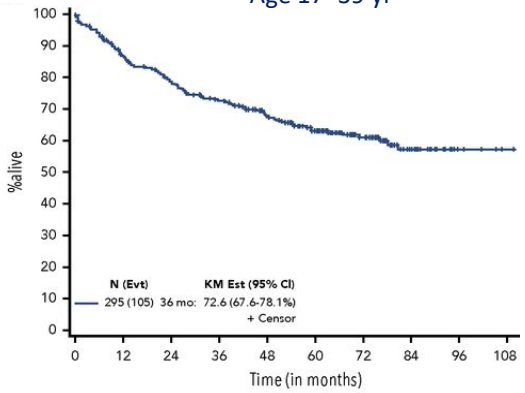
Age 18–45 yr



HSCT: 20% (18–45 yr)

CALGB 10403[2]
(AYA)

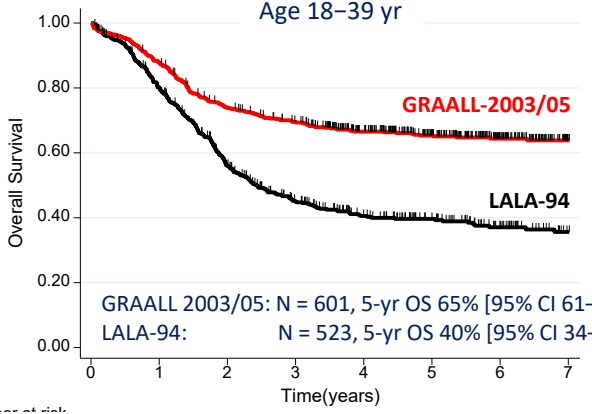
Age 17–39 yr



HSCT: 8%

GRAALL-2003/05[3,4]
(AYA)

Age 18–39 yr



HSCT (GRAALL): 31%

- More intensive trials improve the outcome of AYA
- Early MRD response is the most robust prognostic factor
- Disparities in HSCT eligibility criteria persist

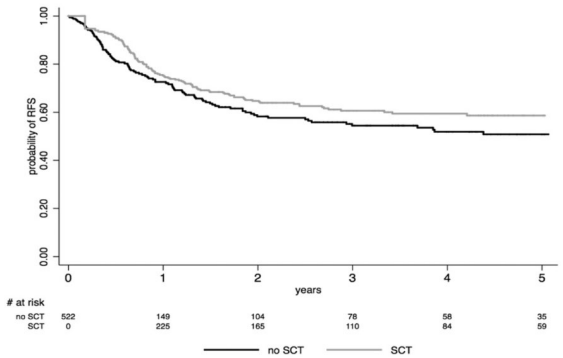
1. Toft N, et al. *Leukemia*. 2018;32:606-615; 2. Stock W, et al. *Blood*. 2019;133:1548-1559;
3. Updated from Huguet F, et al. *J Clin Oncol*. 2009;27:911-918; 4. Updated from Huguet F, et al. *J Clin Oncol*. 2018;20;36:2514-2523.

GRAALL-2003/05
Which alloHSCT indications?

Historical VHR factors (alloHSCT)

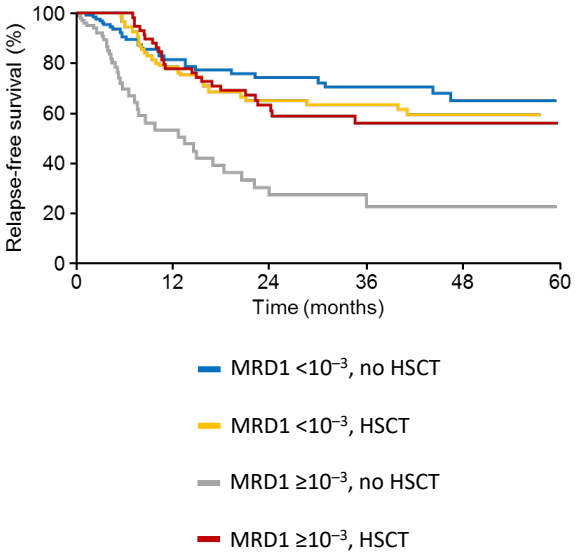
- **Baseline**
  - **WBC ≥30 × 10^9/L for B-lineage ALL**
  - **CNS disease**
  - **Immature CD10-negative B-lineage ALL***
  - **t(4;11) and/or *KMT2A::AF4*, t(1;19) and/or *TCF3::PBX1***
  - **Low hypodiploidy, near triploidy**
  - **Complex karyotype (≥5 abnormalities)***
- **Early response**
  - **No hematologic CR after the first induction course**
  - **Slow PDN response at the end of pre-phase**
  - **Slow BM blast clearance at day 8 of chemotherapy**
  - ***IG/TR MRD ≥10^{-2} after induction†***

Relapse-free survival
Simon-Makuch plots



In patients with VHR-ALL, as defined by historical risk factors

Relapse-free survival
Simon-Makuch plots
According to EOI MRD (10^{-3})

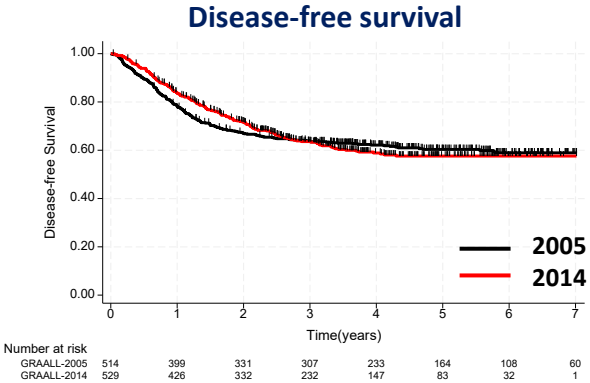


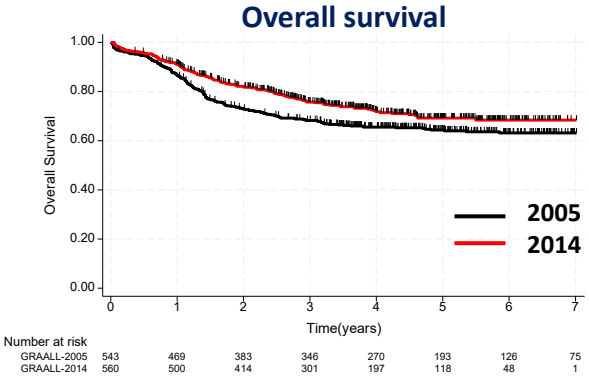
*Introduced in GRAALL-2005.
†In GRAALL-2003 only (1 single patient classified as high-risk due to MRD only).
ASCT, allogeneic stem cell transplant; BM, bone marrow; CNS, central nervous system; CR, complete response; IG, immunoglobulin; MRD, minimal residual disease; TR, T-cell receptor; WBC, white blood cell count.

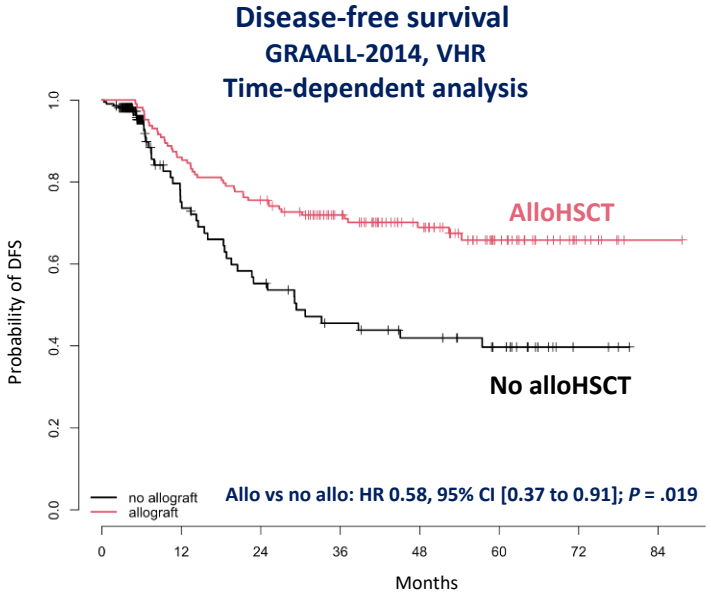
Dhédin N, et al. *Blood*. 2015;125:2486-2496.

GRAALL-2005 to 2014

MRD-oriented alloHSCT





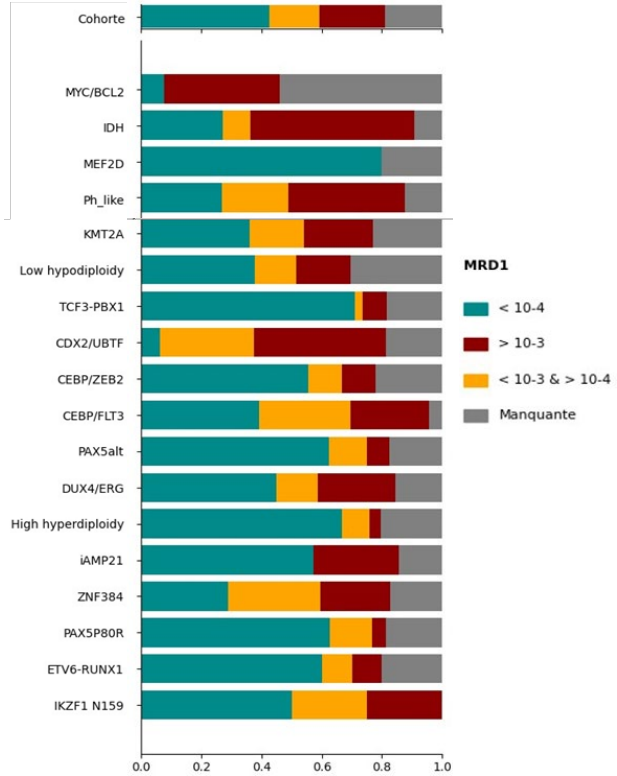


- MRD-oriented alloSCT indications reduced from 40% to 18% the rate of CR patients transplanted (VHR)
- This reduction was safe in terms of DFS and OS
- VHR patients benefited from alloSCT

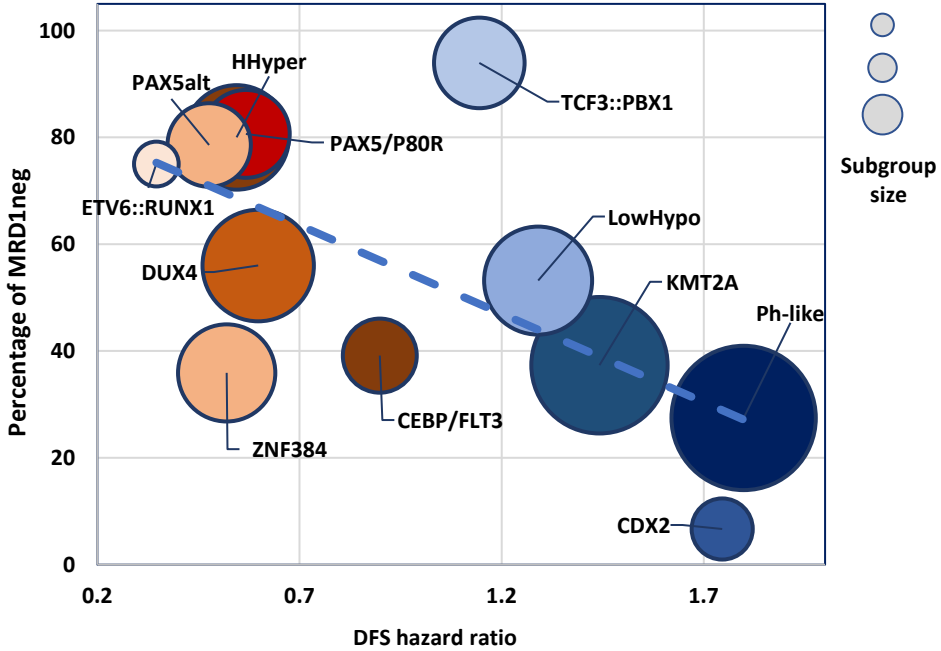
Boissel N, et al. ASH 2022. Abstract 2683;
Boissel N. Personal communication.

B-ALL oncogenetics and MRD

EOI MRD by oncogenic subgroup
GRAALL-2014



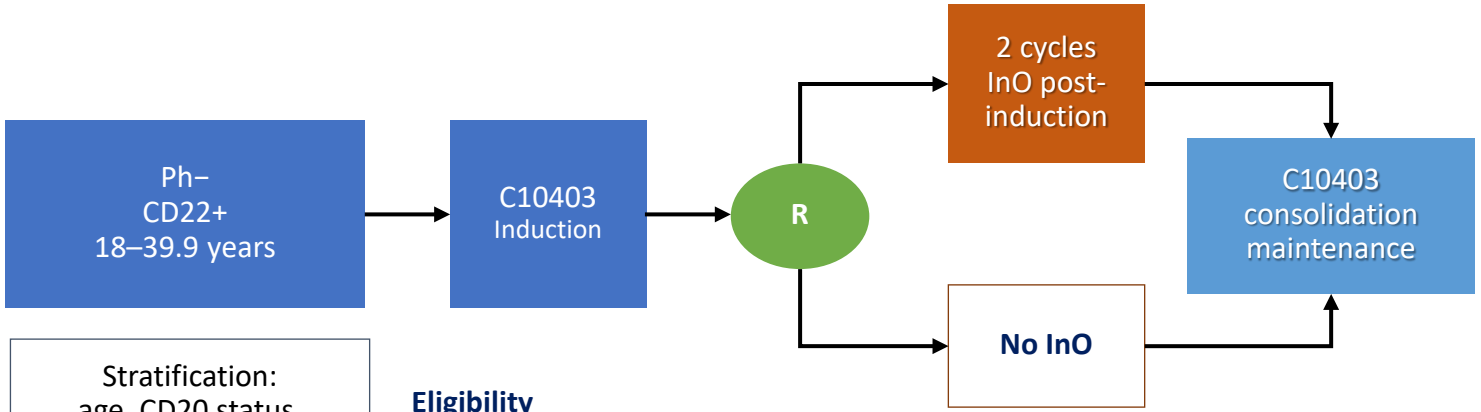
Correlation between EOI MRD response and impact on DFS (GRAALL-2014)



GRAALL, unpublished results. E. Clappier lab.

Alliance A041501 Phase III

Early consolidation with inotuzumab



Stratification:
age, CD20 status,
LDA card (Ph-like
signature)

Primary endpoint:
3-year EFS

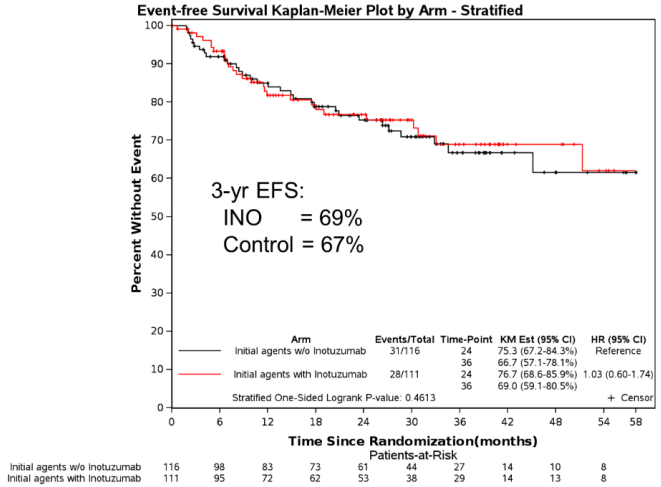
Eligibility

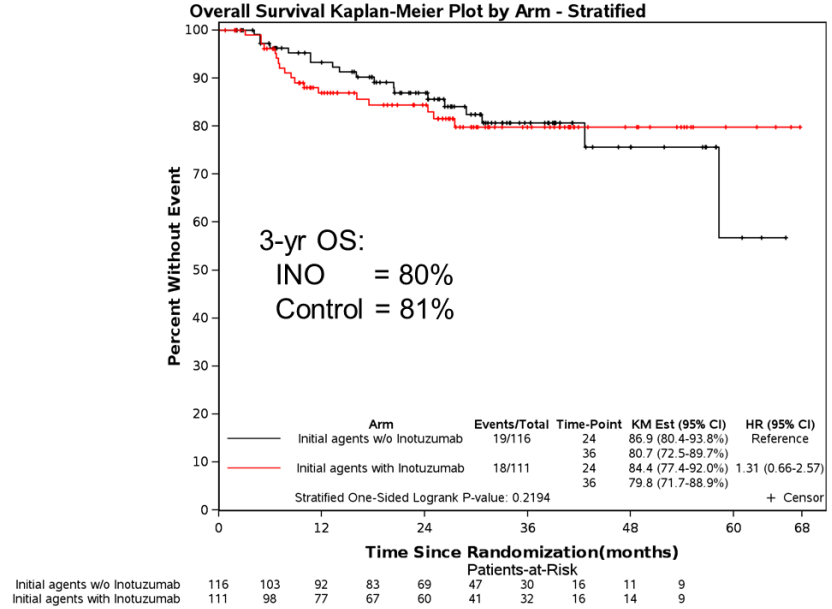
- Previously untreated B-cell ALL
- Patients aged 18–39.9 years
- Presence of surface CD22+ lymphoblasts
- Philadelphia-negative cytogenetics
- **Initial run-in safety phase in 6–12 patients before randomized trial opens**

Trial halted by DSMB due to late infectious deaths on InO arm during neutropenia in Course III and mostly Course IV.

DeAngelo DJ, et al. ASH 2024. Abstract 308.

Alliance A041501 Phase III
Outcomes





	Chemo (n = 116)	InO (n = 111)	Total (N = 227)
Event, n (%)			
Censor	85 (73.3%)	82 (73.9%)	167 (73.6%)
Death	4 (3.4%)	14 (12.6%)	18 (7.9%)
Progression	27 (23.3%)	15 (13.5%)	42 (18.5%)

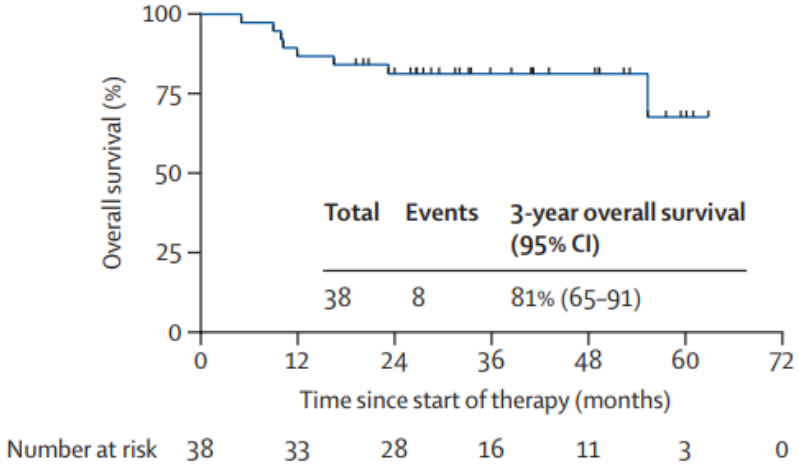
DeAngelo DJ, et al. ASH 2024. Abstract 308.

Blinatumomab frontline

Consolidation phase II

MDACC[1]

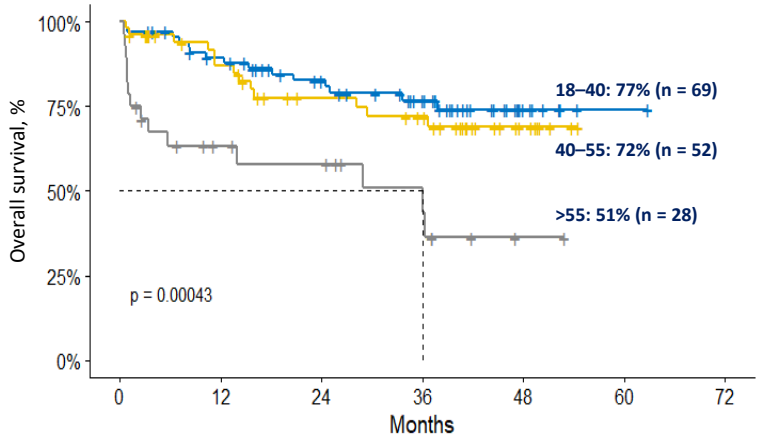
HyperCVAD + blinatumomab
N = 38, 17–59 yr



Grade 3+ neurotoxicity: 11%

GIMEMA LAL2317[2]

Blinatumomab in consolidation
N = 149, 18–65 yr



Grade 3+ neurotoxicity: 15.5%

1. Jabbour E, et al. *Lancet Haematol.* 2022;9:e878-e885; 2. Bassan R, et al. *Blood*. 2025;145:2447-2459.

Blinatumomab frontline

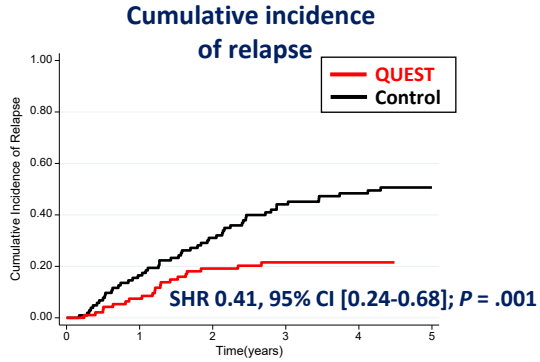
GRAALL-QUEST for Ph– HR patients

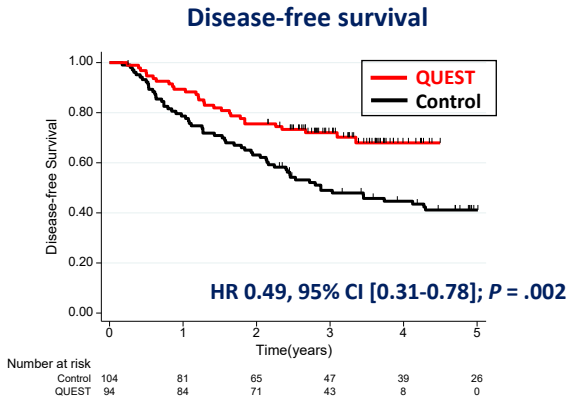
HR definition

- End of induction MRD ≥10^{-4}
- *KMT2A*r
- *IKZF1*del

	QUEST N = 94	Control* N = 104	*P*
MRD3 undetectable	62/86 (72%)	42/79 (53%)	.02
MRD3 und. if MRD2 ≥10^{-4}	23/41 (56%)	4/29 (14%)	<.001
Median follow-up (yr)	3.5	5.5	<.001
AlloHSCT rate	44 (47%)	38 (37%)	.15
4-yr CIR (95% CI)	22% (14-31)	48% (39-59)	.001
4-yr DFS (95% CI)	70% (59-78)	45% (35-54)	.002
4-yr OS (95% CI)	78% (67-86)	67% (57-75)	.09

*Patients included in the GRAALL-2014/B study with same HR criteria but not exposed to blinatumomab.



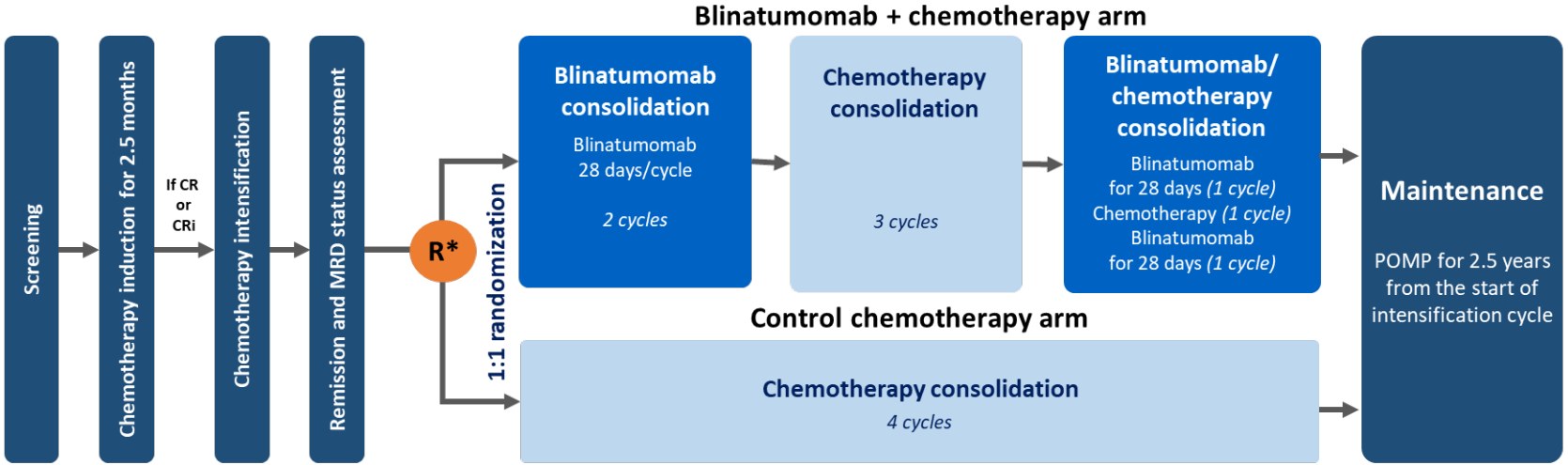


- The rate of complete MRD3 response was significantly higher after blinatumomab
- Blinatumomab was associated with a significantly lower CIR and improved DFS

Boissel N, et al. ASH 2022. Abstract 1232.

ECOG-ACRIN E1910 (phase III)

Blinatumomab as consolidation for newly diagnosed adult B-ALL



Key eligibility criteria

- Newly diagnosed Ph-negative B-ALL
- Age 30–70 years
- ECOG PS ≤3

Stratification

- Age </> 55
- CD20 status
- Rituximab
- HSCT intent
- MRD

Study endpoints

- **Primary:** OS among MRD-negative patients
- **Secondary:** RFS, MRD status, AEs

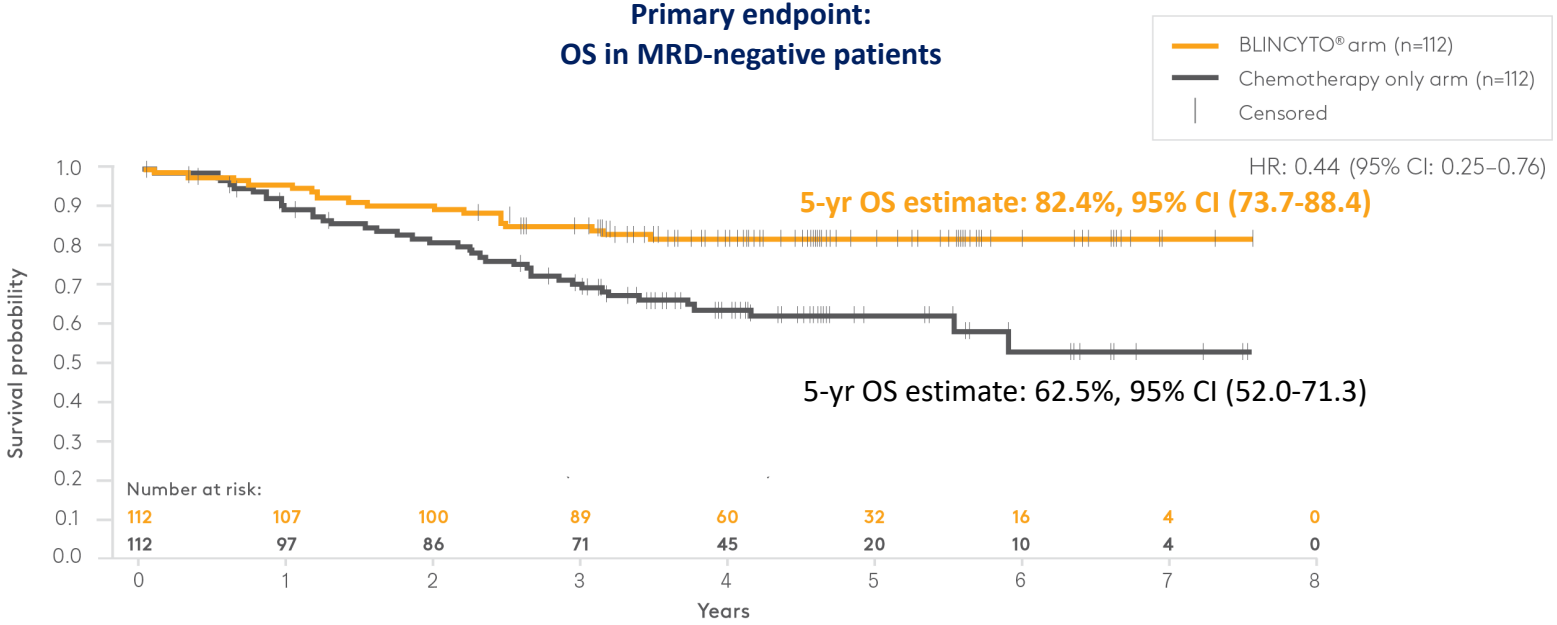
***Following FDA approval of blinatumomab for MRD+ disease in March 2018, patients who were MRD+ after intensification were assigned to the blinatumomab + chemotherapy arm of the study and no longer randomized.**

Litzow MR, et al. *N Engl J Med*. 2024;391:320-333.

ECOG-ACRIN E1910 (phase III)

Overall survival

Primary endpoint:
OS in MRD-negative patients



Median follow-up time: **4.5 years**

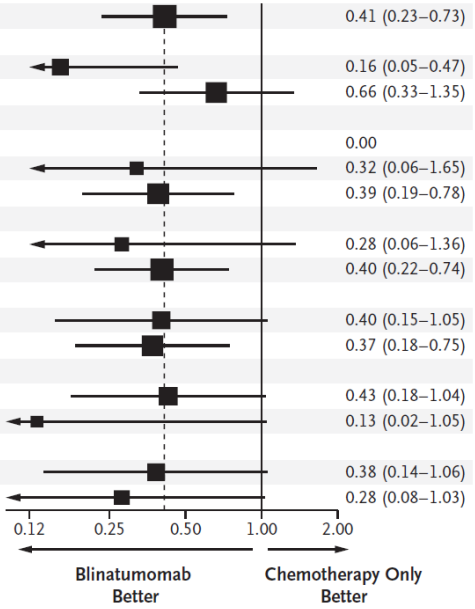
Blinatumomab associated with a 56% reduced risk of death vs chemotherapy alone

Amgen. Data on file; 2024.

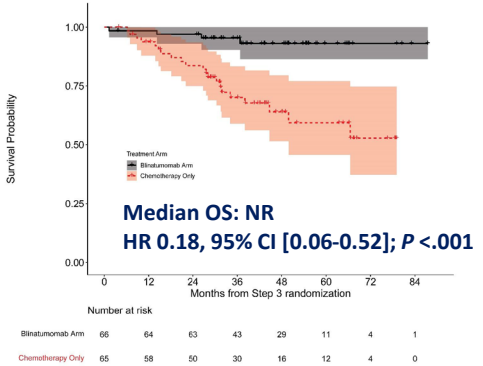
ECOG-ACRIN E1910

Subgroup analysis

Subgroup	Blinatumomab	Chemotherapy Only
	no. of deaths/total no.	
All MRD-negative patients	17/112	40/112
Age		
<55 yr	4/66	21/65
≥55 yr	13/46	19/47
Combined molecular risk		
Favorable	0/19	6/28
Intermediate	2/22	5/19
Unfavorable	12/50	24/45
BCR::ABL1–like genotype		
BCR::ABL1–like	2/16	7/15
Not *BCR::ABL1*–like	15/96	33/97
Transplantation intended		
Yes	6/36	13/35
No	11/76	27/77
CD20 status		
Positive	7/45	16/46
Negative	1/26	7/26
Rituximab use		
Yes	5/33	14/36
No	3/38	9/36

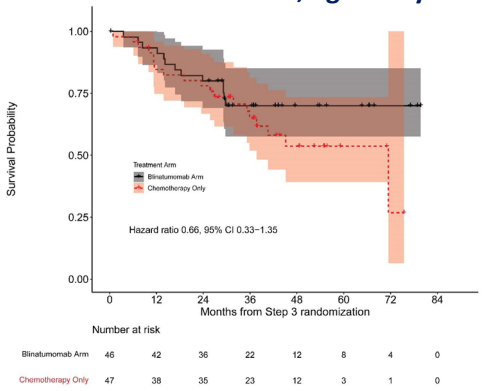


OS in MRD–, age 30-55 yr



Median OS: NR
HR 0.18, 95% CI [0.06-0.52]; *P* <.001

OS in MRD–, age 55+ yr

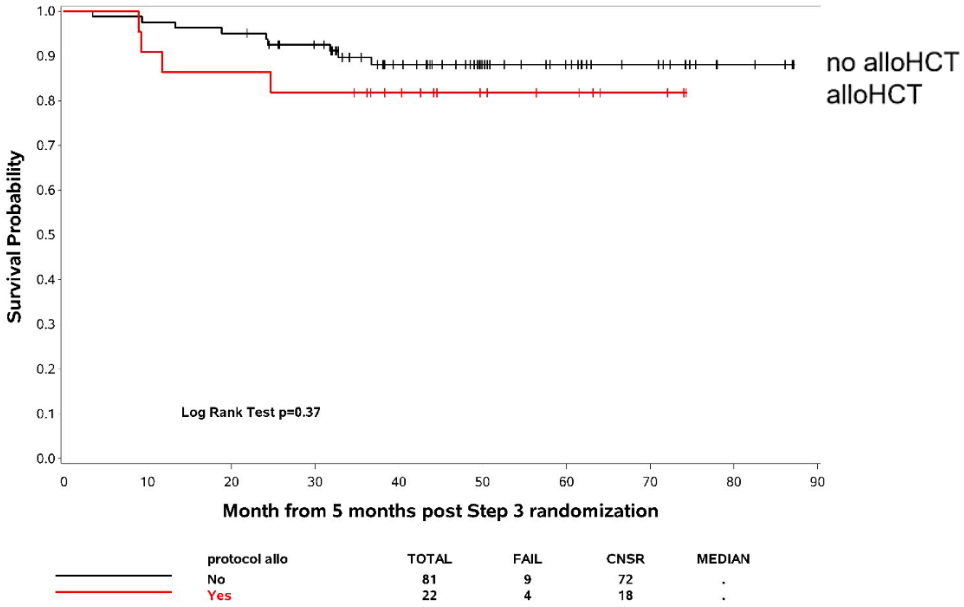


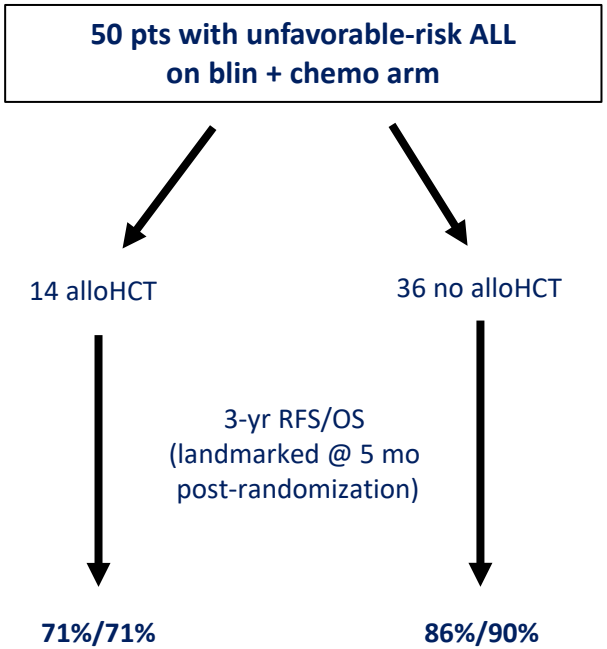
Litzow MR, et al. *N Engl J Med*. 2024;391:320-333.

ECOG-ACRIN E1910

No benefit of alloHSCT

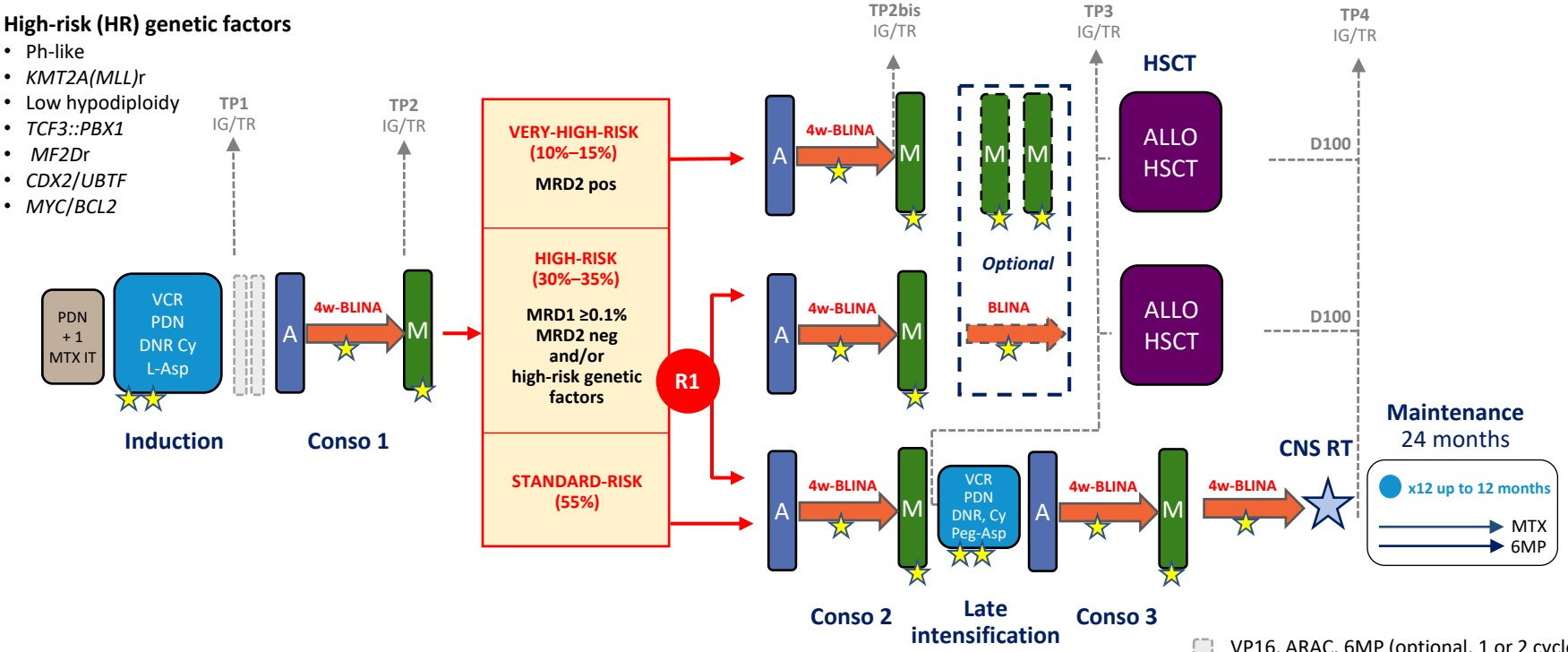
Overall survival by alloHSCT
Blin + chemo arm
Landmark @ 5 mo





Liedtke M, et al. ASH 2024. Abstract 779.

GRAALL-2024 Ph– B-ALL



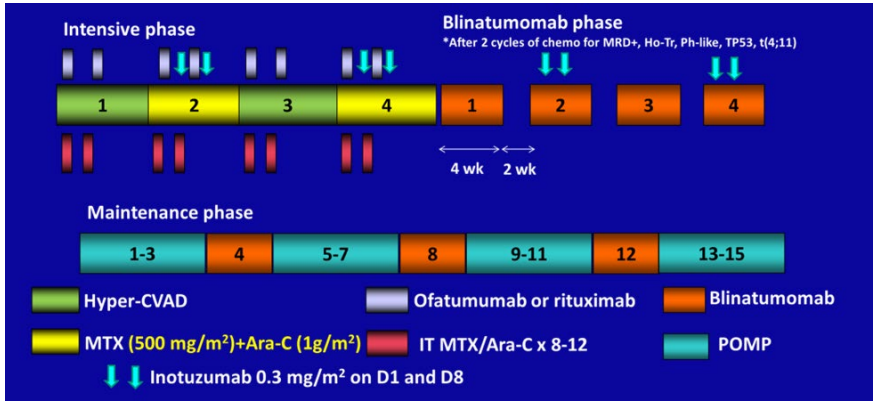
PDN, PO prednisone; DXM, dexamethasone; VCR, vincristine; DNR, daunorubicin; IDA, idarubicin; ARAC, cytarabine; L-Aspa, recombinant L-asparaginase; Peg-Aspa, Peg-asparaginase; MTX, methotrexate; Cy, cyclophosphamide; 6MP, 6-mercaptopurine; IT, intrathecal; HD, high-dose triple IT, MTX/ARAC/steroids ☆ (prophylaxis only), CNS RT, CNS radiotherapy (prophylactic/curative).

HyperCVAD + blinatumomab ± inotuzumab

Ph– ALL

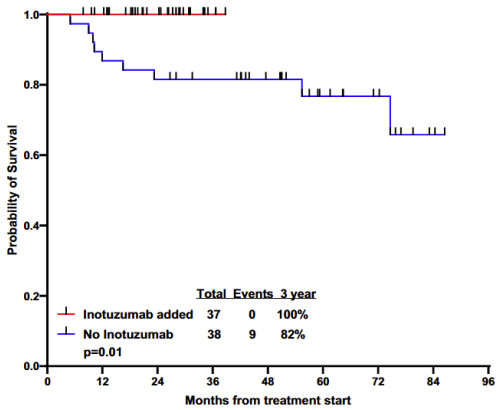
Treatment schedule (cohort 2, N = 37)

Median age 25 yr, range 18–57

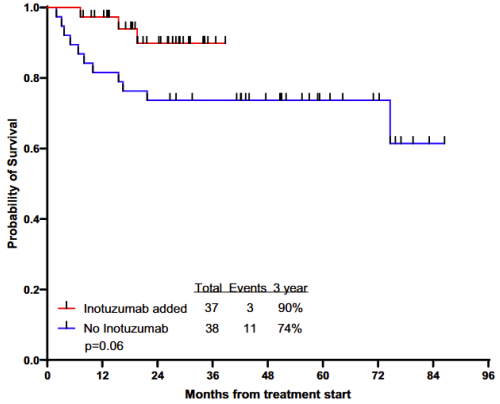


10 alloHSCT

Overall survival



Relapse-free survival



No SOS after InO

Kantarjian H, et al. *Am J Hematol*. 2025;100:402-407.

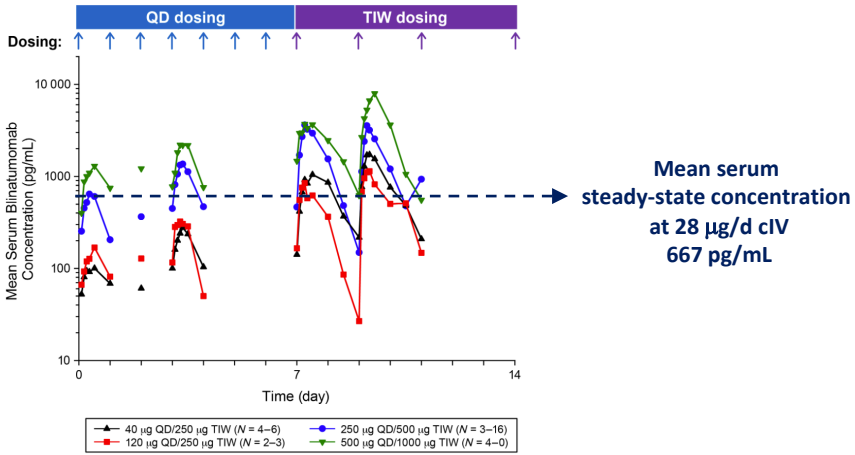
Blinatumomab SC

Phase I/II in R/R B-ALL

- R/R B-ALL
- Week 1 QD, week 2-4 TIW
- 2 dosing schedules: 250/500 and 500/1000µg

Pharmacokinetics

Half-life: 8-12h vs 2h for cIV



Mean serum steady-state concentration at 28 µg/d cIV 667 pg/mL

Response

Outcome	250 µg/500 µg (n = 36)	500 µg/1000 µg (n = 52)
Complete remission (CR)	69%	60%
CR + CRh	75%	79%
MRD-negative CR/CRh ($<10^{-4}$)	67%	73%
CR + CRh + CRi	89%	92%
MRD-negative CR/CRh/CRi ($<10^{-4}$)	81%	83%

Safety

	250-µg/500-µg group (n = 36)				500-µg/1000-µg group (n = 52)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
ICANS	17%	14%	3%	0	25%	15%	2%	0
CRS	72%	17%	0	0	73%	21%	2%	0

Jabbour E, et al. *Lancet Haematol*. 2025;12:e529-e541.

Conclusion

- **Blinatumomab used in consolidation** improves outcomes, independent of prior MRD status
- **Inotuzumab + low-intensity chemotherapy** is effective in patients with Ph– B-ALL who are unfit for intensive regimens
- The optimal integration of **inotuzumab with intensive chemotherapy** remains to be determined
- **The role of alloHSCT after blinatumomab** (± TKI) in first CR is still unresolved
- Future directions include combining immunotherapy (± TKI) with de-escalated chemotherapy and refined transplant indications

Question 1

In survivors of ALL after allo-HSCT, what is the most frequent cause of late mortality?

A. Secondary cancers
B. Relapse
C. Cardiovascular disease
D. Chronic graft-vs-host disease

Question 2

Which of the following factors is most strongly associated with avascular necrosis in AYA patients with ALL?

A. Cumulative dose of corticosteroids

B. Anthracycline exposure

C. Cranial radiotherapy

D. Age >30 years

Question 3

What proportion of female patients typically develop premature ovarian failure after myeloablative allo-HSCT for ALL?

A. ≤20%

B. 21%–50%

C. 51%–80%

D. >80%

Question 4

Which of the following statements about Ph-like ALL is correct?

A. Ph-like ALL is associated with favorable MRD responses after induction

B. TKI is recommended in ABL-class fusion-positive cases

C. JAK inhibitors are recommended for *CRLF2*-rearranged cases

D. Ph-like is a rare subgroup of Ph– B-ALL in AYA

Question 5

In the ECOG-ACRIN E1910 trial, what was the impact of blinatumomab consolidation compared to chemotherapy?

A. Improved MRD response
B. Improved OS
C. Improved rate of transplant
D. Benefit only in patients over age 55 years

Global Leukemia Academy

BREAK

APTITUDE HEALTH®

Global Leukemia Academy

ALL case-based panel discussion Case 1: Adult high risk

Fabian Lang

APTITUDE HEALTH®

Female patient, 47 years old

- 12/2024 Primary diagnosis: common ALL
  - Initial blood count: leukocytes 53.000/µL; Hb 12,7 g/dL; thrombocytes 285.000/µL
  - Bone marrow: 80% lymphatic blast infiltration
  - Immunology: CD19, CD10, CD34, CD79a, CD22, TdT positive, CD20 negative
  - Cytogenetics: 46 XX t(9;22)(q34;q11)
  - Molecular genetics: *BCR::ABL1* positive, p190
  - No extramedullary disease

- Comorbidities
  - Breast cancer in 10/2016
  - Depression

Treatment course: Female patient, 47 years old

Induction I
GMALL EVOLVE
VCR/Dex
PEG-Asp
MTX i.th.

12/2024

Imatinib 600 mg QD

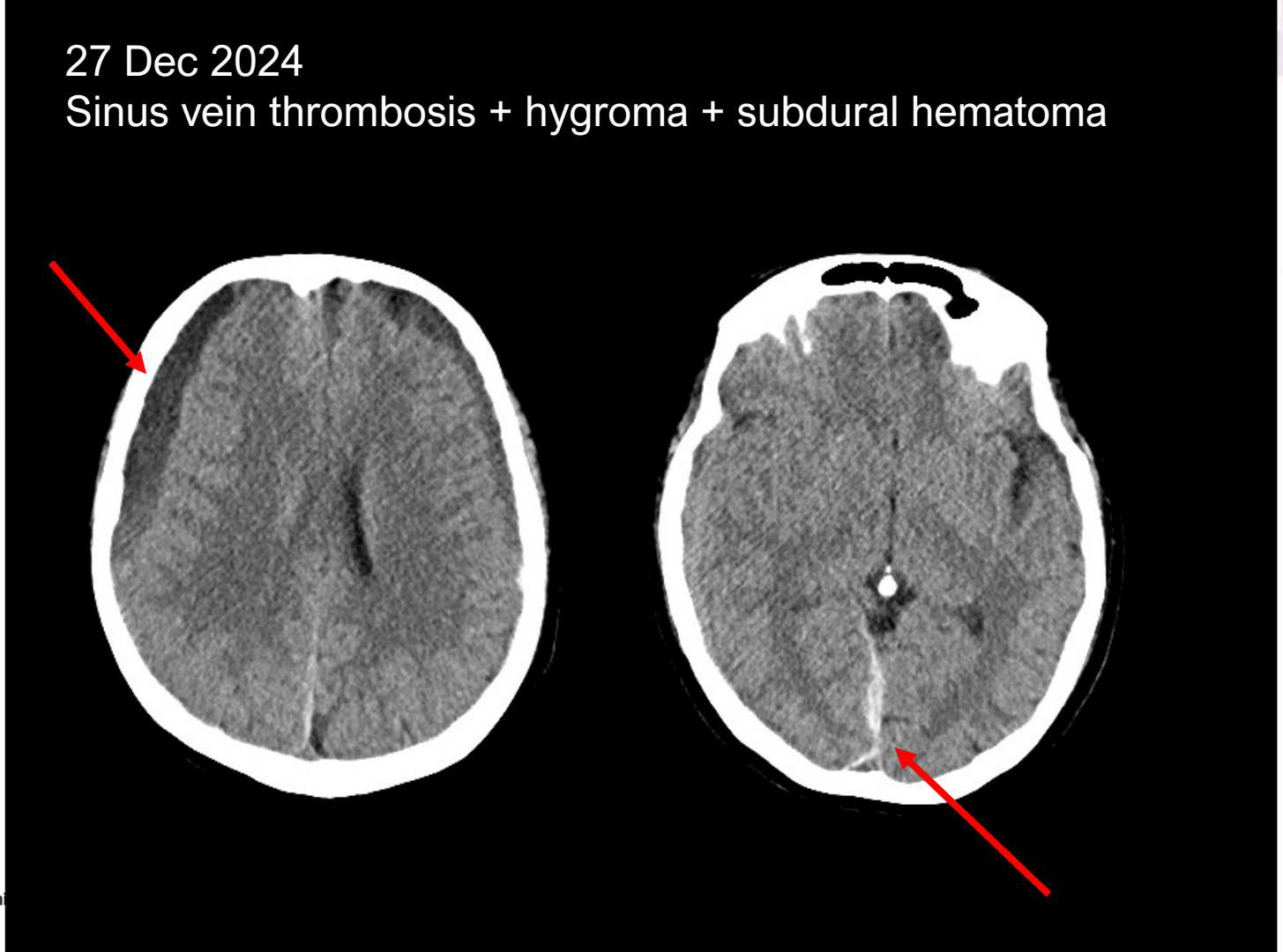
During treatment:
constant nausea

Intermittent headache

Global Leukemia Academy

27 Dec 2024

Sinus vein thrombosis + hygroma + subdural hematoma



Female patient, 47 years old, intrathecal bleeding + thrombosis

Which therapeutic option would you choose?

- Ponatinib 45 mg QD + CTX induction
- Dasatinib 140 mg QD + CTX induction
- Nilotinib 400 mg BID + CTX induction
- Cont. imatinib 600 mg QD + CTX induction

Female patient, 47 years old, intrathecal bleeding + thrombosis

Which therapeutic option would you choose?

- Ponatinib 45 mg QD + CTX induction
- Dasatinib 140 mg QD + CTX induction
- **Nilotinib 400 mg BID + CTX induction**
- Cont. imatinib 600 mg QD + CTX induction

Treatment course: Female patient, 47 years old

Induction I
GMALL EVOLVE
VCR/Dex
PEG-Asp
MTX i.th.

Induction II
GMALL EVOLVE
VCR/Dex
No PEG-Asp
No MTX i.th.

12/2024

01/2025

Imatinib 600 mg QD → Nilotinib 400 mg BID

During treatment: constant nausea

Intermittent headache

No further complications

Global Leukemia Academy

Treatment course: Female patient, 47 years old

Induction I
GMALL EVOLVE
VCR/Dex
PEG-Asp
MTX i.th.

Induction II
GMALL EVOLVE
VCR/Dex
No PEG-Asp
No MTX i.th.

Consolidation I
GMALL EVOLVE
HD MTX
HD Ara-C
No further i.th. prophylaxis

12/2024

01/2025

02/2025

Imatinib 600 mg QD

Nilotinib 400 mg BID

During treatment: constant nausea

Intermittent headache

No further complications

No neurologic symptoms

Response after Cons I

MolFail:
9×10^{-3} *BCR::ABL1*

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Female patient, 47 years old, intrathecal bleeding + thrombosis, MolFail after Cons I

Which therapeutic option would you choose?

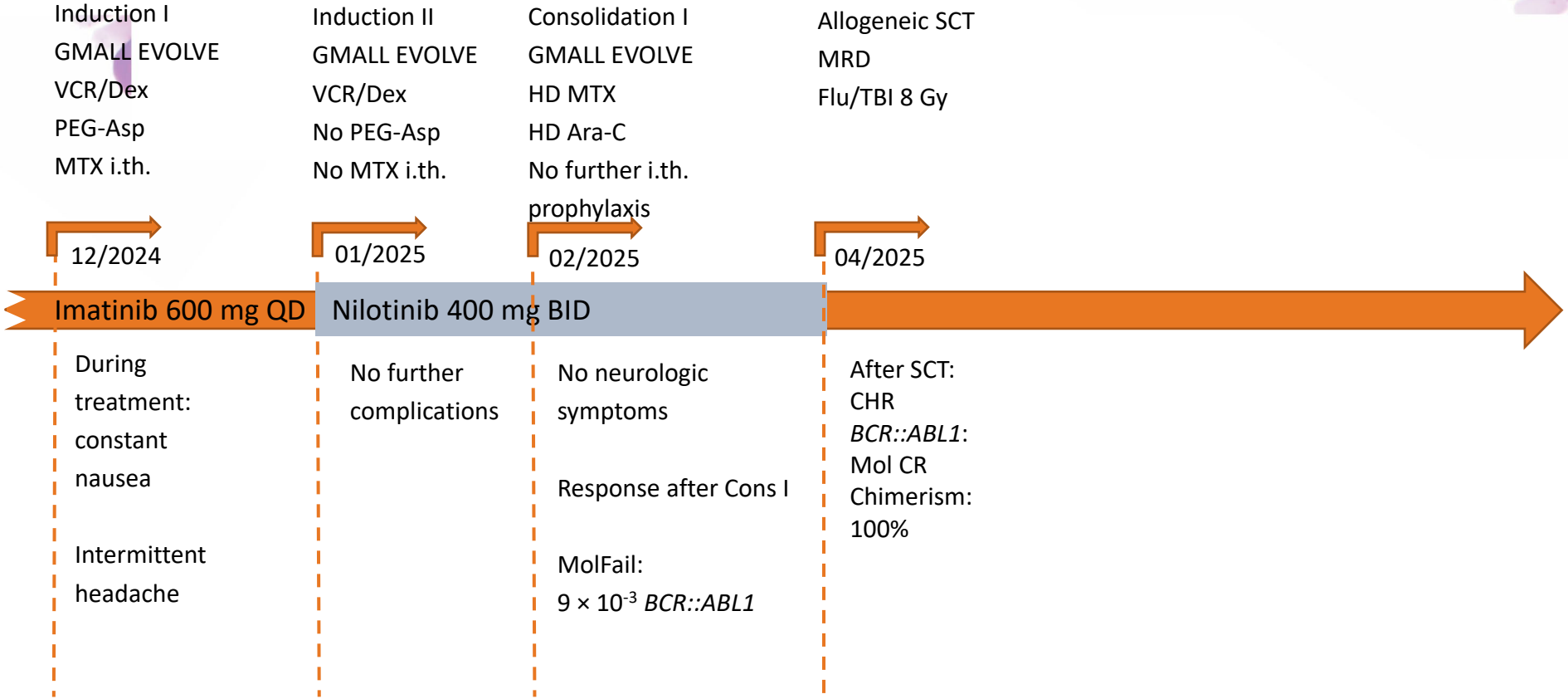
- Blinatumomab + nilotinib + inrathec. MTX
- CTX + nilotinib + intrathec. MTX
- Allogeneic SCT incl. TBI
- Nilotinib + CTX without intrathec. MTX

Female patient, 47 years old, intrathecal bleeding + thrombosis, MolFail after Cons I

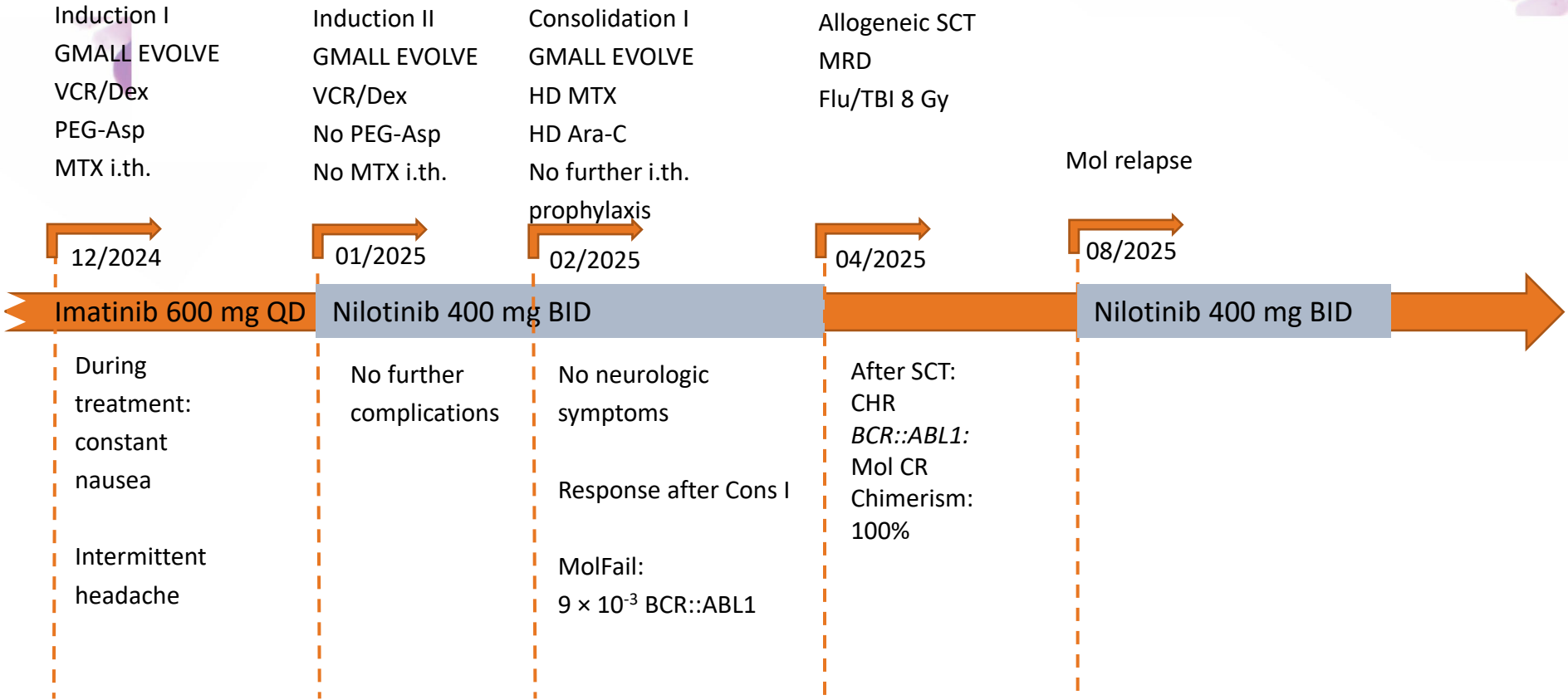
Which therapeutic option would you choose?

- Blinatumomab + nilotinib + inrathec. MTX
- CTX + nilotinib + intrathec. MTX
- **Allogeneic SCT incl. TBI**
- Nilotinib + CTX without intrathec. MTX

Treatment course: Female patient, 47 years old



Treatment course: Female patient, 47 years old



Main messages/questions from this case

- Risk of intrathecal bleeding may be associated with imatinib
- Allogeneic SCT including TBI in MolFail feasible
- How to ensure intrathecal prophylaxis in this setting?
- Which TKI to use in bleeding/thrombotic events?
- Which TKI shows the best CNS activity?

Global Leukemia Academy

ALL case-based panel discussion Case 2: AYA

Nicolas Boissel

APTITUDE HEALTH®

Global Leukemia Academy

September 18, 2025

ALL Case: AYA

Nicolas BOISSEL, MD, PhD

Hematology Adolescent and Young Adult Unit, Saint-Louis Hospital, APHP

Institut de Recherche Saint-Louis, Université Paris Cité, Paris, France

Group for Research in Acute Lymphoblastic Leukemia

GRAALL LALA GOELAMS SAKK

Hôpital Saint-Louis AP-HP

INSTITUT DE RECHERCHE SAINT-LOUIS Hématologie I Immunologie I Oncologie

Université Paris Cité

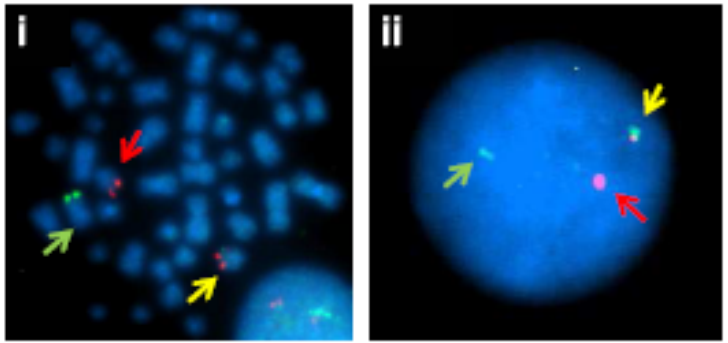
INSTITUT CARNOT OPALE

A 28-year-old female with Ph-like ALL

- A 28-yr-old woman with fatigue and hemorrhagic syndrome
- **CBC:** leukocytes 35 G/L, Hb 5,5 g/L, platelets 24 G/L
- **Bone marrow aspiration**: 96% of lymphoblasts
- **CNS-1**
- **Phenotype**: HLADR+, CD19+, CD10+, CD20+, CD22+
- Normal **karyotype**
- **FISH:** absence of *BCR-ABL1*, *ETV6-RUNX1*, *TCF3-PBX1,* or *KMT2A*r, ***IgH* locus rearrangement**
- **Molecular biology:** absence of *IKZF1*del, ***CRLF2* overexpression**
- **Ph-like ALL with *IgH::CRLF2***, absence of *JAK2* mutation

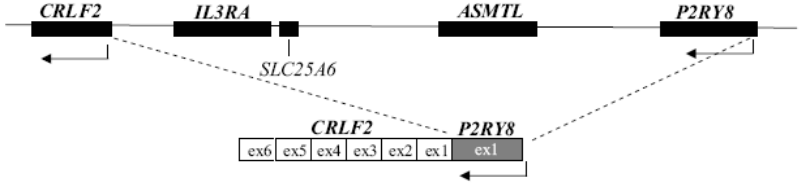
CRLF2 deregulation

Translocation involving *IGH* @ locus:
t(X;14)(p22;q32) or t(Y;14)(p11;q32)



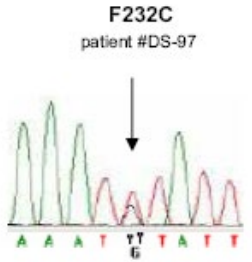
***JAK2* mutation in 50% of cases**

Interstitial PAR1* deletion: *P2RY8-CRLF2* fusion



*PAR1, pseudo-autosomal region 1.

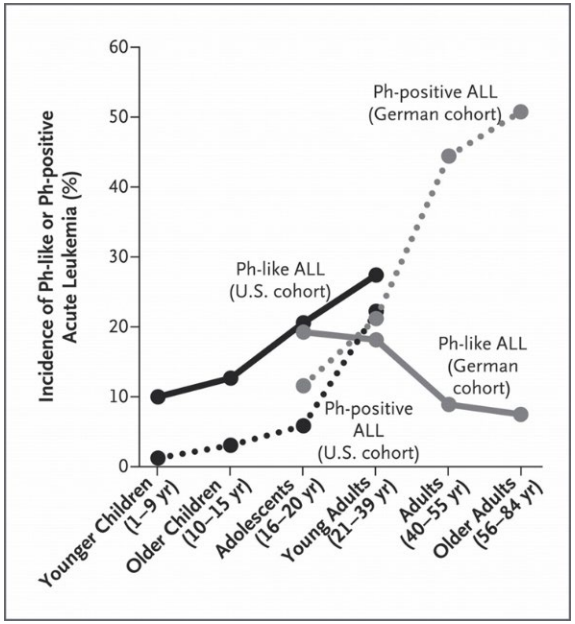
***CRLF2* gene point mutation:**



Russell LJ, et al. *Blood*. 2009;114:2688-2698; Mullighan CG, et al. *Nat Genet*. 2009;41:1243-1246; Yoda A, et al. *Proc Natl Acad Sci USA*. 2010;107:252-257.

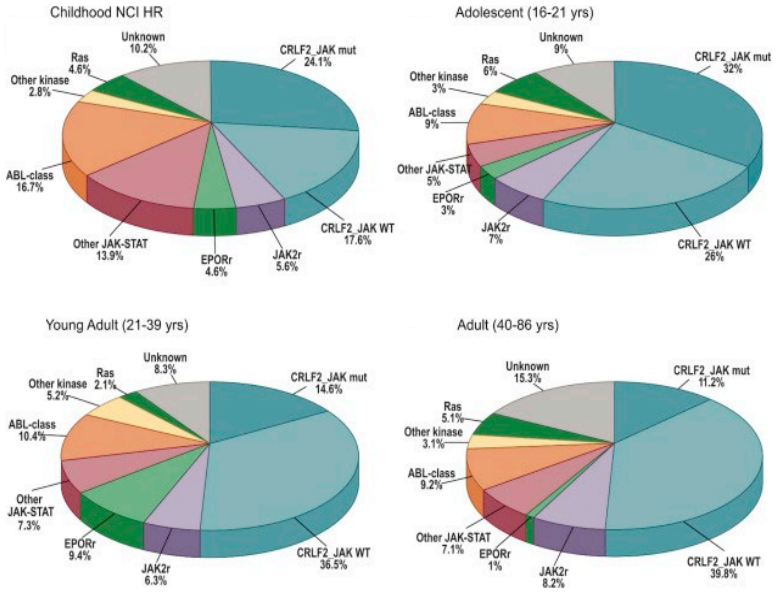
Genetic landscape of Ph-like ALL

Incidence of Ph-like and Ph-positive ALL by age



Herold T, et al. *N Engl J Med*. 2014;371:2235.

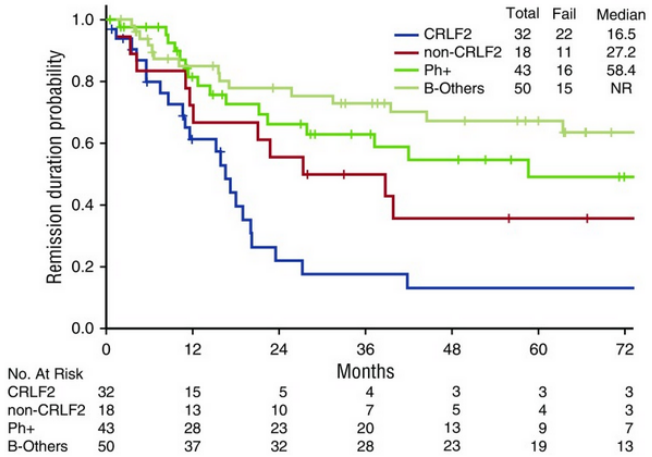
Prevalence of Ph-like subgroups by age

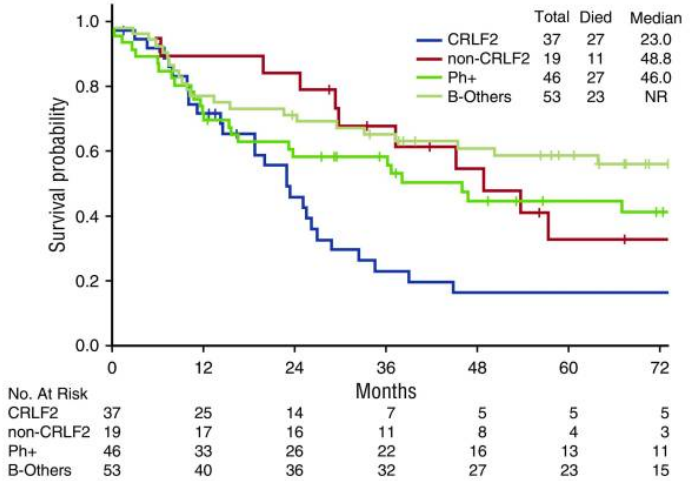


Pui CH, et al. *Clin Lymphoma Myeloma Leuk*. 2017;17:464-470.

Heterogeneous disease and outcome?

MDACC: HyperCVAD/A-BFM





Jain N, et al. *Blood.* 2017;129:572-581.

A 28-year-old female with Ph-like ALL

- Treated according to the GRAALL-2014 trial
- **4-drug BFM-like induction** with L-asparaginase
- Good early prednisone and bone marrow responses (M1 bone marrow)
- **End of induction**
  - Complete remission
  - TP1 2×10^{-2}
- **Consolidation** with high-dose MTX and AraC
  - TP2 5×10^{-3}

What is your decision at this point?

1. Continue chemotherapy
2. Proceed to alloHSCT
3. Blinatumomab and MRD reassessment
4. Blinatumomab in bridge to alloHSCT

A 28-year-old female with Ph-like ALL

- Treated according to the GRAALL-2014 trial
- **4-drug BFM-like induction** with L-asparaginase
- Good early prednisone and bone marrow responses (M1 bone marrow)
- **End of induction**
  - Complete remission
  - TP1 2×10^{-2}
- **Consolidation** with high-dose MTX and AraC
  - TP2 5×10^{-3}
- **Decision: blinatumomab in bridge to transplant**

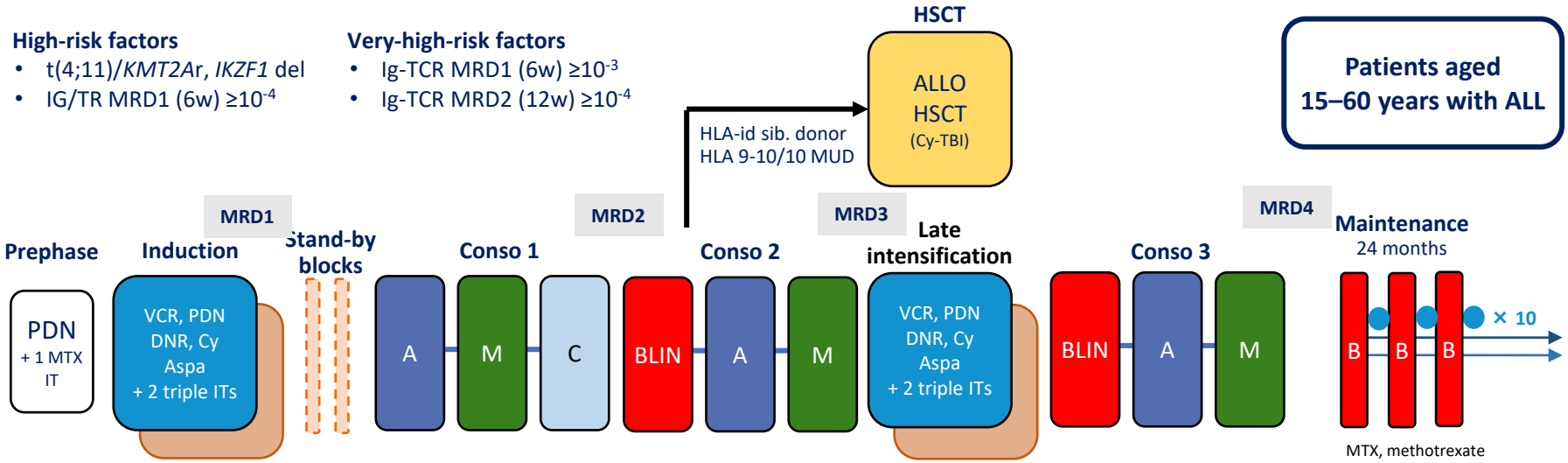
GRAALL-2014/B – QUEST substudy

Blinatumomab for HR patients

High-risk factors
- t(4;11)/*KMT2Ar*, *IKZF1* del
- IG/TR MRD1 (6w) ≥10^{-4}

Very-high-risk factors
- Ig-TCR MRD1 (6w) ≥10^{-3}
- Ig-TCR MRD2 (12w) ≥10^{-4}

Patients aged 15–60 years with ALL



PDN, PO prednisone*
DXM, dexamethasone
VCR, vincristine
DNR, daunorubicin*
IDA, idarubicin
Aspa, L-asparaginase*

MTX, methotrexate
Cy, cyclophosphamide
AraC, cytarabine
6MP, 6-mercaptopurine
VP16, etoposide
TBI, total body irradiation
IT, intrathecal; HD, high-dose triple IT, MTX/ARAC/steroids

*PDN, DNR, and Aspa doses reduced in patients ≥45 yr.
**HD-MTX dose increased in patients aged <45 yr.
***Switch to Erwinaze on the basis of Aspa activity/immunization monitoring.

A 28-year-old female with Ph-like ALL

Blinatumomab

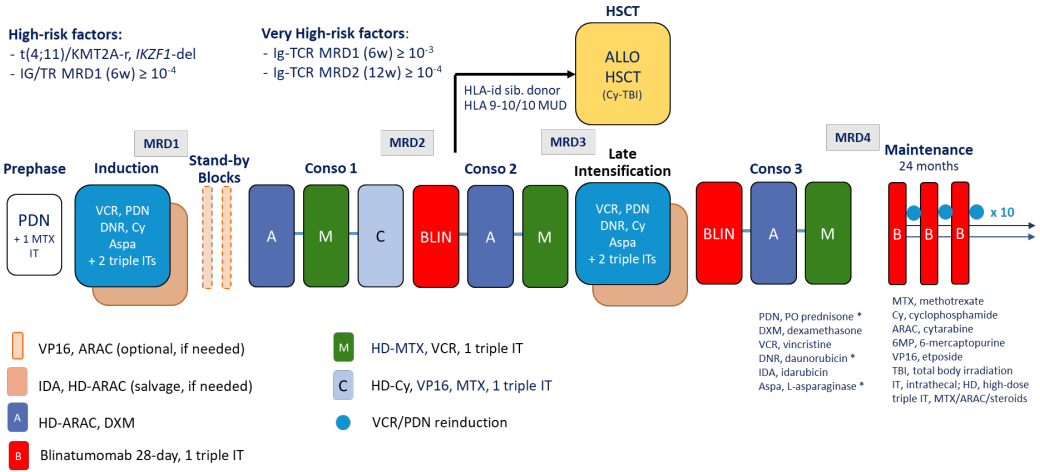
- **Blinatumomab** started as inpatient for MRD-positive B-ALL
  - 28 μg/day IVC (relapse)
  - No tumor lysis prophylaxis
  - Dexamethasone 20 mg TD IV, 1 hr before blinatumomab
- Daily physical examination and writing test
- Prophylactic triple IT (MTX, AraC, MP) given at D1
- **At D2/D3:** isolated fever treated by acetaminophen
- **At D5:** patient feels drowsy, slow response to stimuli but normal physical examination, normal writing test

A 28-year-old female with Ph-like ALL

- **Day 6:** mother's call due to “abnormal movements”
  - Tremors
  - Resolution after clonazepam IV
  - Stop blinatumomab, dexamethasone 20 mg IV
  - Normal CT scan, MRI, EEG

GRAALL-2014/B – QUEST

Grade 2+ AEs, adherence



Adherence to blinatumomab schedule

Median number of cycles: 3 (range 1–7)

- If alloHSCT: 2 (range 1–7)
- If no alloHSCT: 5 (range 1–6)

In patients with no alloHSCT

- 10 (21%) received <5 cycles
- Reasons for discontinuation
  - Progression: 4 + 1 MRD
  - Neurotoxicity: 3 (two G4, one G3)
  - Patient decision: 2

**After subsequent alloHSCT.*

Boissel N, et al. ASH 2023. Abstract 4349; Personal communication.

A 28-year-old female with Ph-like ALL

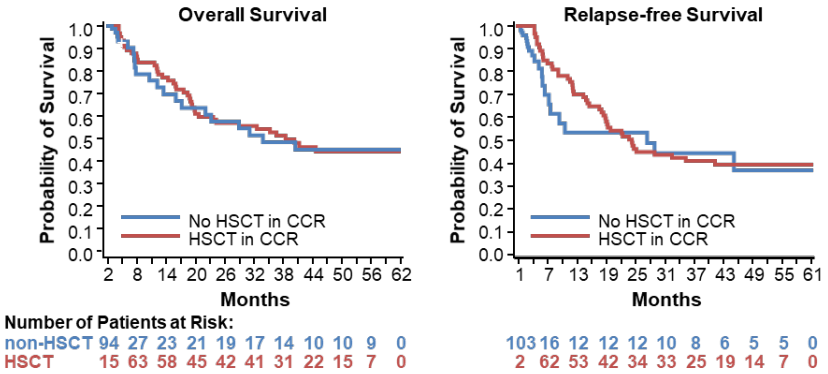
- **Day 6:** mother's call due to “abnormal movements”
  - Tremors
  - Resolution after clonazepam IV
  - Stop blinatumomab, dexamethasone 20 mg IV
  - Normal CT scan, MRI, EEG
- **Day 10:** blinatumomab restarted
  - Dose 9 µg/day in combination with levetiracetam
  - No side effects, increased to 28 µg/day after 1 wk
- Outpatient from day 4 at 28 µg/day
- **MRD after cycle 1 undetectable (day 28)**
- Second cycle started 2 wk after the first cycle
- Outpatient from day 4 without any adverse events

What is your decision at this point?

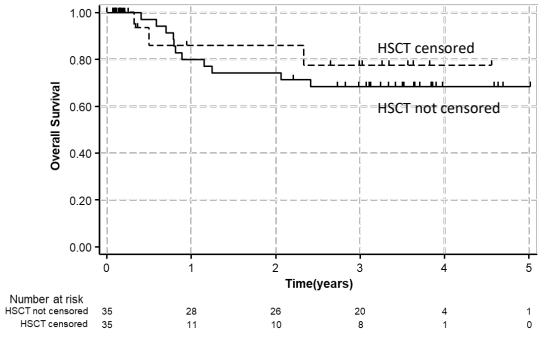
1. Proceed to alloHSCT
2. Continue alternate cycles of chemotherapy and blinatumomab
3. Continue blinatumomab only

Beyond blinatumomab: To transplant or not?

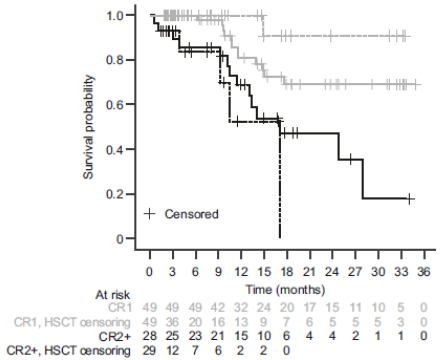
BLAST study[1,2]
CR1/2+ patients, w/wo HSCT (landmark)



Real-world "FRENCH-CYTO" study[3]
CR1 patients ± HSCT censoring



Real-world "NEUF" study[4]
CR1/2 patients ± HSCT censoring



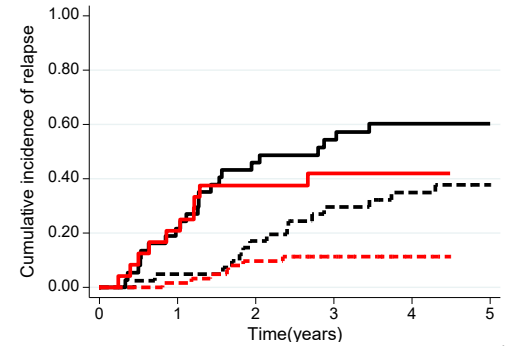
- Few studies have evaluated the role of HSCT post-blinatumomab
- In the BLAST study, no impact on OS/RFS in CR1/2+ (landmark analysis)[1,2]
- In real-world studies, no impact on OS/RFS in CR1 (HSCT censoring)[3,4]
- More robust evaluations are needed

1. Gökbuget N, et al. *Blood*. 2018;131:1522-1531; 2. Gökbuget N, et al. ASH 2018. Abstract 554;
3. Cabannes-Hamy A, et al. *Haematologica*. 2022;107:2072-2080; 4. Boissel N, et al. *Blood Cancer J*. 2023;13:2.

Heterogeneity of response to blinatumomab

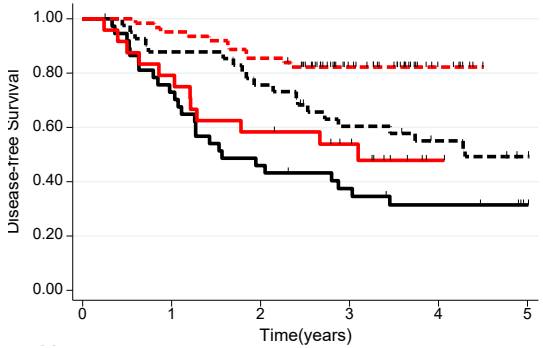
Post-blinatumomab EOC MRD

Cumulative incidence of relapse



Control detectable MRD3
undetectable MRD3 SHR 0.44, 95%CI[0.23-0.85], p=0.02
QUEST detectable MRD3
undetectable MRD3 SHR 0.21, 95%CI[0.08-0.55], p=0.002

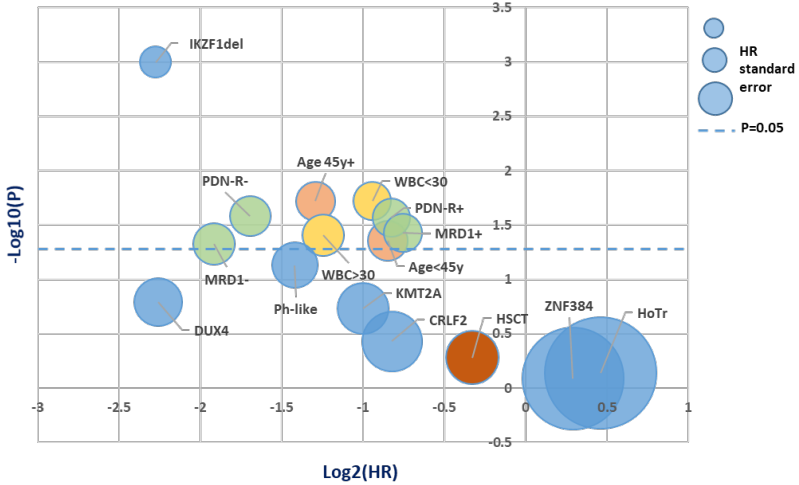
Disease-free survival



Control detectable MRD3
undetectable MRD3 HR 0.51, 95%CI[0.28-0.93], p=0.03
QUEST detectable MRD3
undetectable MRD3 HR 0.28, 95%CI[0.12-0.63], p=0.002

DFS by subgroup

Cox model (-Log[P] vs Log2[HR])



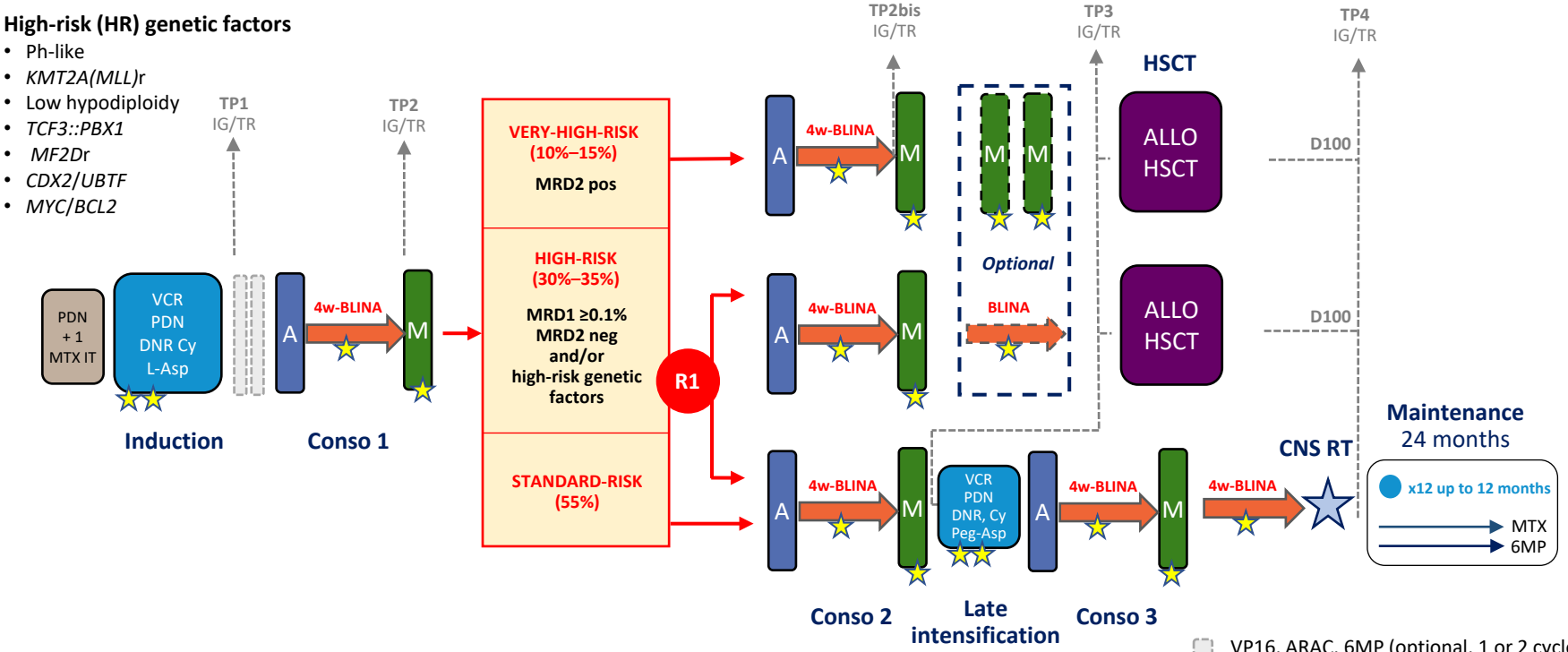
Boissel N, et al. ASH 2022. Abstract 211. Updated June 2023.

A 28-year-old female with Ph-like ALL

AlloSCT

- **AlloSCT in CR1** (Cy-TBI, SIB donor)
  - Grade 2 GUT/skin aGvHD, good response to MP2
  - Undetectable MRD at D100

GRAALL-2024 Ph– B-ALL



PDN, PO prednisone; DXM, dexamethasone; VCR, vincristine; DNR, daunorubicin; IDA, idarubicin; ARAC, cytarabine; L-Aspa, recombinant L-asparaginase; Peg-Aspa, Peg-asparaginase; MTX, methotrexate; Cy, cyclophosphamide; 6MP, 6-mercaptopurine; IT, intrathecal; HD, high-dose triple IT, MTX/ARAC/steroids ☆ (prophylaxis only), CNS RT, CNS radiotherapy (prophylactic/curative).

A 28-year-old female with Ph-like ALL
AlloSCT

- **AlloSCT in CR1** (Cy-TBI, SIB donor)
  - Grade 2 GUT/skin aGvHD, good response to MP2
  - Undetectable MRD at D100

- **Bone marrow relapse 14 mo after ASCT**
  - Bone marrow aspiration: 65% blasts
  - Same characteristics of the disease as at diagnosis
  - Persistence of CD19 expression, 80% of blast cells

A 28-year-old female with Ph-like ALL

Blinatumomab n°2

- **Ambulatory treatment** with non-myelosuppressive chemotherapy (VCR, DEXA, PEG-ASPA)
  - Blast clearance after 4 wk, 7×10^{-3}
- **Blinatumomab for R/R BCP-ALL**
  - 4 cycles, prophylactic IT × 3 before each cycle
  - MRD undetectable after 1 cycle
  - 2 donor lymphocyte infusions (DLI)
- **Patient mostly treated as outpatient for 6 mo**
  - Persistence of negative MRD
  - Absence of GvHD
- **POMP maintenance for 2 yr**

Global Leukemia Academy

Panel discussion: How treatment in first line influences further therapy approaches in ALL

APTITUDE HEALTH®

Global Leukemia Academy

Panel discussion: How treatment in first line influences further therapy approaches in ALL

1. Differences in health care systems and clinical research in US and Europe and consequences for treatment approaches?

2. How have bispecifics changed the landscape of first-line therapy in adult ALL in Europe?

3. How to increase access to CAR-T-cells and study use in earlier phases of ALL treatment?

4.Is there any chance to agree on uniform prognostic factors for treatment stratification and transplant indication in adult ALL?

5. What is the difference in terms of treatment approach to AYA/Young adults, adults and older patients and how to stratify these approaches?

6. How to generate reliable clinical trial data in a rare and complex disease with more and more new compounds available? What can we learn from pediatric groups?

Global Leukemia Academy

ARS questions

Elias Jabbour

APTITUDE HEALTH®

Question 1 [REPEATED]

If an elderly patient with Ph– ALL remains positive for MRD after dose-adjusted Hyper-CVAD induction, assuming full access, what is your preferred next intervention?

A. Proceed directly to transplant
B. Consolidation chemotherapy
C. Blinatumomab
D. Inotuzumab ozogamicin
E. CAR T-cell therapy
F. Other

Question 2 [REPEATED]

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. Kinase inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. There are no effective consolidation treatments for patients who remain MRD+ after induction therapy

Global Leukemia Academy

Session close

Elias Jabbour

APTITUDE HEALTH®

Day 2: Virtual Plenary Sessions

Friday, September 19, 2025
18.00 – 21.00 UTC +2 (Central European Summer Time)

Time (UTC -5)	Time (UTC +2)	Title	Speaker
11.00 AM – 11.10 AM	18.00 – 18.10	Welcome to Day 2	Elias Jabbour
11.10 AM – 11.40 AM	18.10 – 18.40	Current treatment options for relapsed/refractory (R/R) ALL in fit adults	Nicola Gökbuget
11.40 AM – 12.00 PM	18.40 – 19.00	Current treatment options for R/R ALL in elderly and frail patients	Josep-Maria Ribera
12.00 PM – 12.20 PM	19.00 – 19.20	Current and future role of transplantation in ALL in Europe	Nicola Gökbuget
12.20 PM – 12.30 PM	19.20 – 19.30	Break	
12.30 PM – 1.00 PM	19.30 – 20.00	ALL case-based panel discussion for R/R ALL • Case ALL: Young (Dr Ribera) • Case ALL: Elderly (Dr Lang)	All faculty
1.00 PM – 1.20 PM	20.00 – 20.20	Long-term safety considerations for ALL	Nicolas Boissel
1.20 PM – 1.50 PM	20.20 – 20.50	Panel discussion: Open questions in ALL – regional challenges (transplant, CAR T studies, and other) • Who are the ideal patients for CAR T therapy, bispecifics, and transplants in your practice? • What would be needed to make CAR T therapy available to all of your patients? • What would be needed to best position bispecifics in the continuum of care for ALL in adults? • How should transplant be strategically combined with the new therapy modalities?	Moderated by Nicolas Boissel Led by Elias Jabbour and all faculty
1.50 PM – 2.00 PM	20.50 – 21.00	Session close	Elias Jabbour

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Bridging Science and Practice: From Newest Clinical Approaches to Real-World Clinical Cases

September 18–19, 2025 – Europe

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