Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

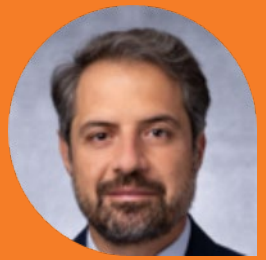
23 September 2022

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour



APTITUDE HEALTH

CHAIR

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

CO-CHAIRS

Franco Locatelli, MD
IRCCS Bambino Gesù
Children's Hospital, Rome, Italy

Naval Daver, MD
MD Anderson Cancer Center
Houston, TX, USA

Gail J. Roboz, MD
Weill Cornell Medicine
New York-Presbyterian
Hospital, NY, USA

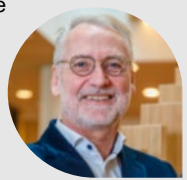
FACULTY

Nicolas Boissel, MD, PhD
Hôpital Saint-Louis, France

Nicola Gökbuget, MD
University Hospital Frankfurt,
Germany

Hagop Kantarjian, MD
MD Anderson Cancer Center,
Houston, TX, USA

Christina Peters, MD
St. Anna Children's Hospital,
Vienna, Austria



Rob Pieters, MD, PhD
Princess Maxima Center for
Pediatric Oncology, Utrecht,
The Netherlands

Jose María Ribera, MD, PhD
Catalan Institute of Oncology,
University Hospital Germans
Trias i Pujol, Barcelona, Spain

Agnieszka Wierzbowska, MD, PhD
Medical University of Lodz,
Poland

Objectives of the program

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

Virtual Plenary Sessions (Day 1)

23 September 2022, 14.30 – 18.00 CEST

Chair: Dr Elias Jabbour
Co-chairs: Dr Gail J. Roboz/Dr Naval Daver

Time (CEST)	Title	Speaker
14.30 – 14.40	**Welcome and Meeting Overview**	Elias Jabbour
14.40 – 15.05	**What's New in ALL? Recent Developments in Research and Management**	Hagop Kantarjian
15.05 – 15.25	**The Clinical Value of MRD in ALL: How MRD Can Guide the Use of Targeted Agents or Immunotherapy**	Josep-Maria Ribera
15.25 – 15.45	**How to Optimally Sequence CD19-Targeted Approaches in ALL**	Elias Jabbour
15.45 – 16.05	**Hot Topics and Regional Challenges of ALL Management**	Moderator: Elias Jabbour All faculty
16.05 – 16.15	***Break***	
16.15 – 16.40	**What's New in AML? Recent Developments in Research and Management**	Naval Daver
16.40 – 17.00	**Genetic Characterization and Risk Stratification in AML**	Agnieszka Wierzbowska
17.00 – 17.20	**Moving the Treatment of AML to the Outpatient Setting: Is It Feasible?**	Gail J. Roboz
17.20 – 17.50	**Hot Topics and Regional Challenges of AML Management**	Moderator: Gail J Roboz and Naval Daver All faculty
17.50 – 18.00	**Session Close**	Elias Jabbour

Virtual Breakout – Pediatric ALL Sessions (Day 2)

24 September 2022, 10.00 – 12.45 CEST

Chair: Dr Franco Locatelli

Time (CEST)	Title	Speaker
10.00 – 10.10	**Session Open**	Franco Locatelli
10.10 – 10.30	**How to Use MRD and Genetics for Stratification and Therapy Guidance in First-Line Therapy of Childhood ALL**	Rob Pieters
10.30 – 10.55	**Optimizing First-Line Therapy in Pediatric ALL: How to Balance Cure and Long-Term Risks?**	Rob Pieters
10.55 – 11.15	**ALL Case-Based Panel Discussion** • Balancing Cure and Toxicity Risks	Moderator: Franco Locatelli Janine Stutterheim All faculty
11.15 – 11.25	***Break***	
11.25 – 11.55	**Current Treatment Options for High-Risk ALL in Children**	Christina Peters
11.55 – 12.35	**ALL Case-Based Panel Discussion** • Relapsed/Refractory ALL (Part 1) • Toxicity Management (Part 2)	Moderator: Franco Locatelli Hannah von Mersi Anna Cvrtak All faculty
12.35 – 12.45	**Session Close**	Franco Locatelli

Virtual Breakout – Adult ALL Sessions (Day 2)

24 September 2022, 11.00 – 13.45 CEST

Chair: Dr Elias Jabbour

Time (CEST)	Title	Speaker
11.00 – 11.10	**Session Open**	Elias Jabbour
11.10 – 11.35	**Optimizing First-Line Therapy in Adult and Older ALL: Integration of Immunotherapy Into Frontline Regimens**	Nicolas Boissel
11.35 – 12.00	**Current Treatment Options for Relapsed ALL in Adult and Older Patients**	Nicola Gökbuget
12.00 – 12.40	**ALL Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderator: Elias Jabbour Anjali Cremer Loic Vasseur All faculty
12.40 – 12.50	***Break***	
12.50 – 13.10	**Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL Patients**	Nicola Gökbuget
13.10 – 13.35	**Interactive Discussion: Treatment Landscape Evolution**	Moderator: Elias Jabbour All faculty
13.35 – 13.45	**Session Close**	Elias Jabbour

Virtual Breakout – AML Sessions (Day 2)

24 September 2022, 14.30 – 17.15 CEST

Chairs: Dr Gail J. Roboz/Dr Naval Daver

Time (CEST)	Title	Speaker
14.30 – 14.40	**Session Open**	Gail J. Roboz and Naval Daver
14.40 – 15.00	**Personalized Induction and Maintenance Approaches for AML**	Gail J. Roboz
15.00 – 15.25	**Fit and Unfit AML Patients: How Do We Distinguish? How Do We Treat Differently?**	Agnieszka Wierzbowska
15.25 – 16.05	**AML Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderators: Gail J. Roboz and Naval Daver Agnieszka Pluta Anna Torrent All faculty
16.05 – 16.15	***Break***	
16.15 – 16.40	**Optimizing Management of Relapsed/Refractory AML**	Naval Daver
16.40 – 17.05	**Interactive Discussion: Treatment Landscape Evolution**	Moderators: Gail J. Roboz and Naval Daver All faculty
17.05 – 17.15	**Session Close**	Gail J. Roboz and Naval Daver

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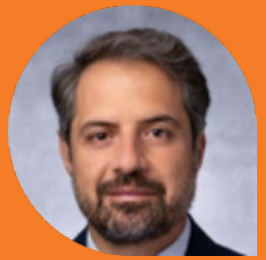
Introduction to the Voting System

Elias Jabbour



APTITUDE HEALTH

Question 1

In what country do you currently practice?

A. Austria
B. France
C. Germany
D. Italy
E. Poland
F. Spain
G. The Netherlands
H. United Kingdom
I. Other country in Europe
J. Outside Europe

Question 2

Which patients do you treat?

A. Adults only
B. Children only
C. Adults and children
D. Other

Question 3

Which of the following is NOT true?

A. Inotuzumab and blinatumomab + chemotherapy is active in both frontline and salvage for ALL

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

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

D. CAR T approaches are active beyond 2L in Ph-negative ALL

Question 4

In AML, the MRD assessment by RT-qPCR is especially useful for:

A. *DNMT3A* mutation
B. *SF3B1* mutation
C. *NPM1* mutation
D. *ASXL1* mutation

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What's New in ALL? Recent Developments in Research and Management

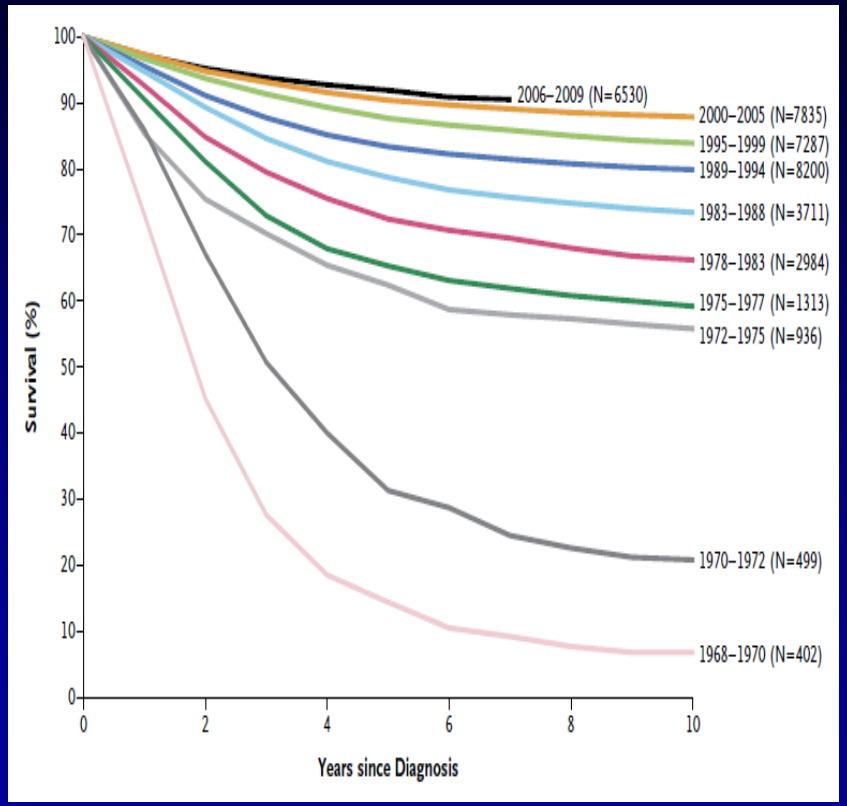
Hagop Kantarjian

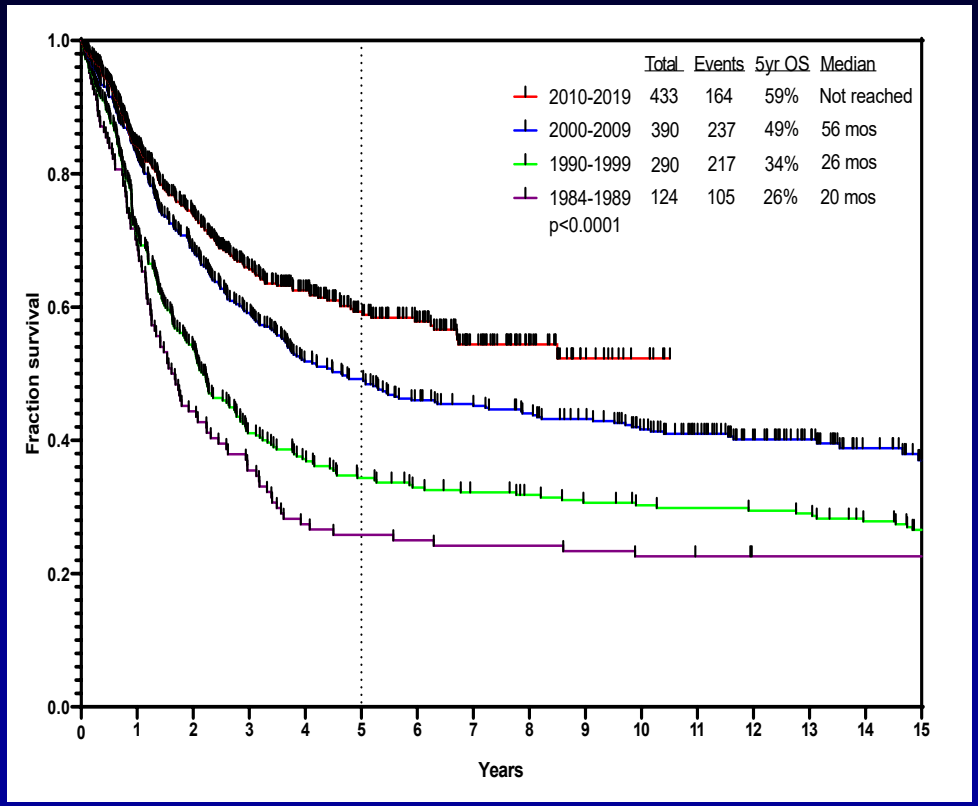
APTITUDE HEALTH

Adult ALL in 2022 – Progress in Research and Therapy

Hagop Kantarjian, MD
MD Anderson Cancer Center, Houston

Survival in Pediatric and Adult ALL With Classical Intensive ChemoRx Regimens





Hunger et al. *N Engl J Med.* 2015;373(16):1541-1552.

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

ALL Outcomes in Practice

Age	Percentage 3-yr OS (Peru, n = 378)	Percentage 4-yr EFS (India, n = 273)
0–10	70	57
10–20	37	35–44
46–65	12	20–27

Espinoza-Morales et al. *J Clin Oncol.* 2022;40(suppl 16):abstract 7012; Vaid T, et al. *HemaSphere.* 2022;6:275-276.

Reasons Why Pediatric ALL Does Better Than Adult ALL

Entity	Prognosis	Percentage Pediatric	Percentage Adult
Hyperdiploid	Favorable	25–30	5
t(12;21), *ETV6-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

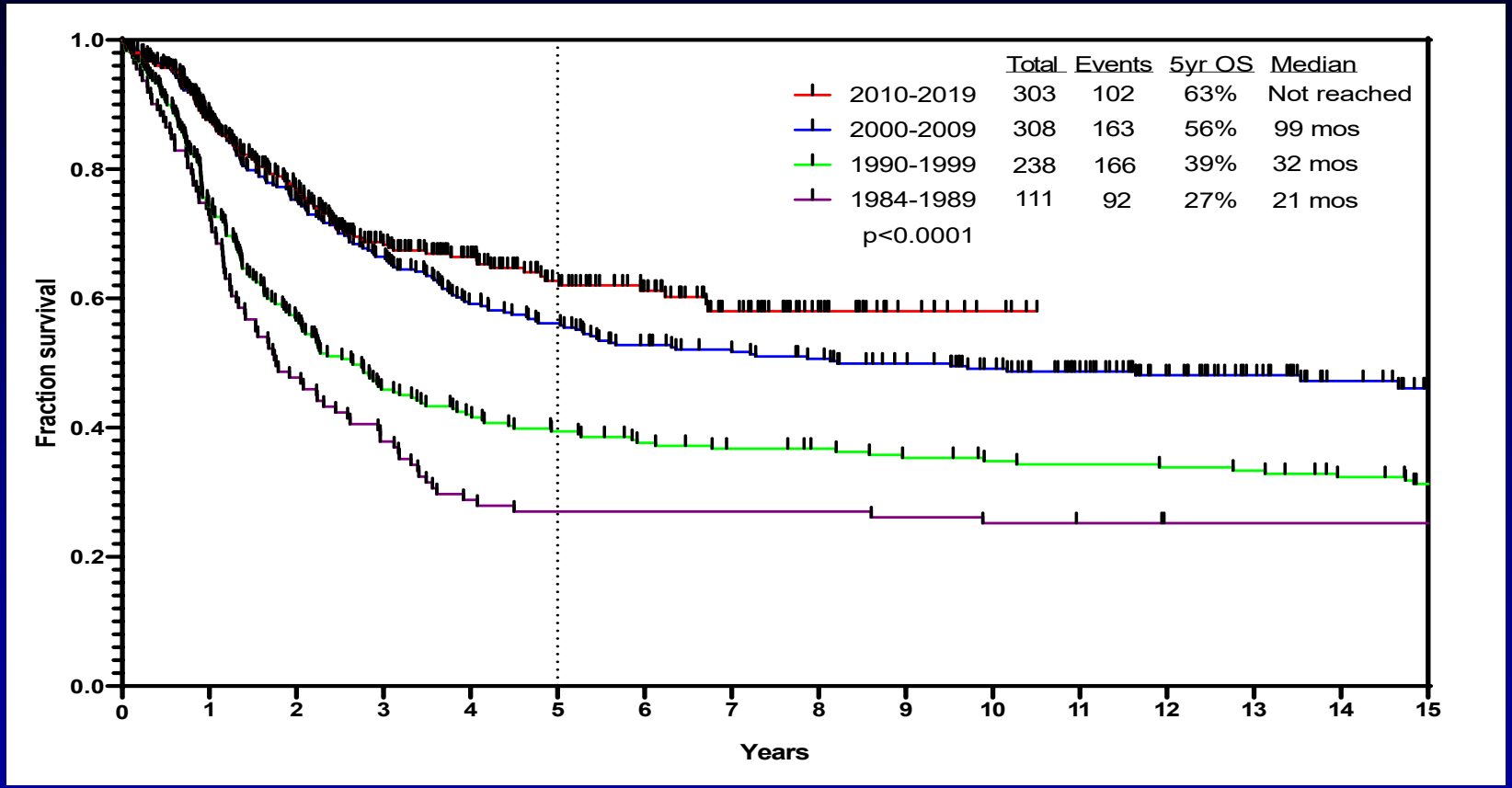
- Addition of TKIs (ponatinib) ± blinatumomab to chemoRx in Ph+ ALL
- Addition of rituximab to chemoRx in Burkitt and pre–B-ALL
- Addition of CD19 bispecific T-cell engager (BiTE) antibody blinatumomab, and of CD22 monoclonal antibody drug conjugate (ADC) inotuzumab to chemoRx in salvage and frontline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

Developmental Therapeutics in ALL

- Hyper CVAD regimen[1]
- CNS prophylaxis with IT chemoRx (no XRT)[1]
- Hyper CVAD + rituximab in Burkitt ALL[2]
- Hyper CVAD + imatinib/dasatinib/ponatinib in Ph+ ALL[3,4]
- Hyper CVAD + rituximab in pre–B-ALL[5]
- Clofarabine in pediatric ALL salvage (FDA approval 2004)[6]
- Liposomal vincristine (FDA approval 2012)[7]
- Activity of antibodies targeting CD19 and CD22 (blinatumomab, inotuzumab) in adult ALL[8,9]

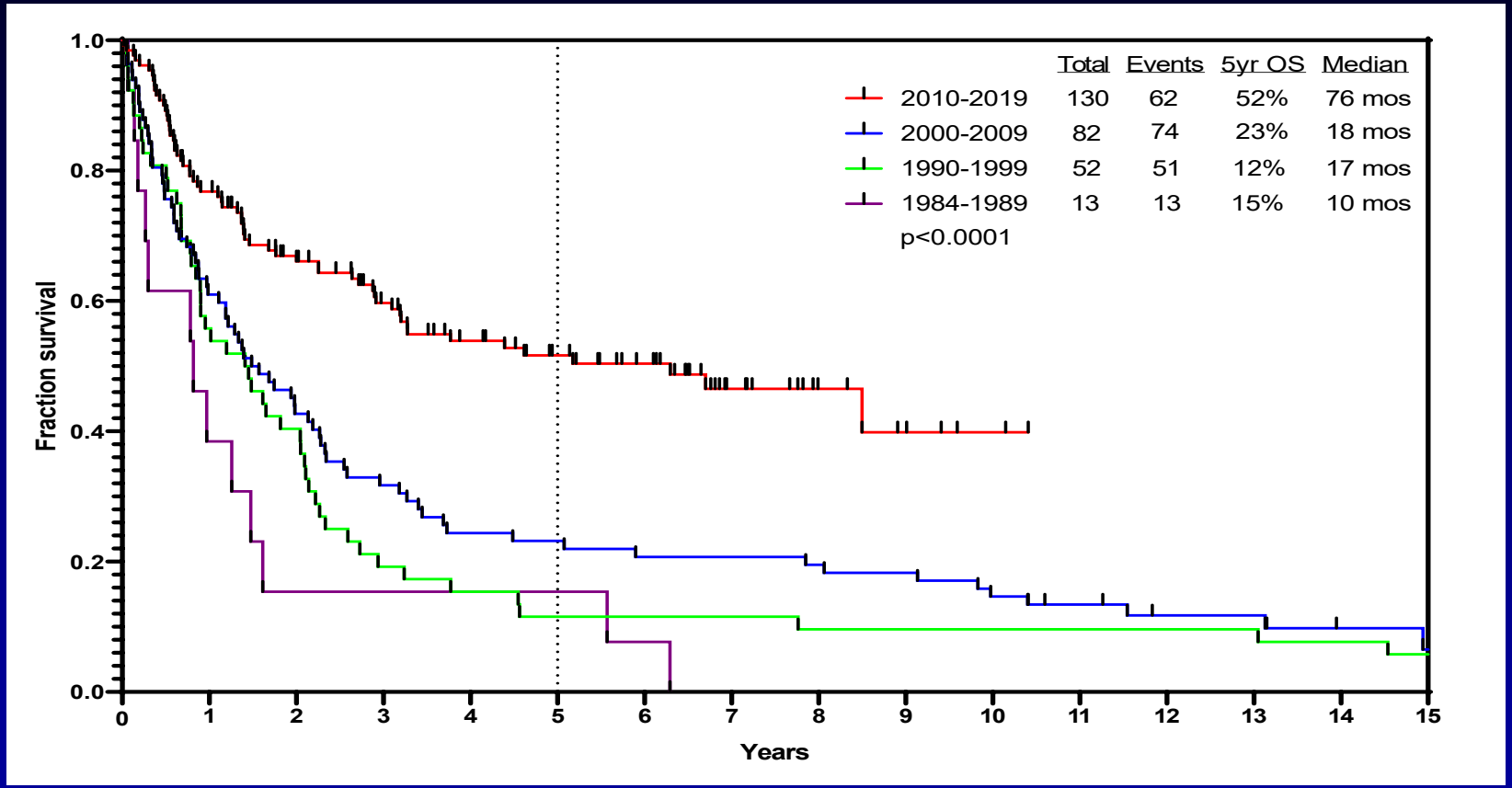
1. Kantarjian. *J Clin Oncol.* 2000;18:547; 2. Thomas. *Cancer.* 2006;106:1569; 3.Thomas. *Blood.* 2004;103:4396; 4. Ravandi. *Blood.* 2010;116:2070; 5. Thomas. *J Clin Oncol.* 2010;28:3880; 6. Jeha. *Blood.* 2004;103:784; 7. O'Brien. *J Clin Oncol.* 2012;31:676; 8. Kantarjian. *J Clin Oncol.* 2012;30:3876; 9. Kantarjian. *Lancet Oncol.* 2012;13:403.

Survival in Younger ALL (16–60 years; MDACC 1985–2020)



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

Survival in Older ALL (≥60 years; MDACC 1985–2020)



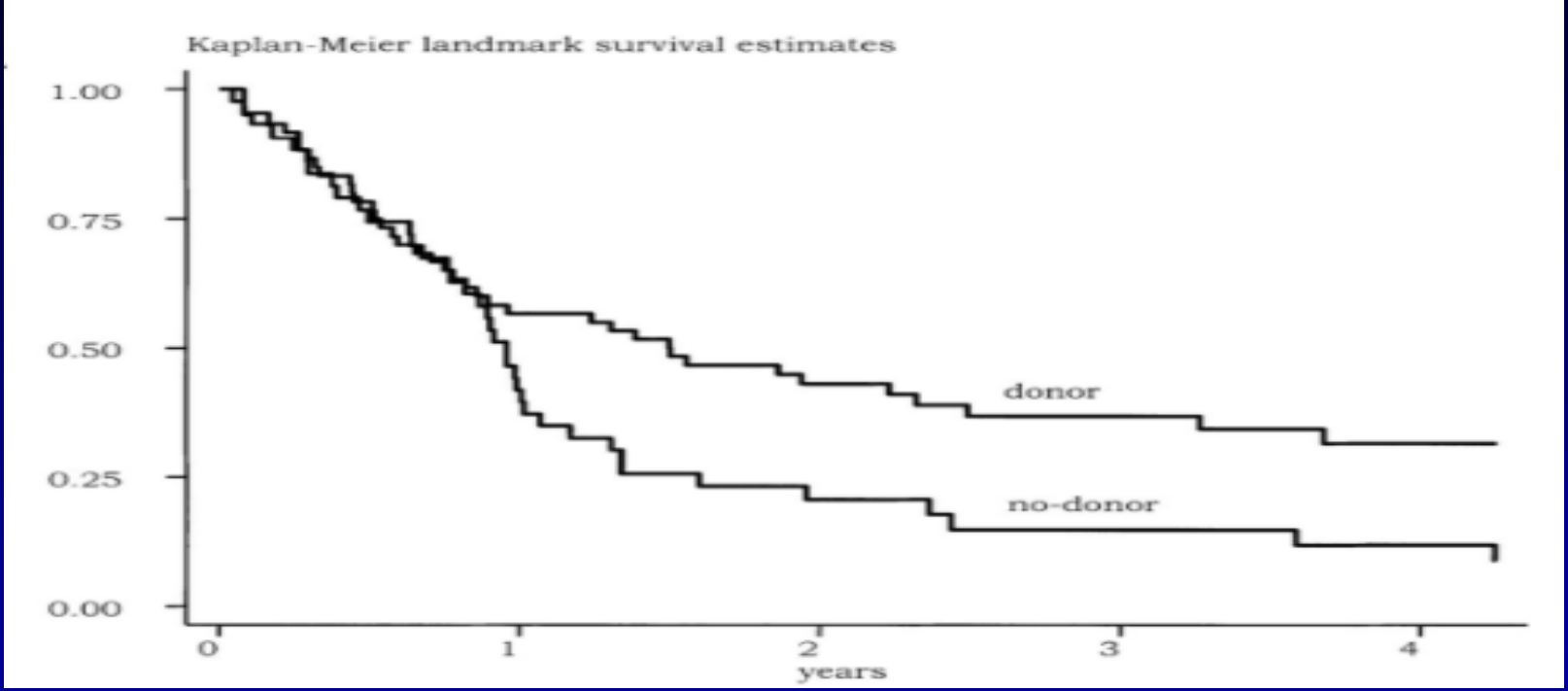
Kantarjian H, et al. *Cancer*. 2022;128:240-259.

Hyper-CVAD in ALL – Pearls and Vignettes to Optimize Rx

- Even courses: MTX 750 mg/m^2; ara-C 2 g/m^2. Dose adjust for older age
- Check Cr after MTX; if increase (>1.4), hold araC (avoid renal failure and cerebellar toxicity)
- VCR 2 mg flat dose (not 2 mg/m^2). If constipation or neuropathy, omit VCR
- Prophylaxis: levo or Vantin, posaconazole or voriconazole, Valtrex
- Hold azoles Day -1, 0, +1 of VCR (avoid excess neurotoxicity)
- Switch IT Day 2 from MTX to ara-C in even courses (neurotoxicity with IT MTX and HD systemic MTX)

Rausch. *Cancer.* 2020;126:1152-1160.

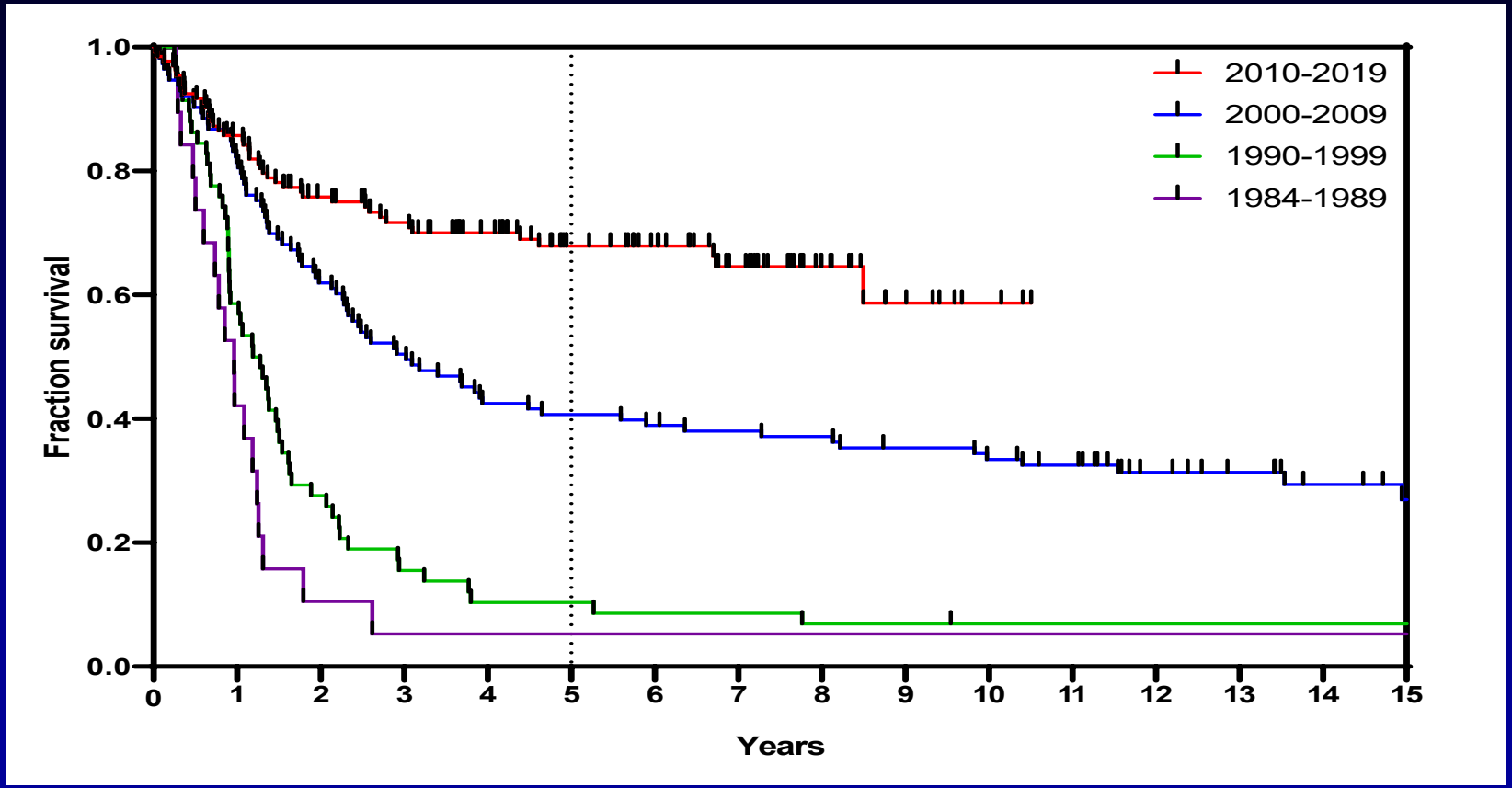
SCT for Ph+ ALL: Pre-TKI



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

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

Ph+ ALL OS With HCVAD + TKIs: MDACC 1985–2020

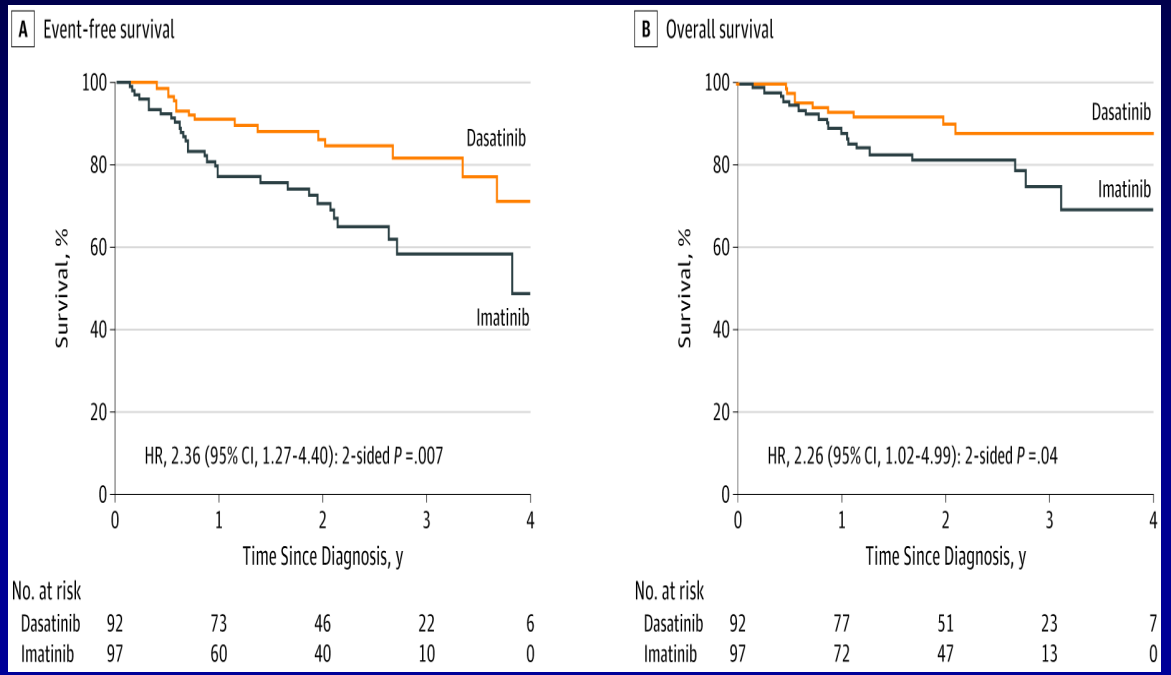


Kantarjian H, et al. *Cancer*. 2022;128:240-259.

Dasatinib vs Imatinib in Pediatric Ph+ ALL

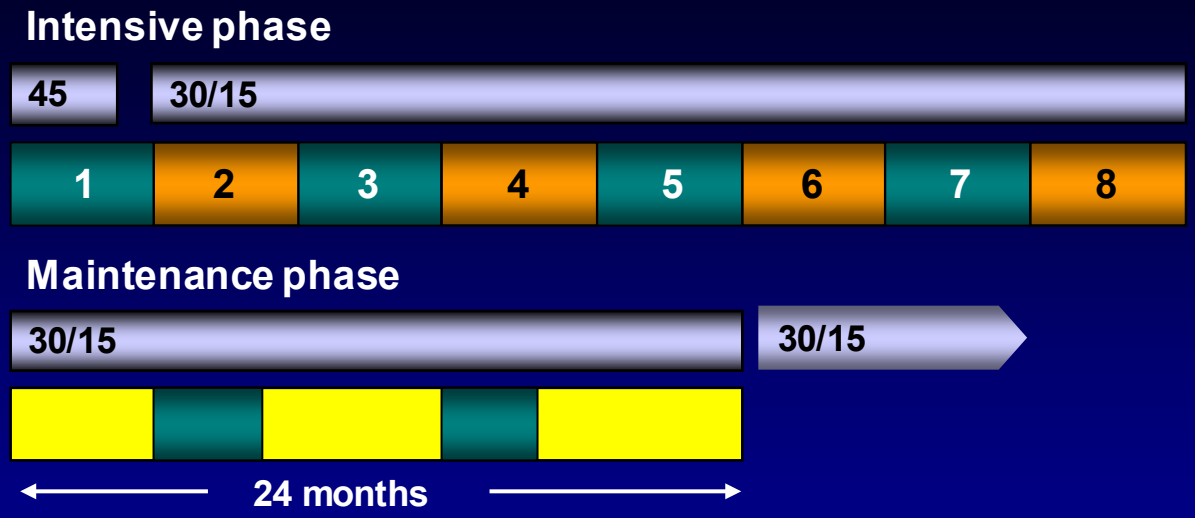
- 189 pts randomized Rx + dasatinib (n = 92) or imatinib (n = 97)
- Median F/U 26 mos; Triple IT 19 or 21

% 4-yr	Dasatinib	Imatinib	*P* Value
EFS	71	49	.005
OS	88	69	.04
Relapse	20	34	.01
CNS	2.7	8.4	.06



Shen et al. *JAMA Oncol.* 2020;6:358-366.

Hyper-CVAD + Ponatinib: Design



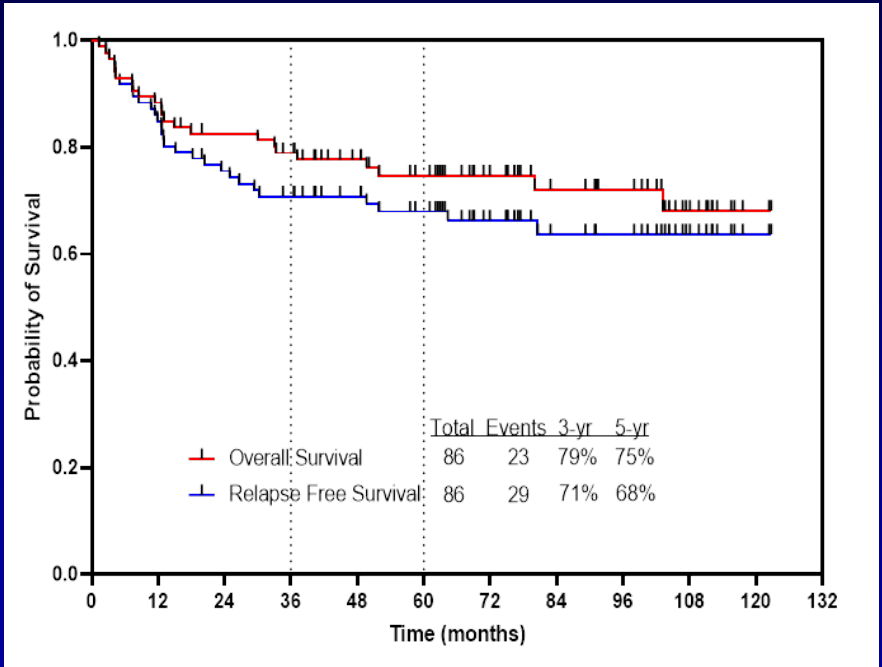
- After the emergence of vascular toxicity, protocol was amended: Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Jabbour E, et al. *Lancet Oncol.* 2015;16:1547; Jabbour E, et al. *Lancet Hematol.* 2018;5:618.

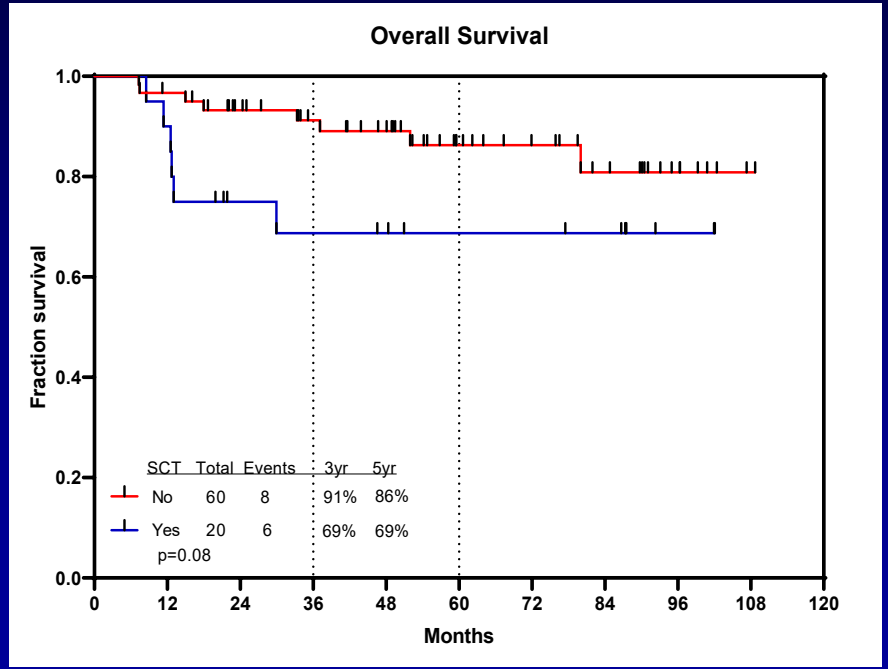
HyperCVAD + Ponatinib in Ph+ ALL

- 86 pts Rx; median age 47 yrs (39–61); median FU 75 mos (16–123)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); CMR 84%; 3/5-yr OS 79/75%, EFS 71/68%

Relapse-Free and Overall Survival

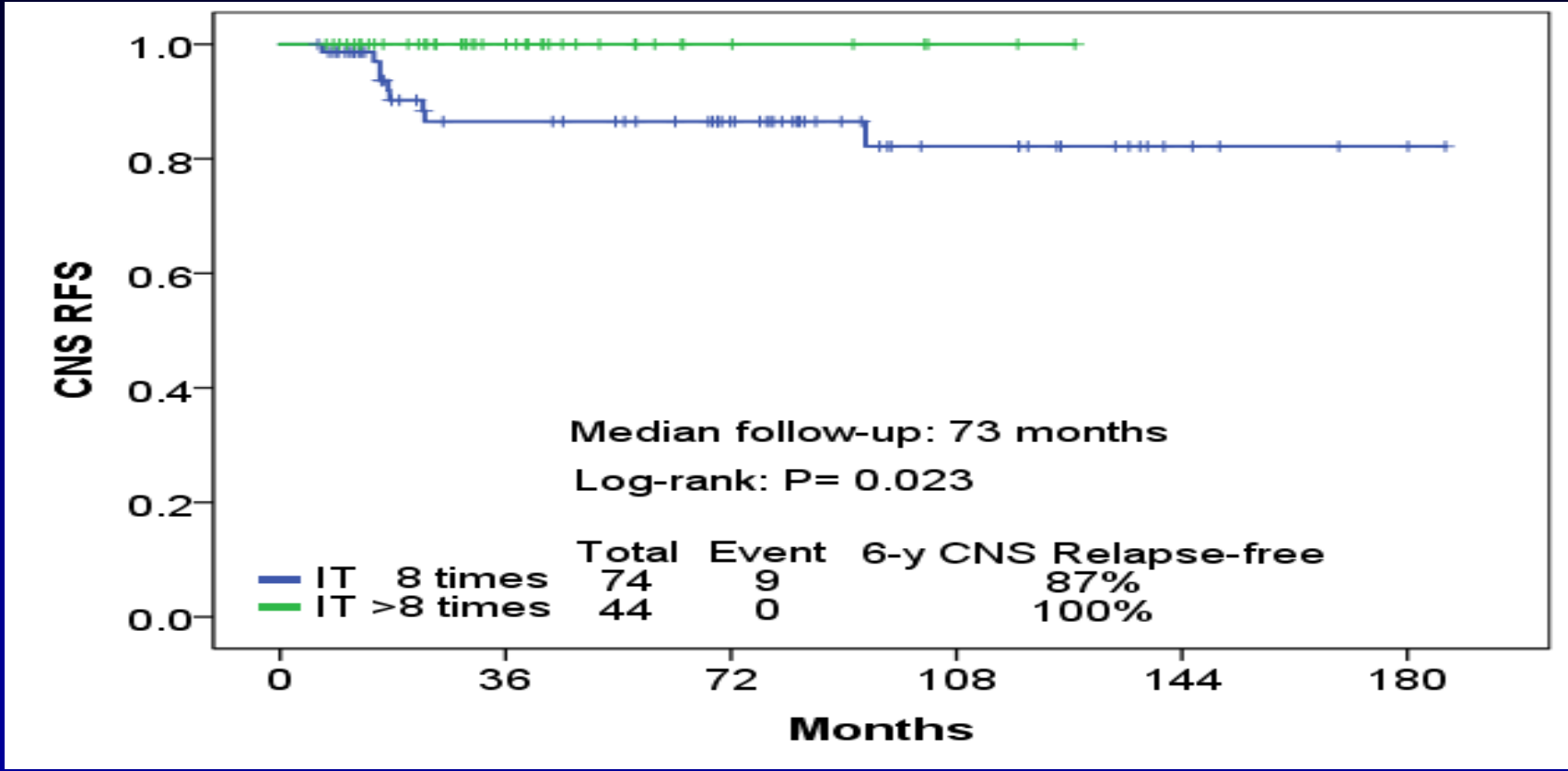


6-Month Landmark



Jabbour E, et al. *Lancet Hematol.* 2018;5:618:(and update April 2022); Short NJ, et al. *Blood.* 2019;134:abstract 283.

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

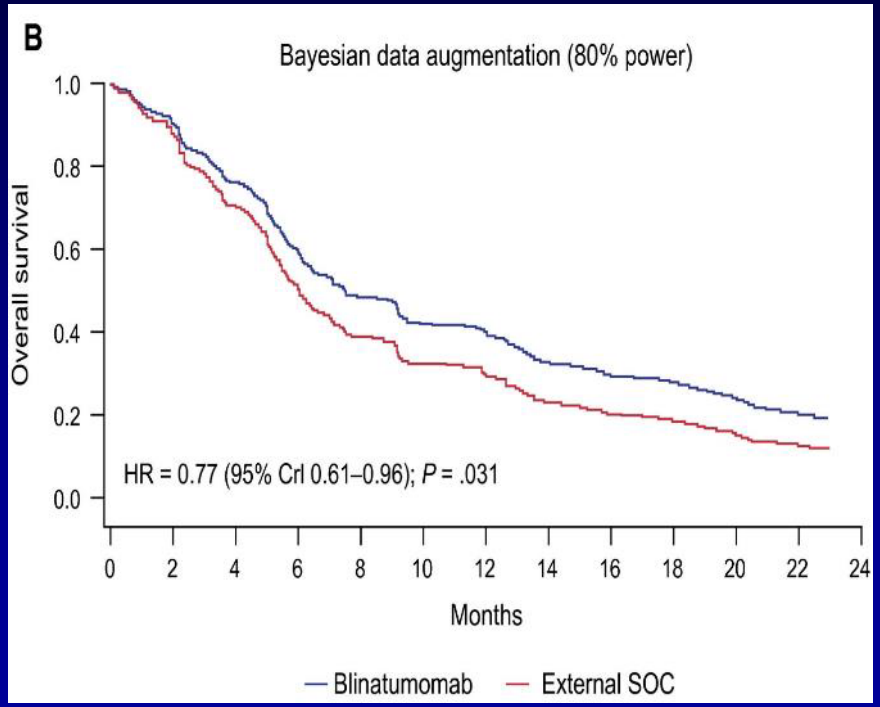


Paul S, et al. *Blood.* 2019;134(suppl):Abstract 3810.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

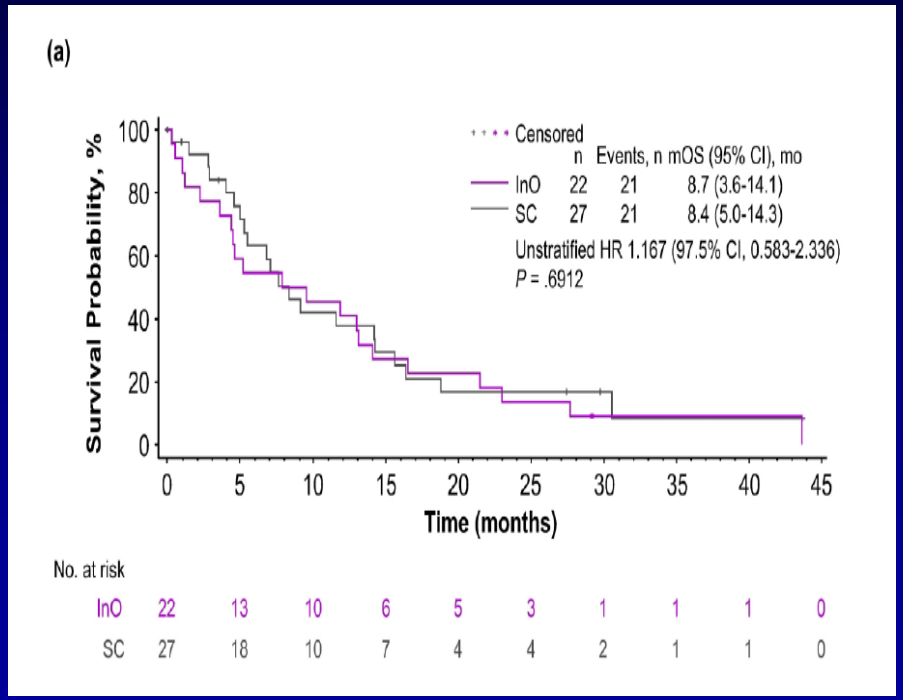
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



Rambaldi et al. *Cancer*. 2019;126:304-310.

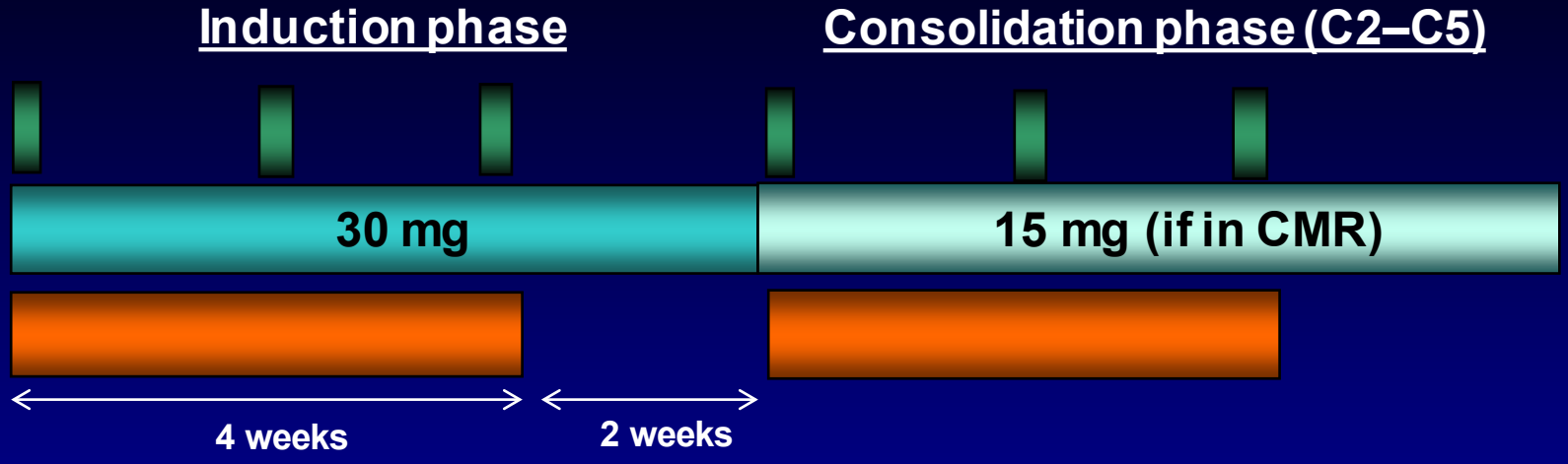
Ino vs SOC

- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%



Stock W, et al. *Cancer*. 2020;127(6):905-913.

Ponatinib + Blinatumomab in Ph+ ALL: Regimen

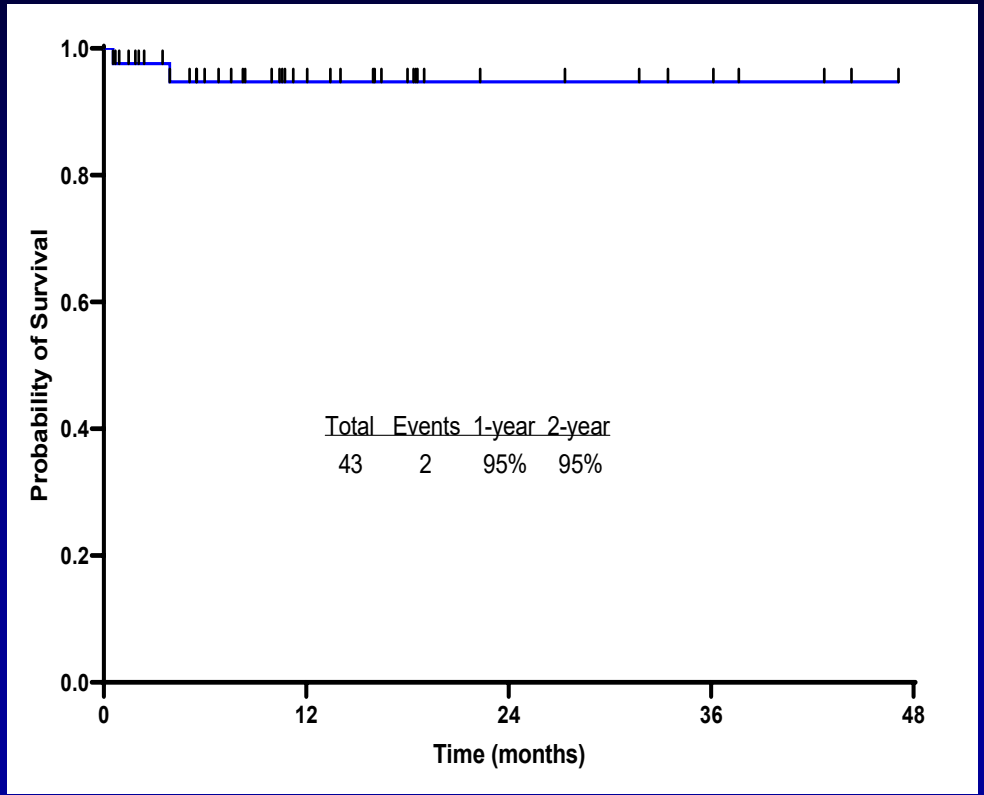


Short NJ, et al. *HemaSphere*. 2022;6:15-16.

Ponatinib and Blinatumomab in Ph+ ALL

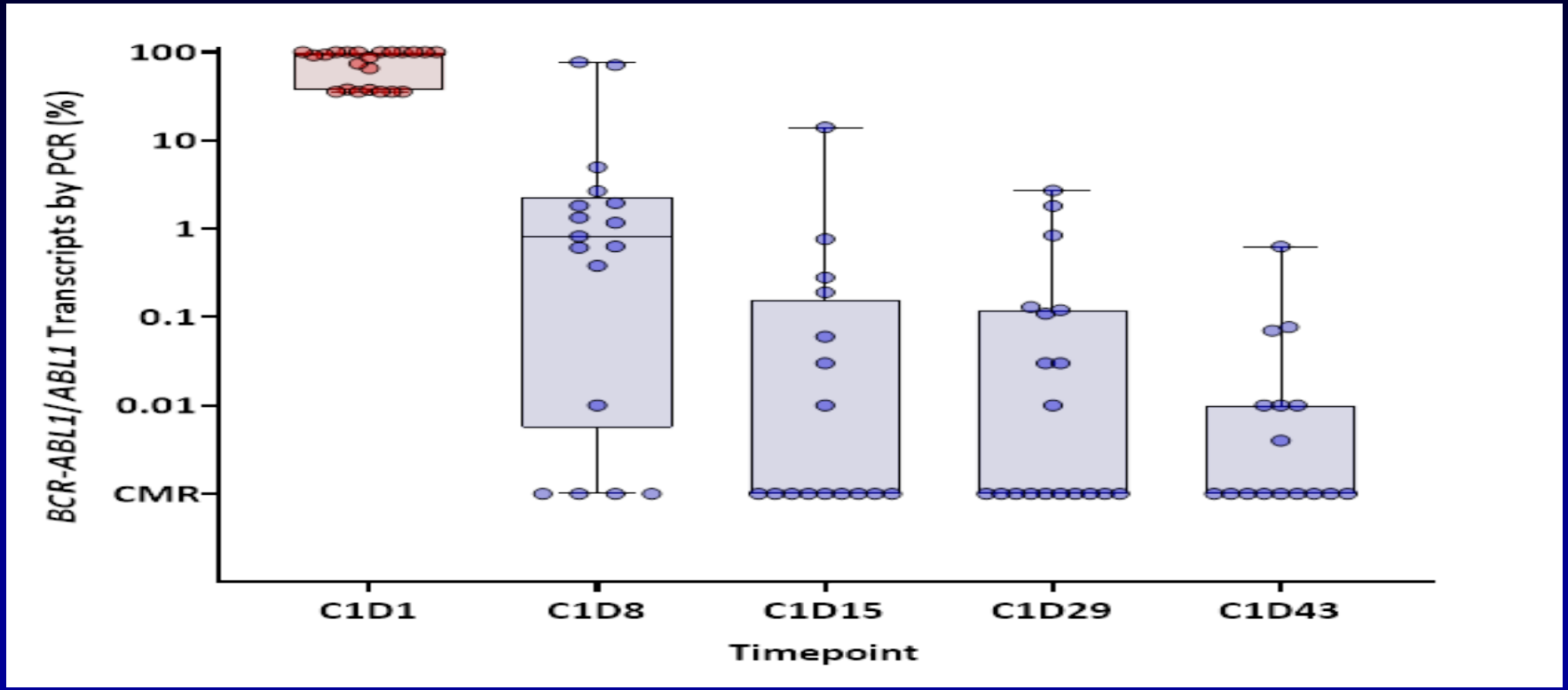
- 63 pts (43 newly Dx, 14 R/R, 6 CML-LBP) Rx with simultaneous ponatinib 45–15 mg/D and blinatumomab × 5 courses
- Only 1 newly Dx pt had SCT (3%)

Parameter	New Dx	R/R	CML-LBP
% CR-CRi	97	92	83
% CMR	79	91	33
% 2-yr OS	95	59	60



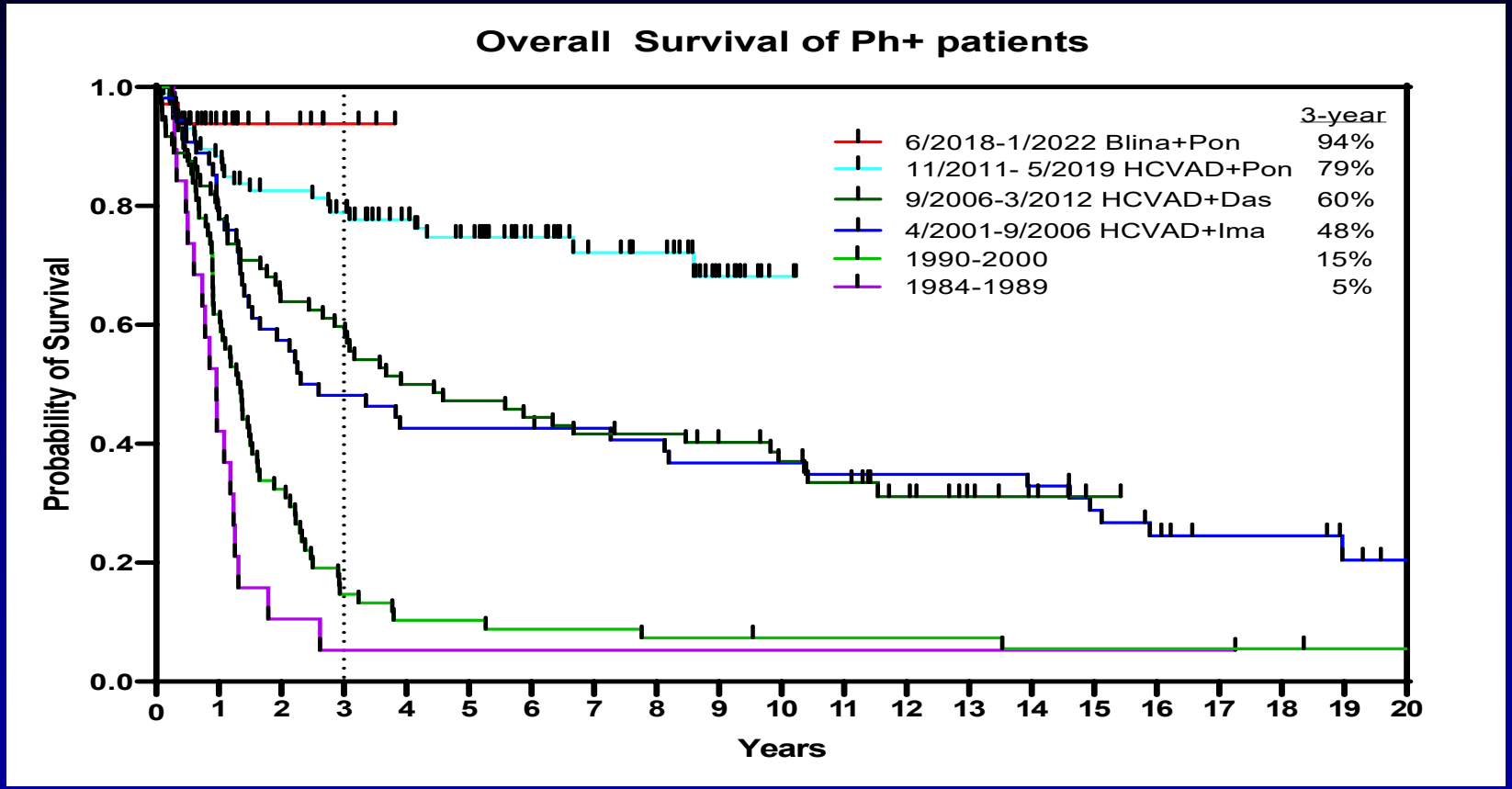
Short NJ, et al. *HemaSphere*. 2022;6:15-16.

Ponatinib + Blinatumomab in Ph+ ALL: Early MRD Responses in Frontline Cohort



Short NJ, et al. *HemaSphere*. 2022;6:15-16.

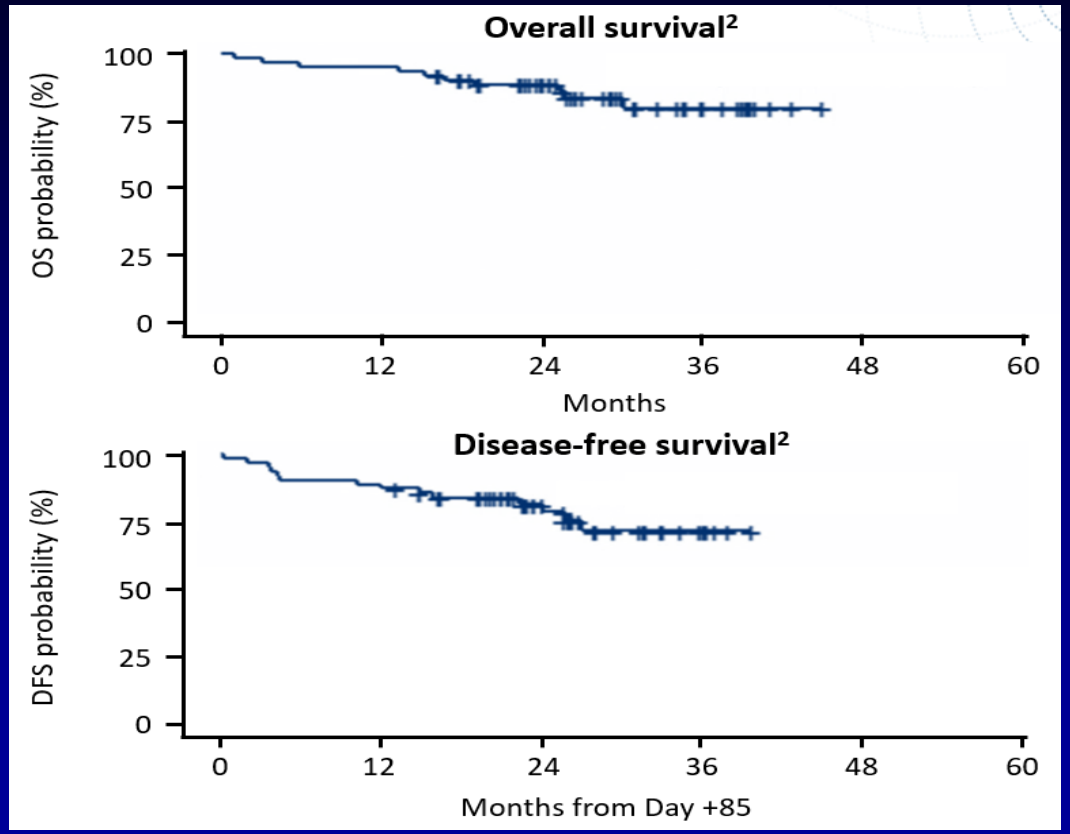
ALL: Survival by Decade (MDACC 1985–2022)



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

Dasatinib-Blinatumomab in Ph+ ALL

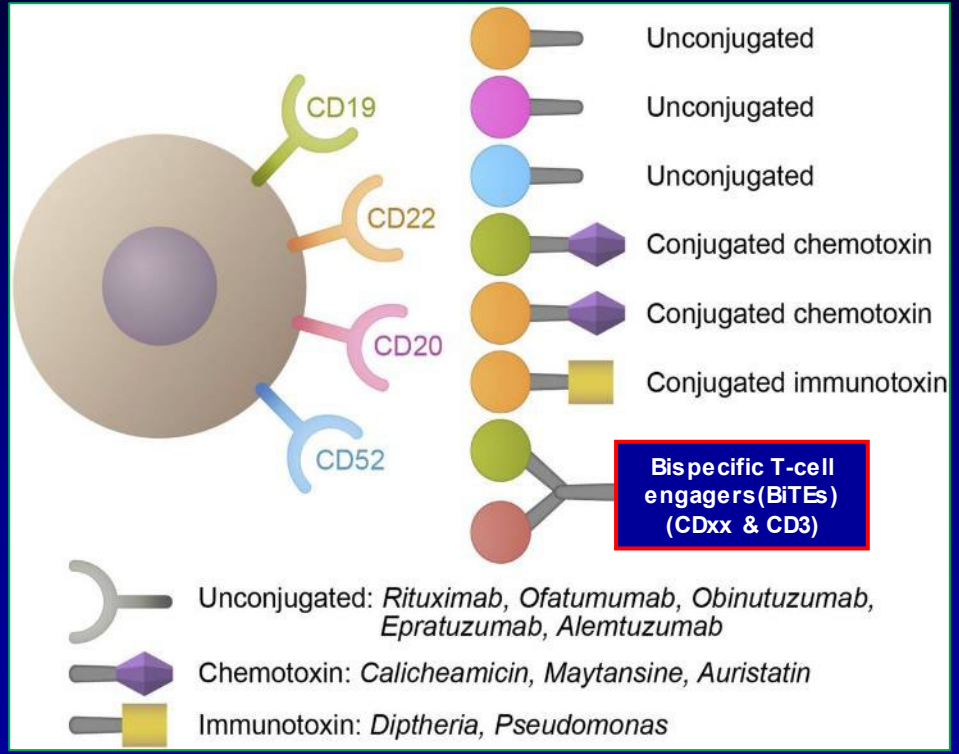
- 63 pts, median age 54 yr (24–82)
- Dasatinib 140 mg/D × 3 mo; add blina × 2–5
- Molecular response 32/53 (60%), 23 CMR (42%). MRD ↑ in 15— 6 T315I
- 4-yr OS 78%; DFS 75%
- 29/58 (50%) allo SCT; no effect of SCT (but 23 went to SCT for no CMR)

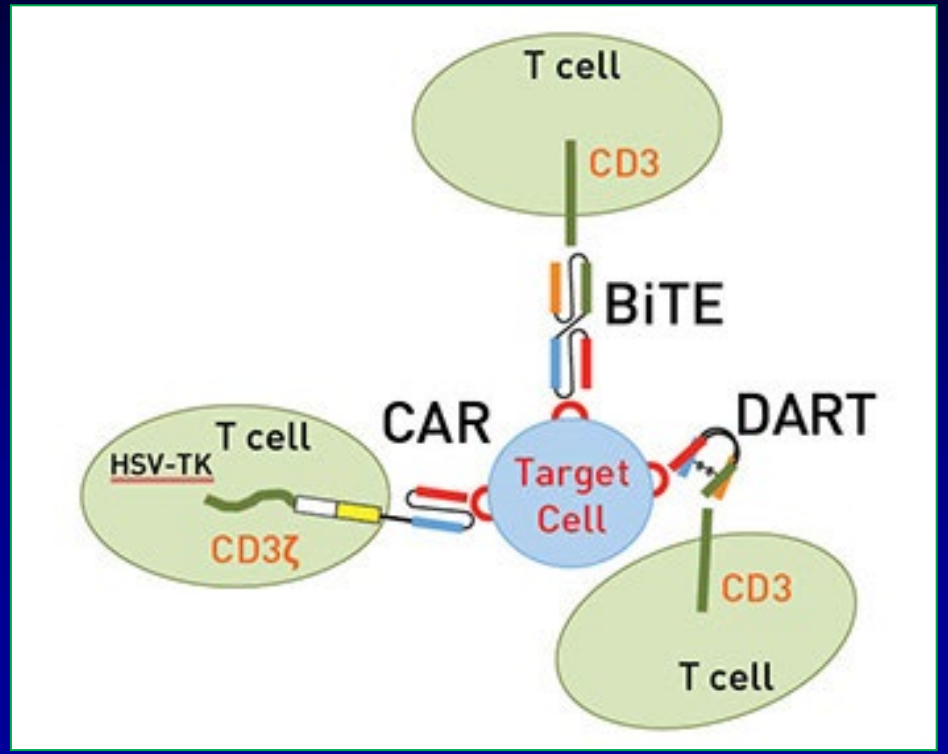


Foa et al. *N Engl J Med.* 2020;383:1613; Chiaretti S, et al. *HemaSphere.* 2022;6:253-254.

Immuno-oncology in ALL

- **Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR T cells**



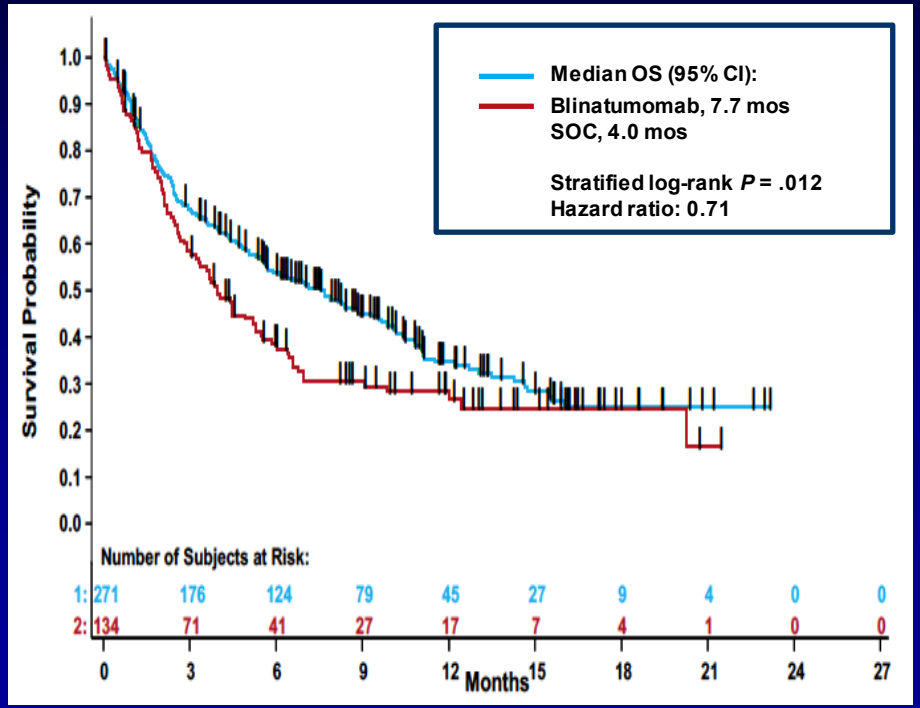


Jabbour E, et al. *Blood.* 2015;125:4010-4016.

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

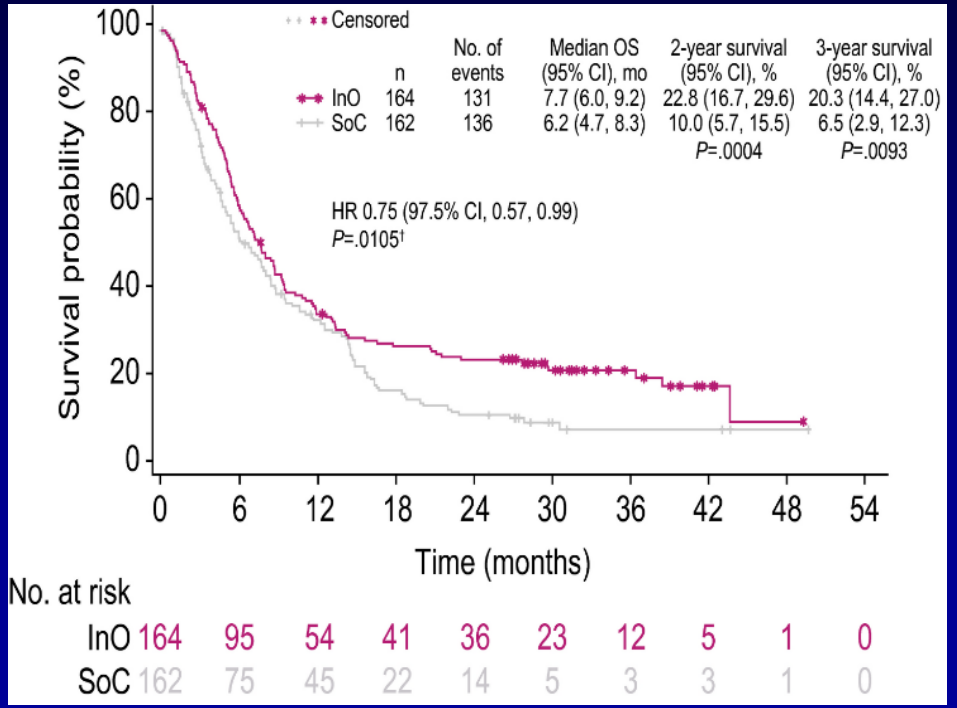
- **Marrow CR**

Blina vs SOC: 44% vs 25%



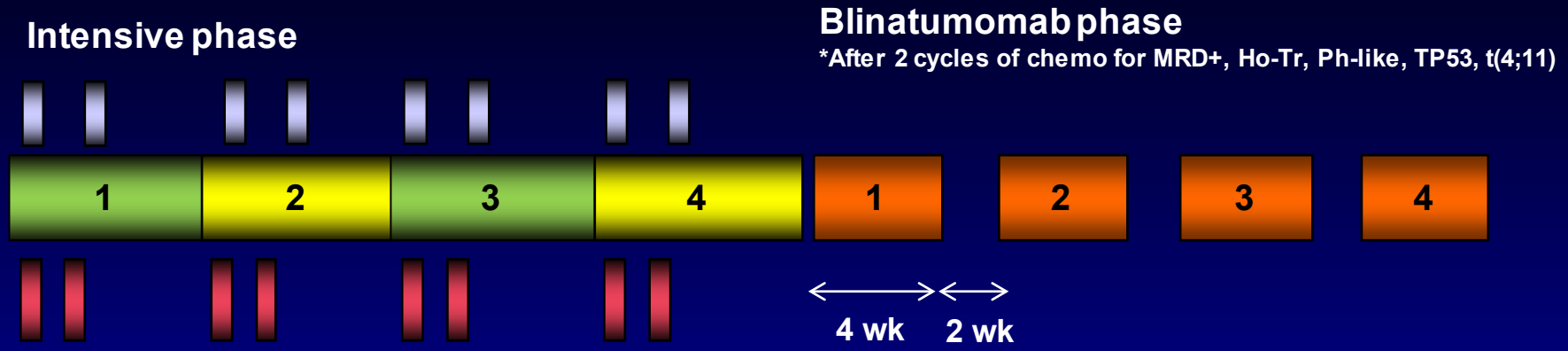
Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Ino vs SOC: 74% vs 31%



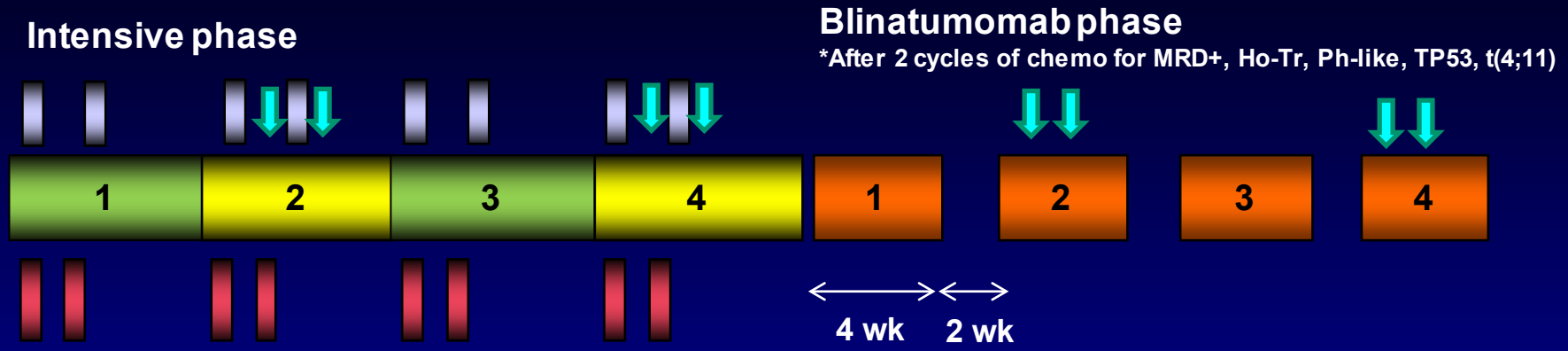
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

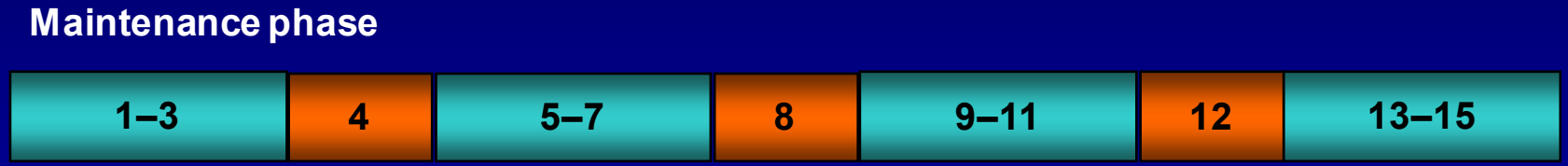
Hyper-CVAD + Blinatumomab in B-ALL: Regimen



Short NJ, et al. *Blood.* 2021;136:abstract 1233.

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





Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX, Ara-C

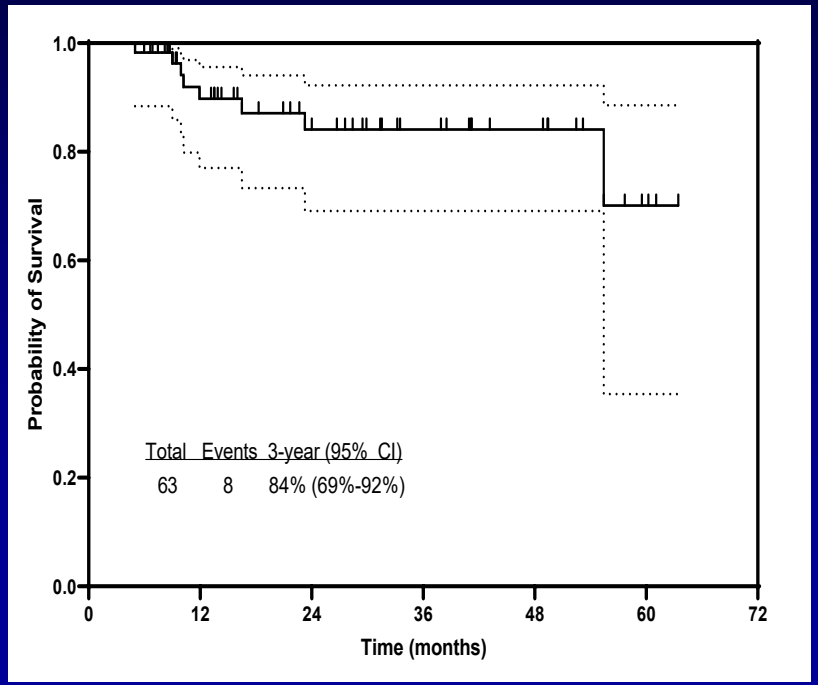
IT MTX, Ara-C × 8

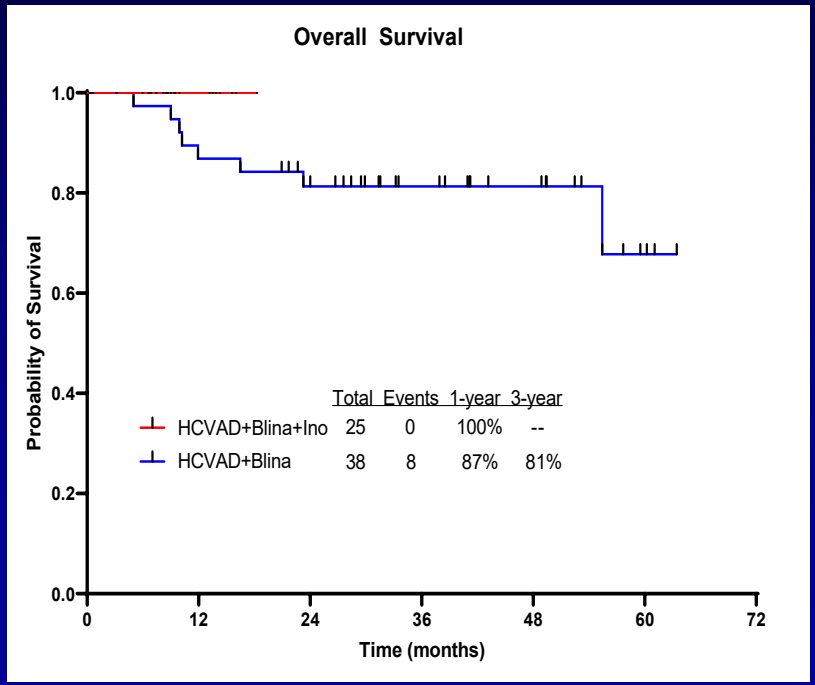
POMP

Inotuzumab 0.3 mg/m^2 on D1 and D8

Hyper-CVAD → Blinatumomab in Newly Dx Adult ALL

- 63 pts; median age 33 yr (18–59). Rx with O-HCVAD × 4; Blina × 4 → POMP 1 yr with blina Q3 mo
- CR rate 100%; MRD negative 95% (75% at CR); 60-day mortality 0%; 12 (32%) allo-SCT; F/U 24 mo

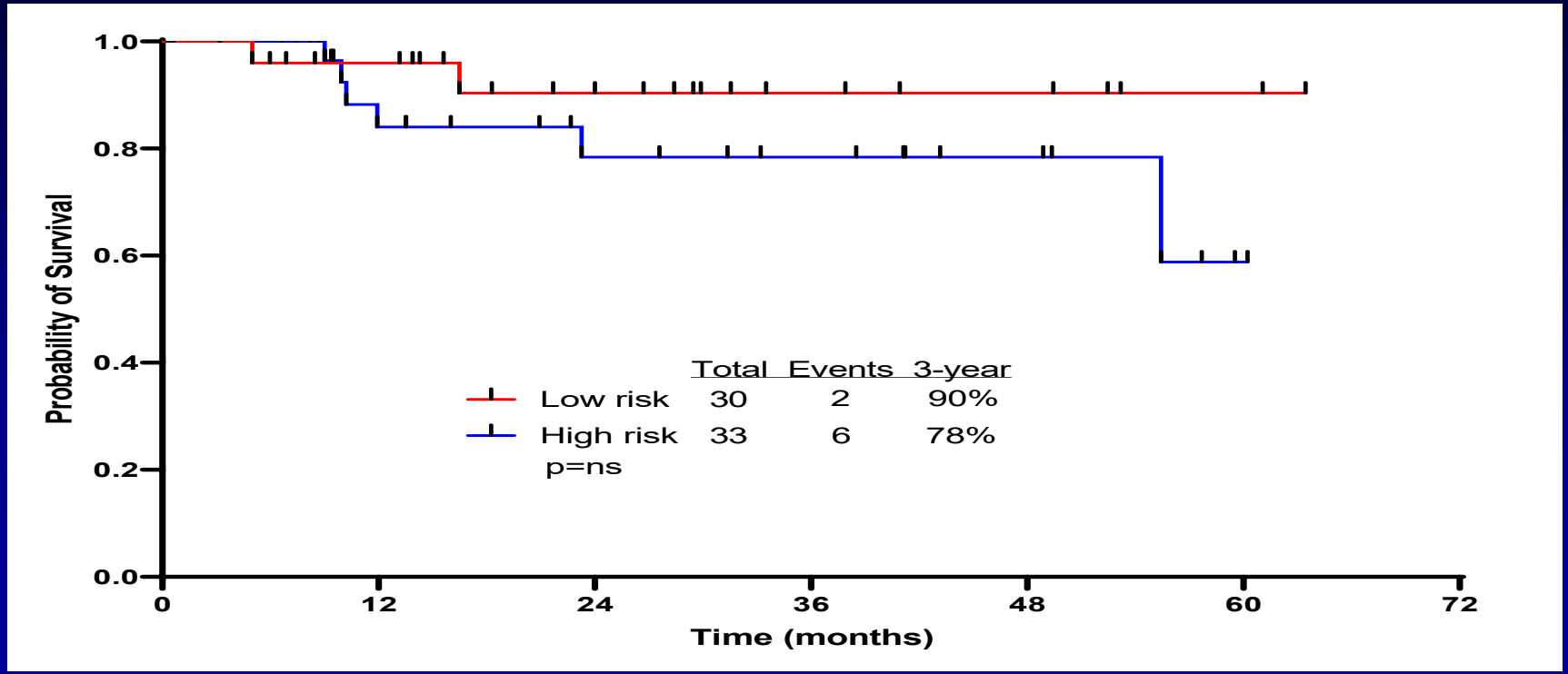




Short NJ, et al. *HemaSphere*. 2022;6:271-272.

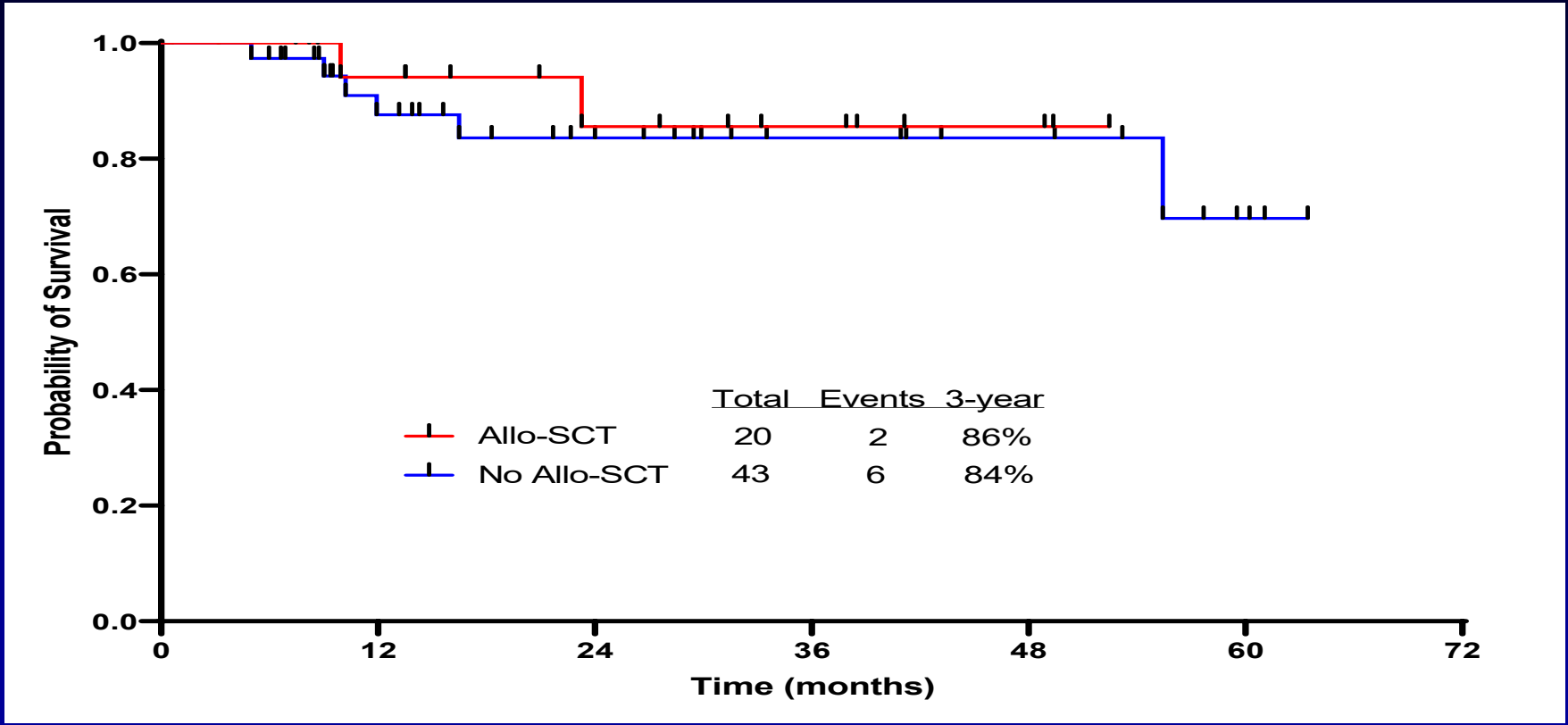
Hyper-CVAD + Blina + InO in B-ALL: Outcome by Risk Categories

- High-risk defined *CRLF2+/JAK2+/TP53*-mutated and poor-risk cytogenetics



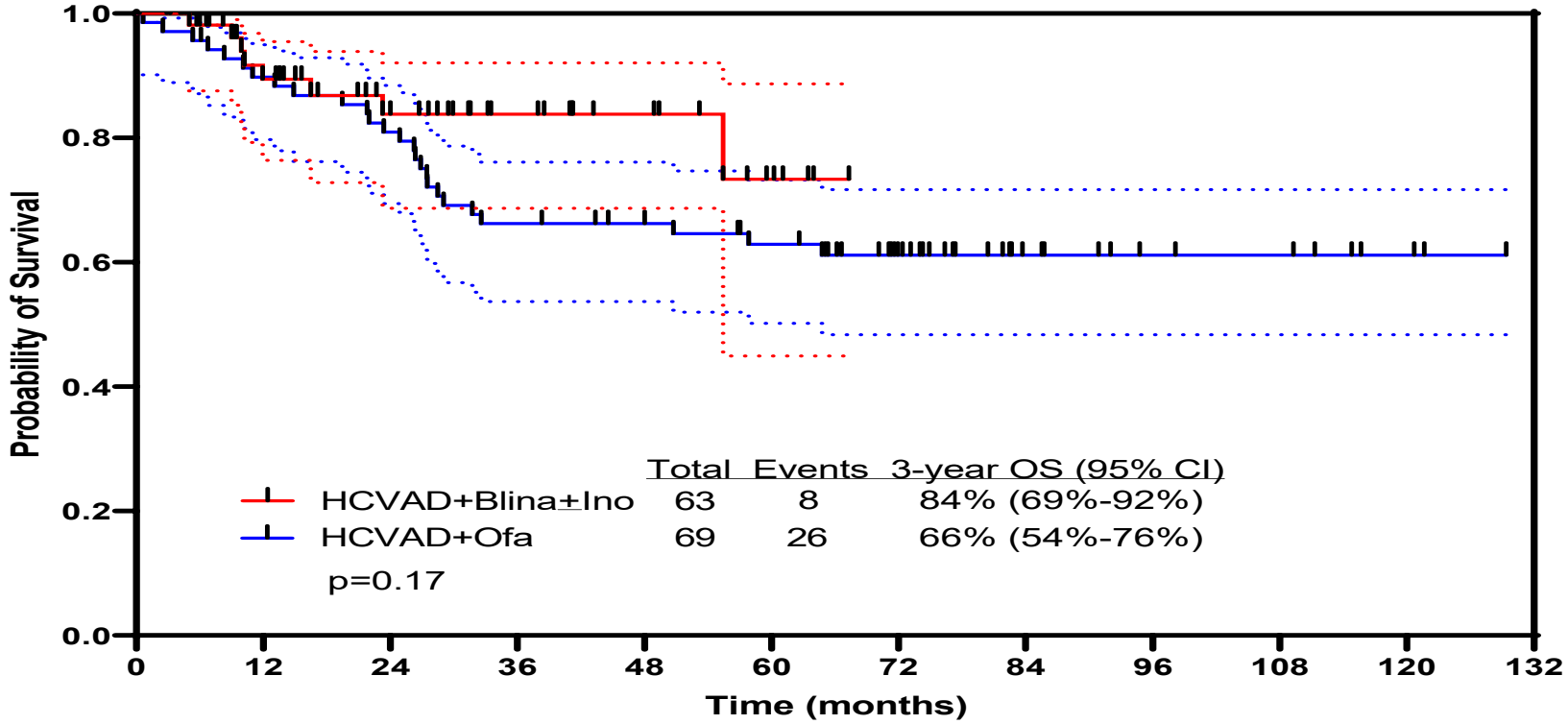
Short NJ, et al. *HemaSphere*. 2022;6:271-272.

Hyper-CVAD + Blina + InO in B-ALL: Outcome by Allo-SCT



Short NJ, et al. *HemaSphere*. 2022;6:271-272.

Hyper-CVAD + Blina + InO in B-ALL: Outcome vs Historical Control



Short NJ, et al. *HemaSphere*. 2022;6:271-272.

Frontline Blinatumomab and Inotuzumab Combinations in Adults With Newly Dx ALL

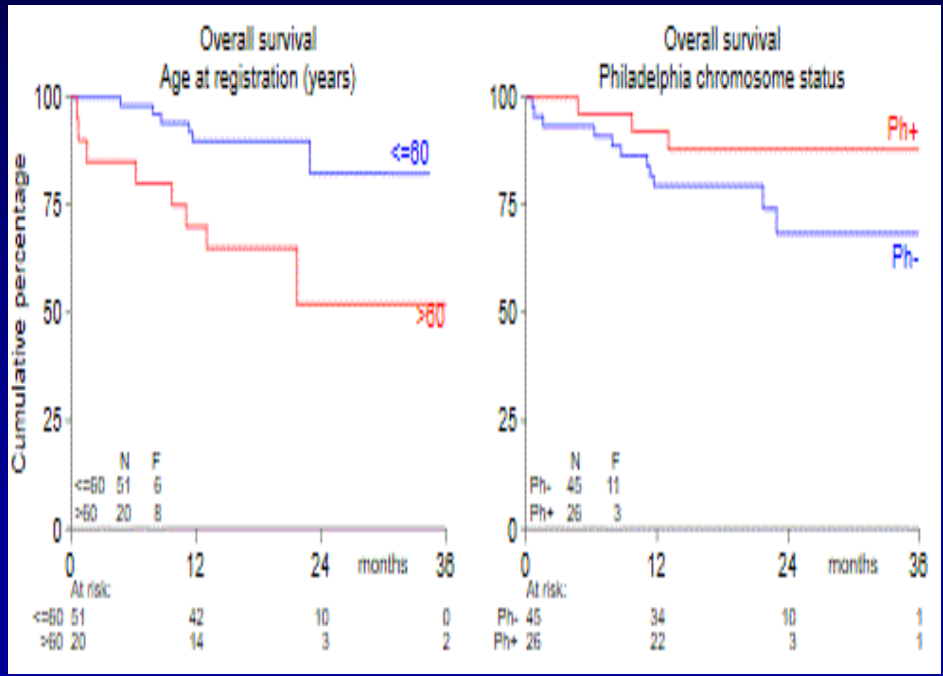
	Agent	N	Median Age (yr, range)	% CR	% MRD negativity	% OS (x-yr)
HCVAD-Blina	Blinatumomab	38	37 (17–59)	100	97	81 (3-yr)
HCVAD-blina-inotuzumab	Blinatumomab and inotuzumab	25	24 (18–47)	100	91	100 (1-yr)
GIMEMA LAL1913	Blinatumomab	149	41 (18–65)	90	96	84 (1-yr)
GRAALL-2014-Quest	Blinatumomab	95	35 (18–60)	NA	74	92 (1.5 yr)
Low-intensity blinatumomab	Blinatumomab	30	52 (39–66)	100	73	69 (2-yr)

Short. *Blood.* 2021;138:1223; Bassan. *HemaSphere.* 2022;6:14-15; Boissel. *Blood.* 2021;140:1232; Fleming. *Blood.* 2021;138:1224.

Blinatumomab Pre-Phase Then 2 Consolidations in ALL (HOVON)

- 71 pts, age 18–70 yr Rx
- Pre-phase 10 days steroids + blina × 14d. ChemoRx HOVON 70 (amended 2x to ↓ PEG-ASP and reduce Int 1). Consolidation-Intensification. Blina × 2 (4-wk courses). Ph+ ALL – add imatinib
- Post-pre phase CR 63%
- 60/71 achieved CR = 85%
- CR 55/56 = 98%; MRD-negativity 50/55 = 91%
- 9 pts DC blina due to toxicity!!
- Ph+ ALL – 2-yr OS 88%
- 22 pts had allo SCT
- 5 relapses (8%), 6 deaths (10%)

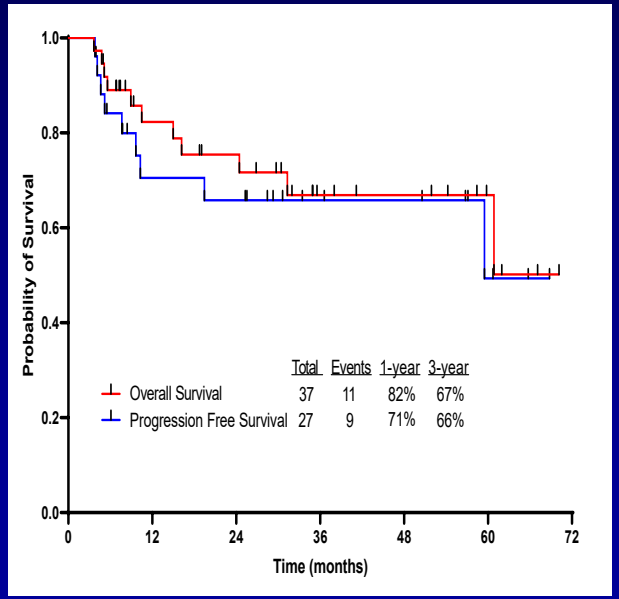
Parameter	Overall	Age <60	Age 60+
% 2-yr EFS	64	71	47
% 2-yr OS	73	82	52

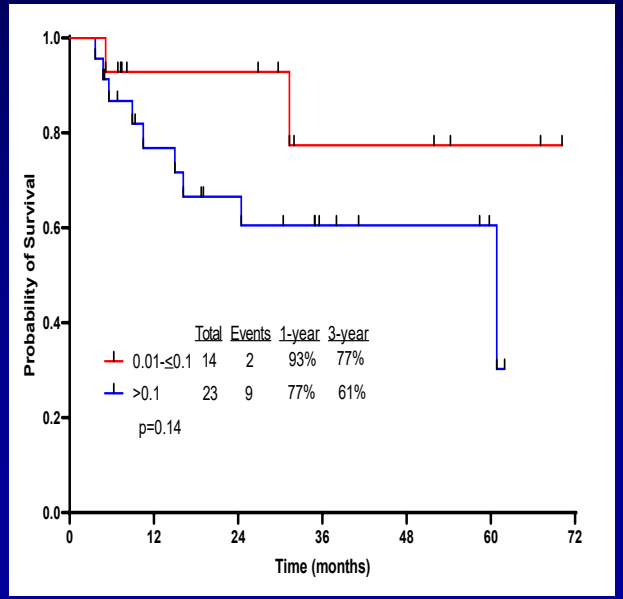


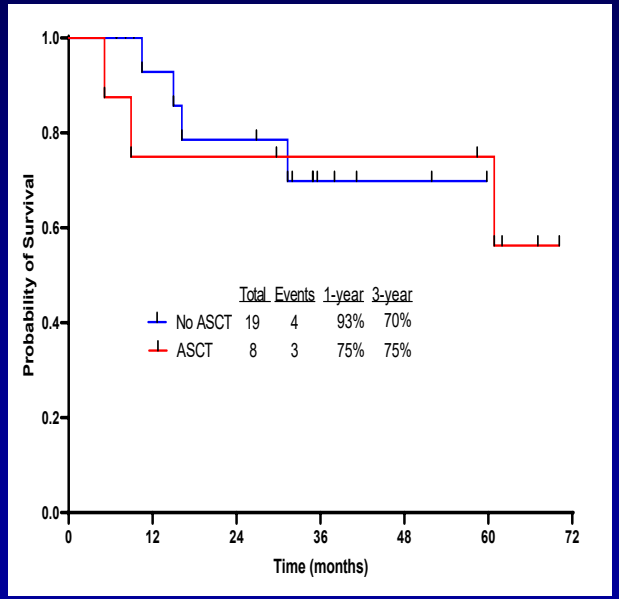
Rijneveld A, et al. *HemaSphere*. 2022;6:266-267.

Blinatumomab for MRD+ ALL in CR1/CR2+

- 37 pts Rx. Post blina MRD– 27/37 = 73%; 83% in Ph– ALL
  - 70% after C1
- Median number of cycles 3 (1–9); Median F/U = 31 mos (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– 72%





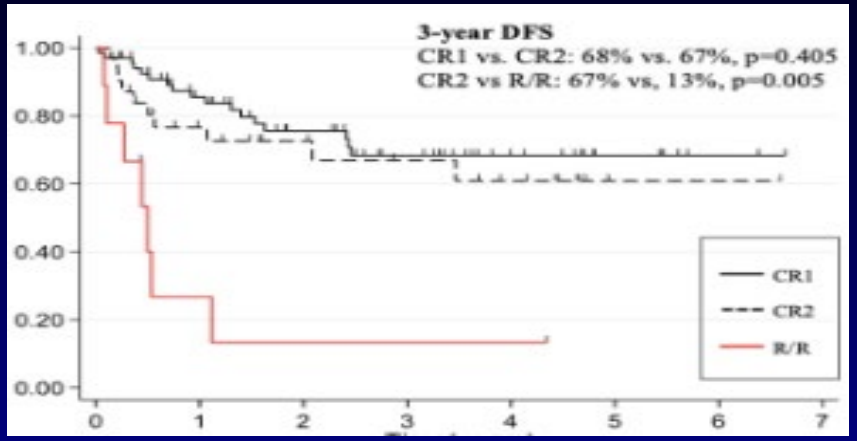


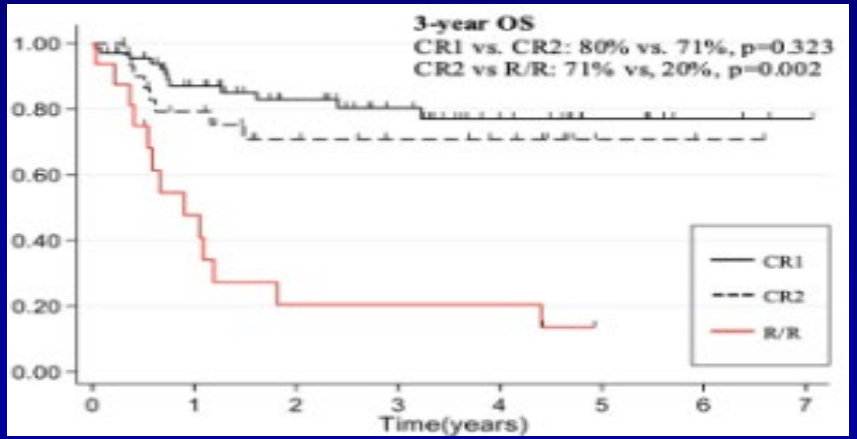
Short NJ, et al. EHA 2021. Abstract EP367.

Blinatumomab Consolidation in ALL: France

- 115 pts Rx with Blina: 68 in CR1, 31 in CR2, 16 in R/R
- Median 2 courses (1–6); 42% later allo SCT

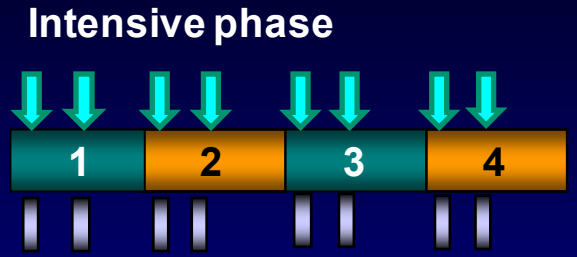
Parameter	CR1	CR2	R/R
% MRD–	83	86	CR9/15 = 60%
% 3-yr DFS	68	67	13
% 3-yr OS	80	71	20





Urbino I, et al. *HemaSphere*. 2022;6:274-275.

Mini-HCVD + INO ± Blina in Older ALL: Modified Design (patients 50+ years)



Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

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

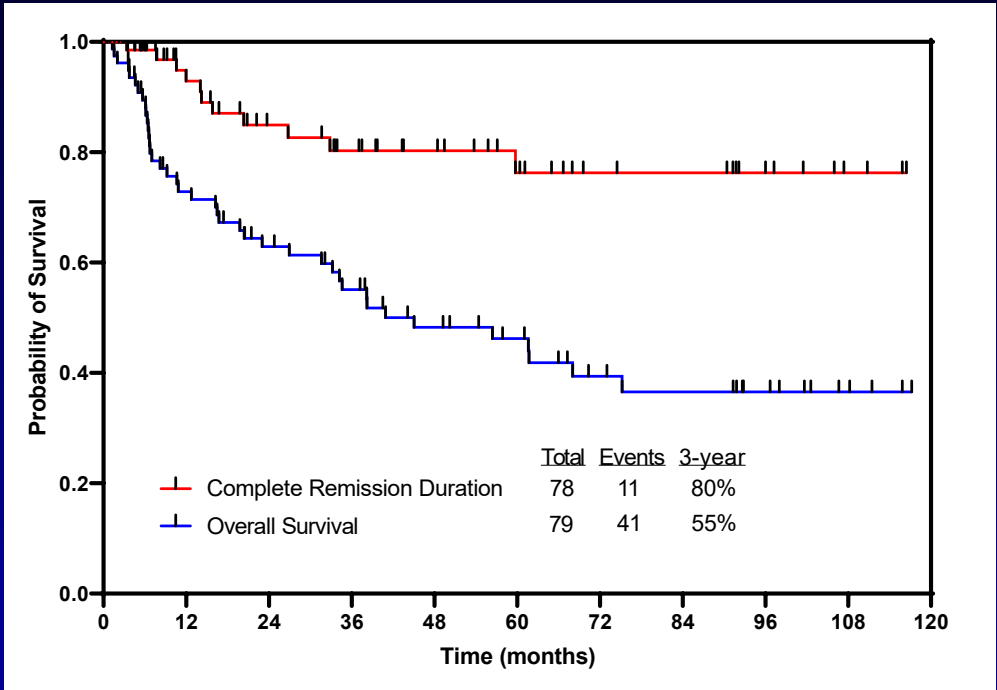
Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

Haddad F, et al. *HemaSphere.* 2022;6:255-256.

Mini-HCVD + Inotuzumab/Blinatumomab in Older ALL

- 80 pts Rx: 74 active ALL; 6 CR
- CR + CRi 73/74 = 99%; CR 89%; MRD– 94%
- 30-D mortality 0%
- Relapse 11 (14%); death in CR 31 (39%)
- 9 pts developed AML/MDS; all age 70+, 7/9 with *TP53*
- 5-yr CR 76%; 5-yr OS 47%



Kantarjian H, et al. *Lancet Oncol.* 2018;19:240-240; Haddad F, et al. HemaSphere. 2022;6:255-256.

Frontline Blina and Inotuzumab Combinations in Newly Dx Older ALL

	Agent	N	Median Age (yr, range)	% CR	% MRD negativity	% OS (x-yr)
Mini-HCVD-INO-blina	Blinatumomab and inotuzumab	79	68 (60–87)	89	94	55 (3-yr)
SWOG-1318	Blinatumomab	31	73 (66–86)	66	92	37 (3-yr)
EWALL-INO	Inotuzumab	115	69 (55–84)	88	73	78 (1-yr)
GMALL Bold	Blinatumomab	34	65 (56–76)	76	69	89 (1-yr)
INITIAL-1	Inotuzumab	45	65 (56–80)	100	74	77 (2-yr)

Short. *Blood.* 2021;138:3400; Advani. *J Clin Oncol.* 2022;40(14):1574-1582; Chevallier. *Blood.* 2021;140:abstract 511; Goekbuget. *Blood.* 2021;140:abstract 3399; Stelljes. *Blood.* 2021;140:abstract 2300.

Hyper-CVAD + Nel in T-ALL/T-LL: Design

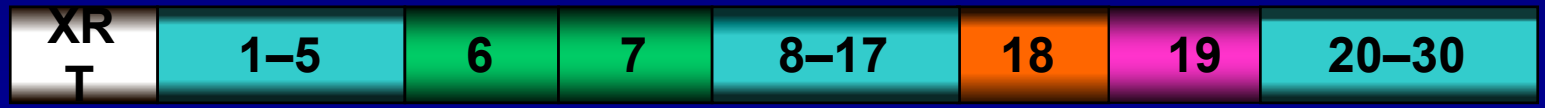
Regimen 4 (N = 15)

Venetoclax: initially 2 weeks per cycle, then 1 week per subsequent cycles

Induction-Consolidation

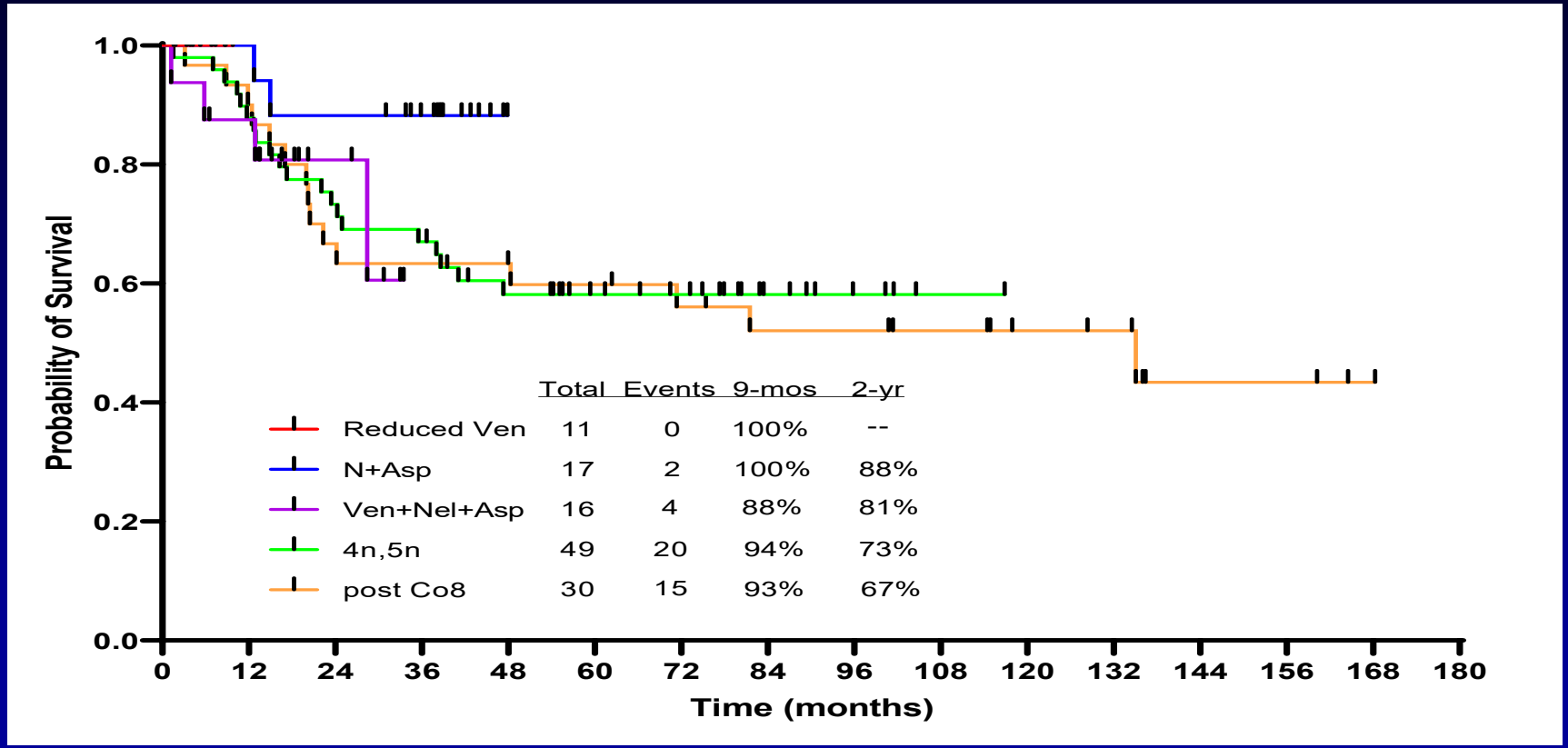
Nelarabine: 650 mg/m^2 IV daily for 5 days
PEG asparaginase: 1500 IU/m^2; capped

Maintenance



Hyper-CVAD
MTX-Ara-C
Nelarabine/PEG asparaginase
IT MTX, Ara-C
POMP
Mediastinal XRT
MTX + Peg-A

T-ALL: Overall Survival With Modified H-CVAD Regimens

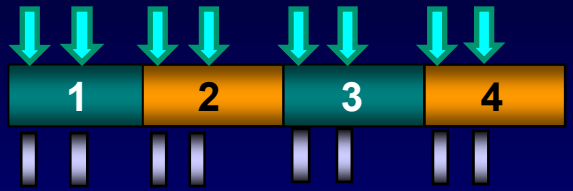


ALL: Role of Allogeneic SCT

- ALL-MLL; t(11q23; ---)
- Precursor T-ALL
- Complex CG ≥5 abn; near hypoploid+p53
- Ph-like if CRLF2 + *JAK2* mutation
- Others: Ph+ ALL PCR+ in CR3 mos; other Ph-like ALL; ALL CR1 MRD+ – may be managed with blina-ino

Mini-HCVD + INO ± Blina in R/R ALL

Intensive phase



Consolidation phase

Maintenance phase

Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

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

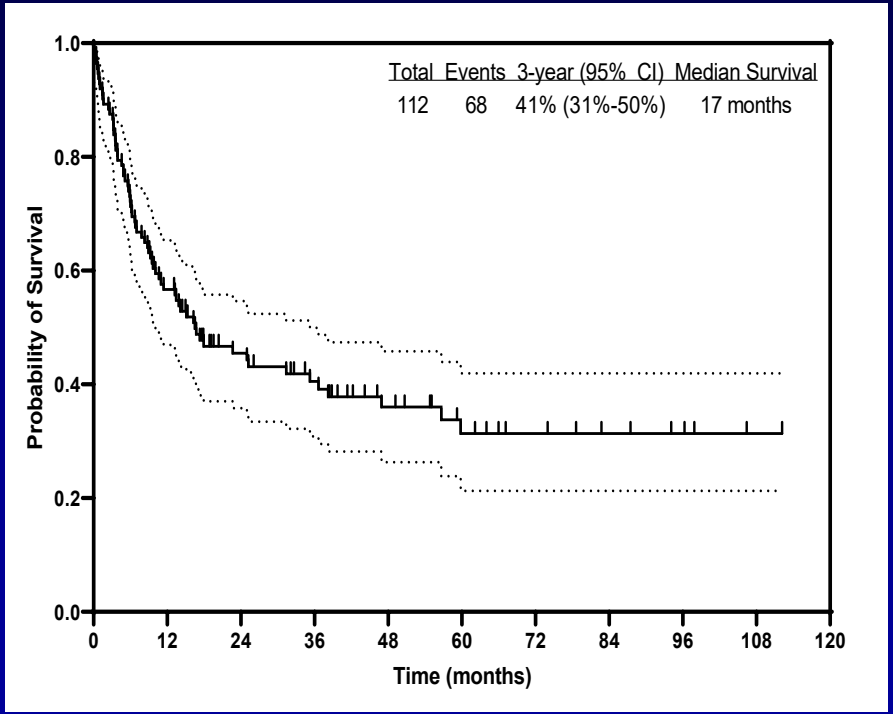
Total INO dose = 2.7 mg/m^2

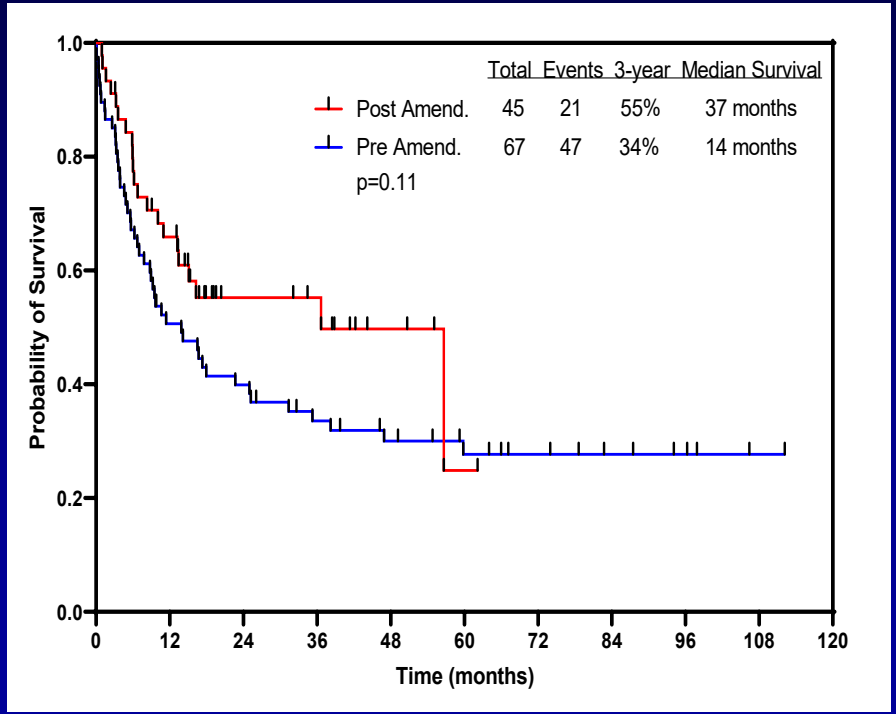
*Ursodiol 300 mg tid for VOD prophylaxis

Haddad F, et al. *HemaSphere*. 2022;6:255-256.

ALL Salvage – MiniCVD-Inotuzumab ± Blinatumomab

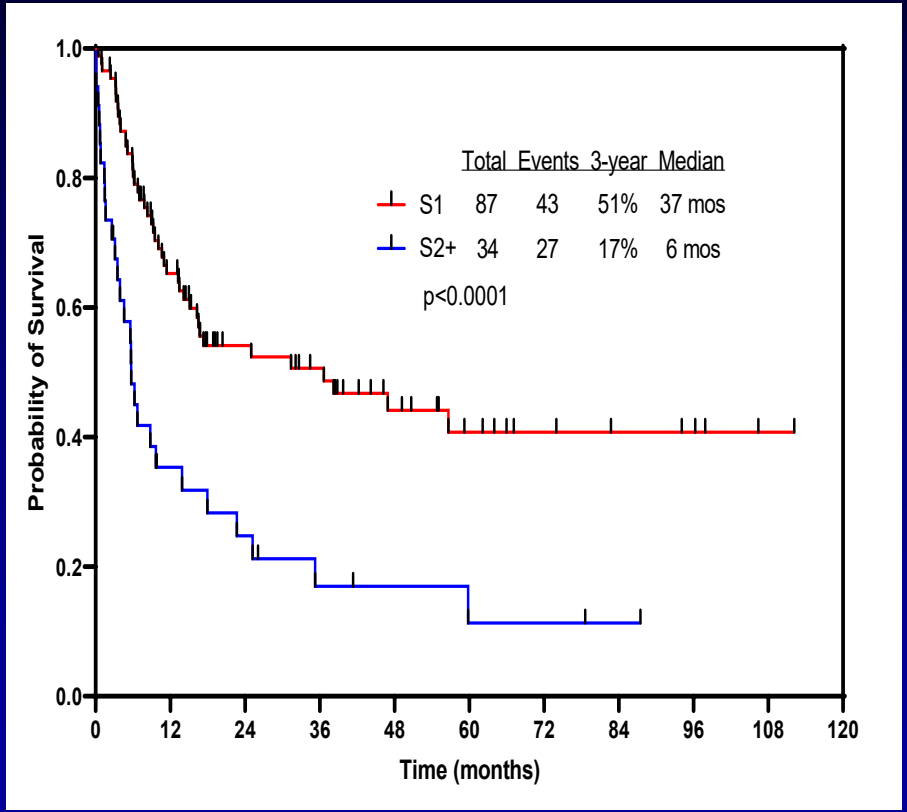
- 112 pts Rx for R/R ALL: 80 in S1; 32 in S2+
- CR 70/112 = 62%; ORR 93/112 = 83%. MRD-neg 76/91 = 83%. VOD 10/112 = 9%; 1% post amendment



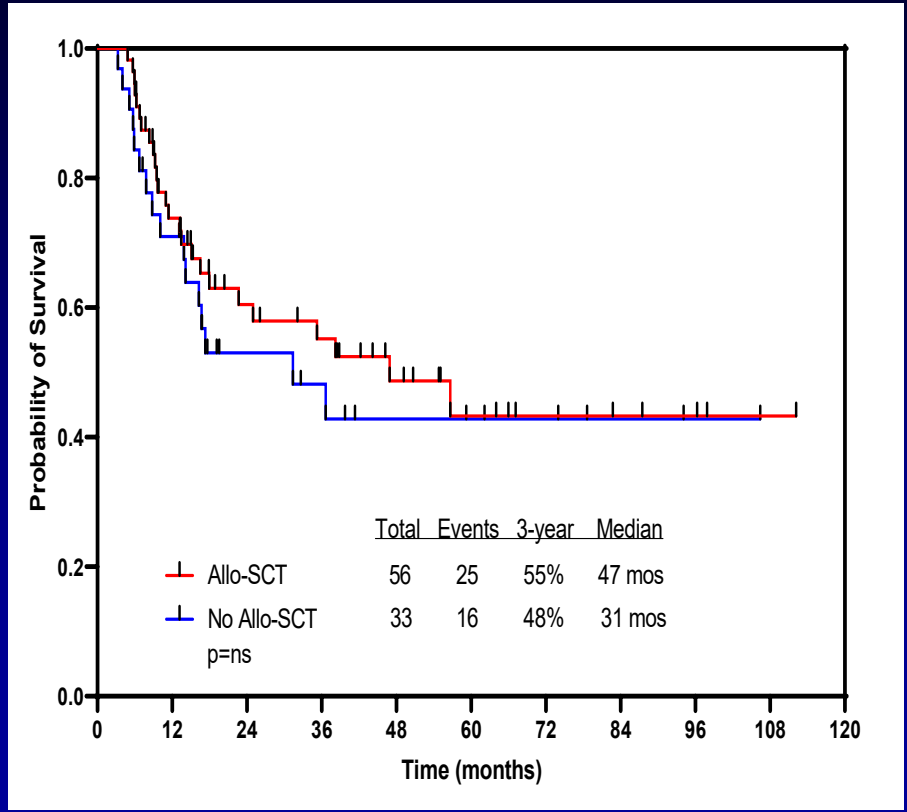


Mini-HCVD + INO ± Blina in R/R ALL. Outcomes

OS by Salvage Status

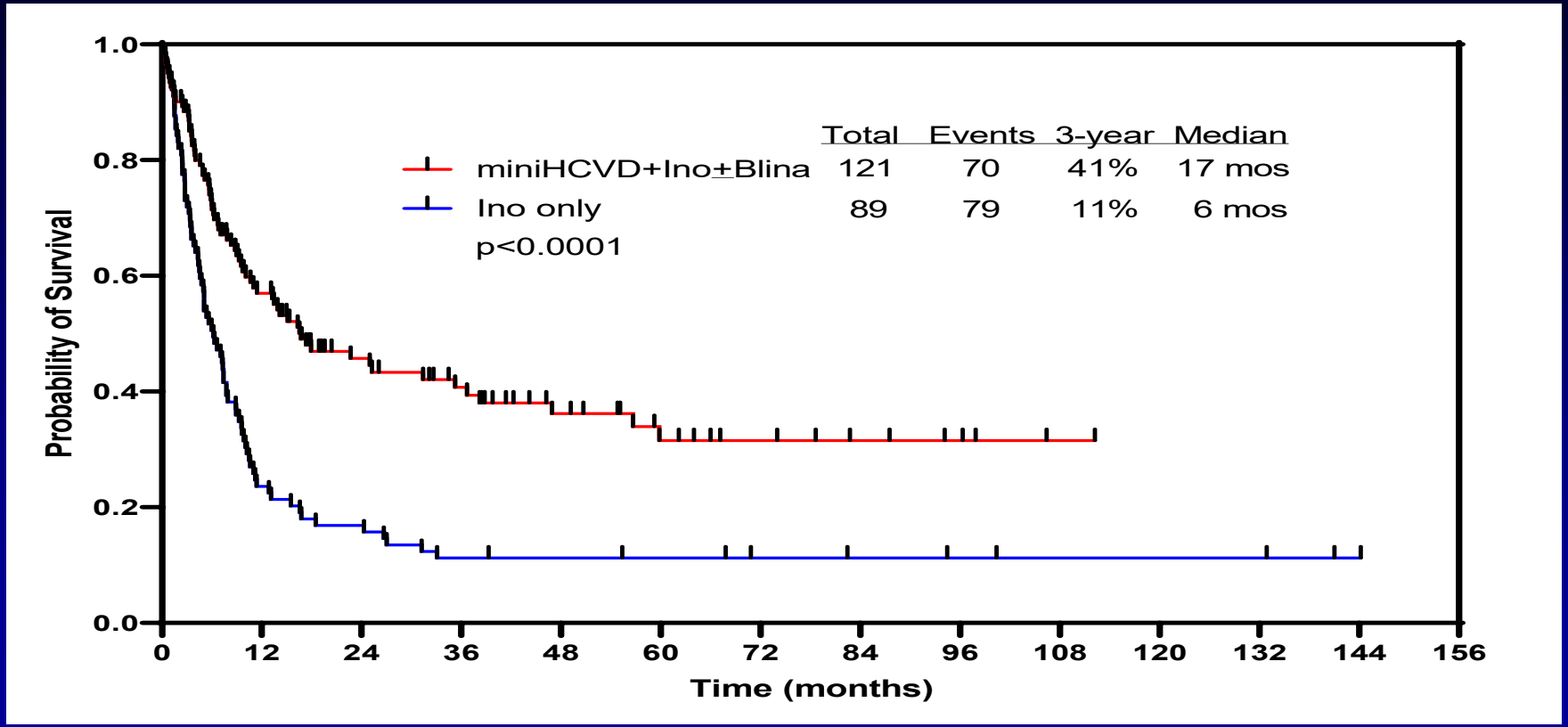


Outcome by Allo-SCT: 3-Month Landmark



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

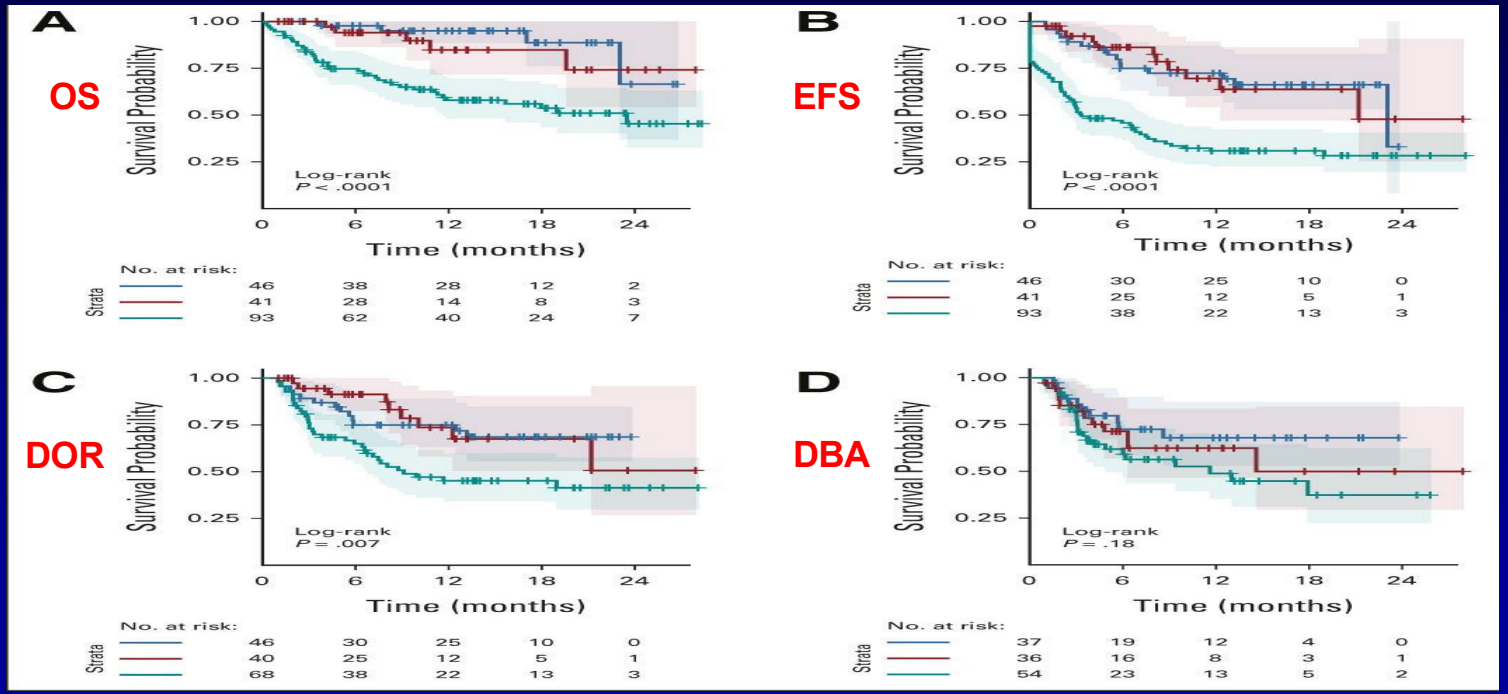
Mini-HCVD + INO ± Blina in R/R ALL: Historical Comparison



Jabbour E, et al. *JAMA Oncol.* 2018;4(2):230-234; Jabbour E, et al. *Cancer.* 2021;127(12):2025-2038.

Real-World CAR Consortium and Disease Burden

- 200 pts (185 pts infused); median age 12 yr (0–26 yr); CR = 85%
- HBD n = 94 (47%); LBD n = 60 (30%); ND n = 46 (23%)
- 12-mo EFS = 50%, 12 mo OS = 72%
- G3 CRS = 21% (35% in HBD); G3 NE = 7% (9% in HBD)



Schultz et al. *J Clin Oncol.* 2022;40:945-955.

ALL – Summary

- Antibody-based Rxs and CAR Ts both outstanding
- Not mutually exclusive/competitive (vs); rather complementary (together)
- Future of ALL Rx: 1) less chemotherapy and shorter durations; 2) combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22; 3) CAR Ts in sequence in CR1 for MRD and replacing allo SCT
- SQ easily deliverable BiTEs
- Monitor MRD by NGS (MRD in 1 million cells) to decide on Rx changes and Rx duration

Leukemia Questions?

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- Cell: 281-705-7207
- Office: 713-792-7026

Global Leukemia Academy

The Clinical Value of MRD in ALL: How MRD Can Guide the Use of Targeted Agents or Immunotherapy

Josep-Maria Ribera

APTITUDE HEALTH

Global Leukemia Academy Focus on Europe
Virtual Plenary Session, September 23, 2022

Clinical value of MRD in ALL: How MRD can guide the use of targeted therapies and immunotherapies

JM Ribera

Clinical Hematology Department

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Josep Carreras Research Institute

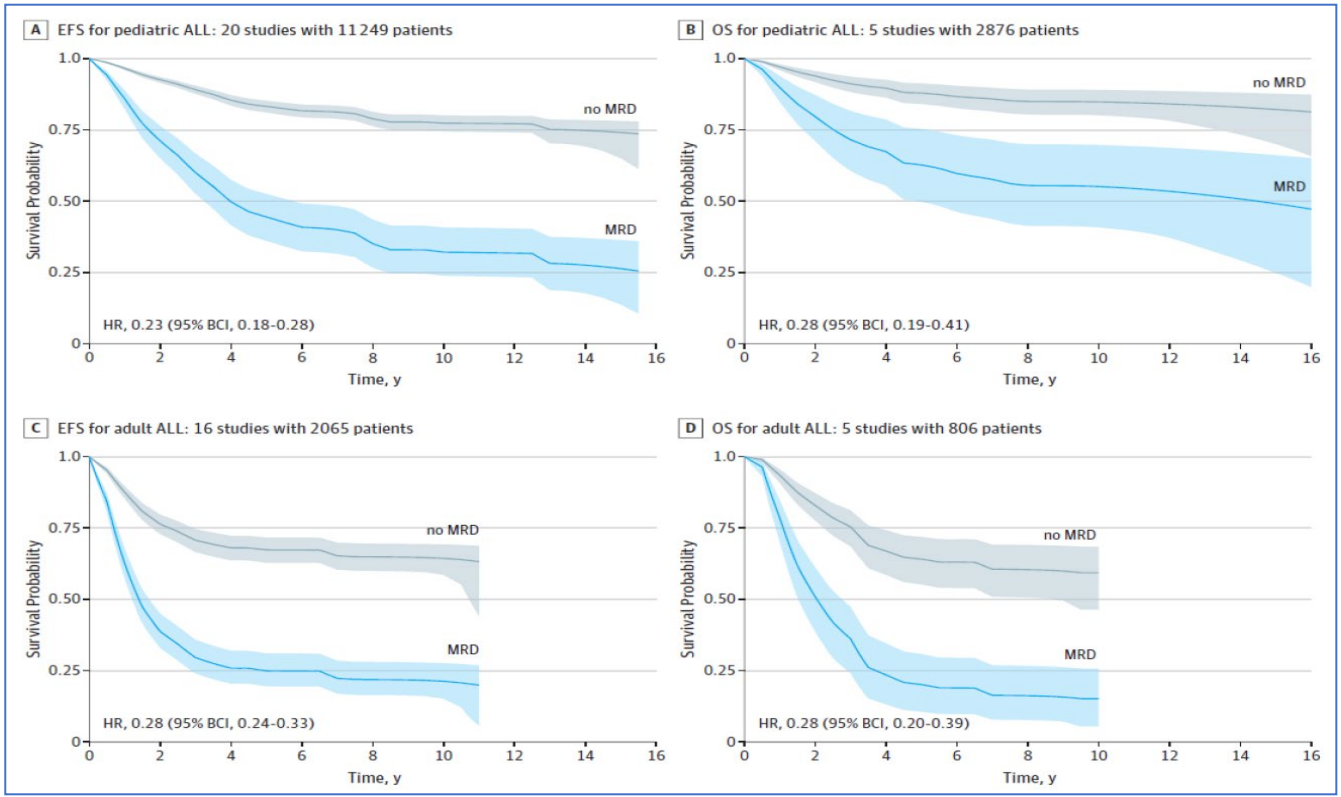
Badalona, Spain

Disclosures

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

Clinical Value of MRD in Acute Lymphoblastic Leukemia

Negative MRD Is Associated With Longer EFS and OS in Pediatric and Adult ALL

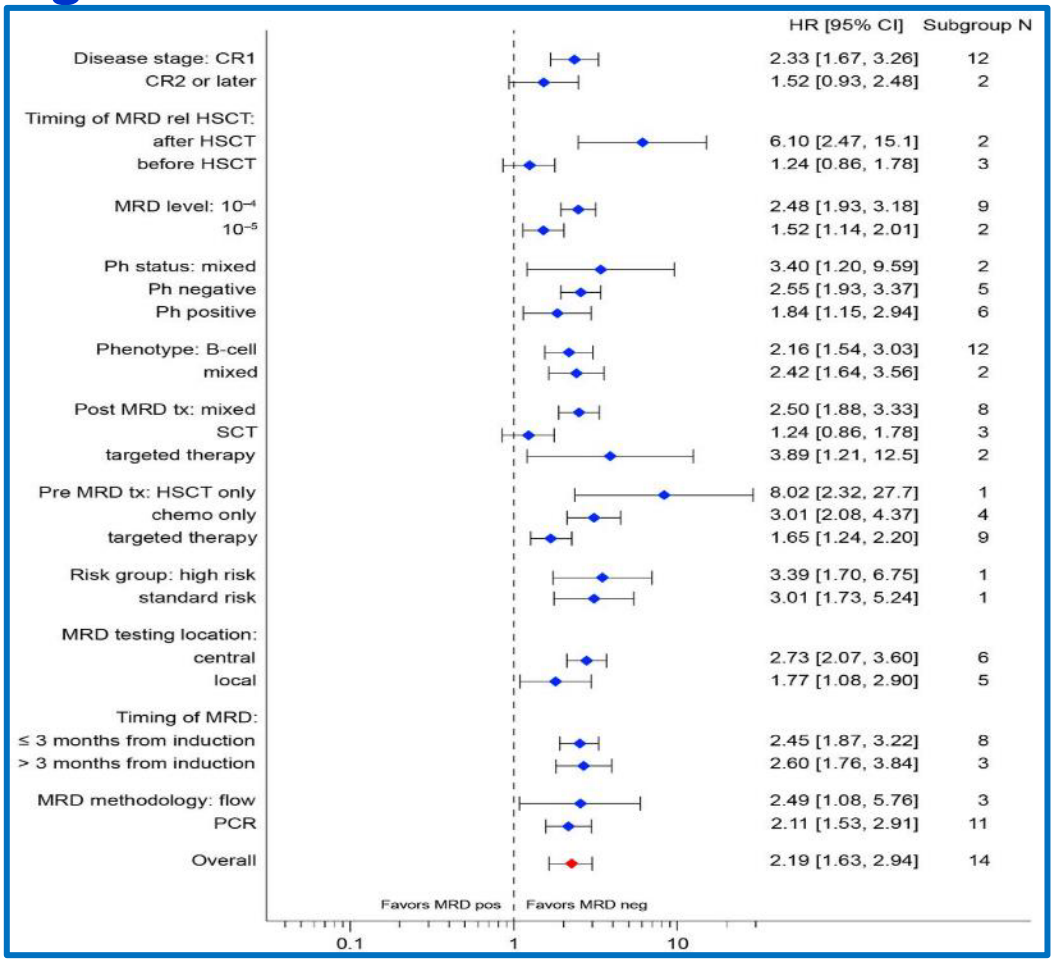


Meta-analysis of 20 pediatric ALL trials >11,000 patients

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

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

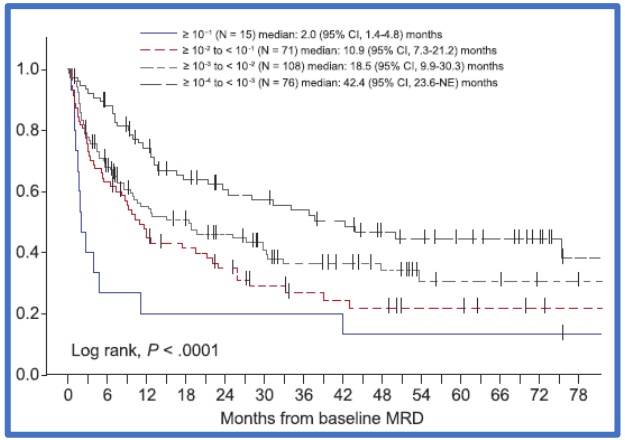
Prognostic Value of MRD in All Situations



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

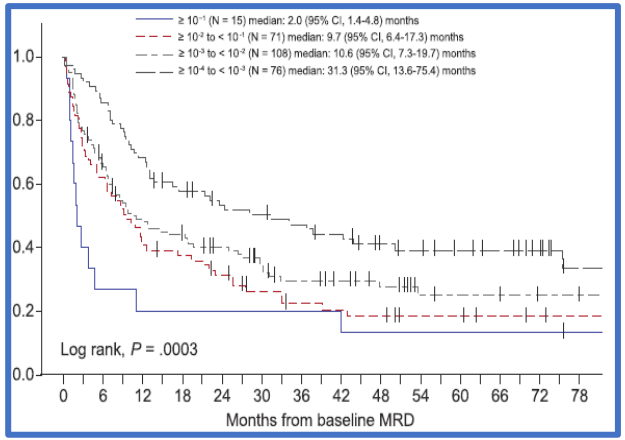
Impact of End-Induction MRD Level on Prognosis in Ph– ALL

Survey From 7 EU Cooperative Groups



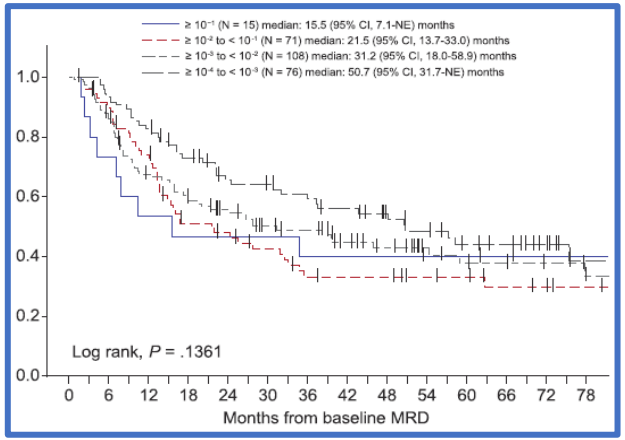
Duration of Remission

≥10^{-1} (N = 15) median 2 months
≥10^{-2} to <10^{-1} (N = 71) median 10.9 months
≥10^{-3} to <10^{-2} (N = 108) median 18.5 months
≥10^{-4} to <10^{-3} (N = 76) median 42.4 months



RFS

≥10^{-1} (N = 15) median 2 months
≥10^{-2} to <10^{-1} (N = 71) median 9.7 months
≥10^{-3} to <10^{-2} (N = 108) median 10.6 months
≥10^{-4} to <10^{-3} (N = 76) median 31.3 months

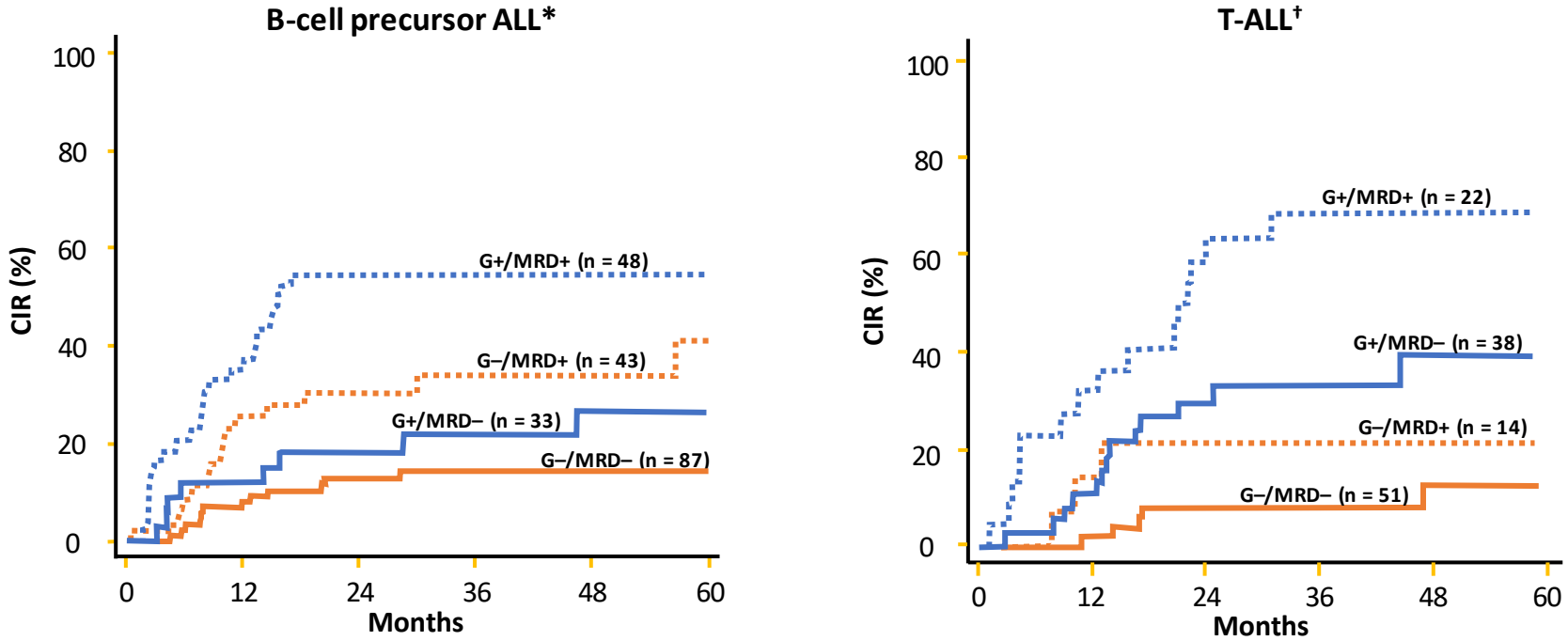


OS

≥10^{-1} (N = 15) median 15.5 months
≥10^{-2} to <10^{-1} (N = 71) median 21.5 months
≥10^{-3} to <10^{-2} (N = 108) median 31.2 months
≥10^{-4} to <10^{-3} (N = 76) median 50.7 months

Gökbuget N, et al. *Hematology*. 2019;24:337-348.

MRD Is Not the Only Prognostic Factor: Genetic Background Counts – GRAALL Data



GENETIC RISK: ***B-cell precursor ALL** – MLL and/or *IKZF1* mutation; †**T-ALL** – no *NOTCH* and/or *RAS*/*PTEN* mutation

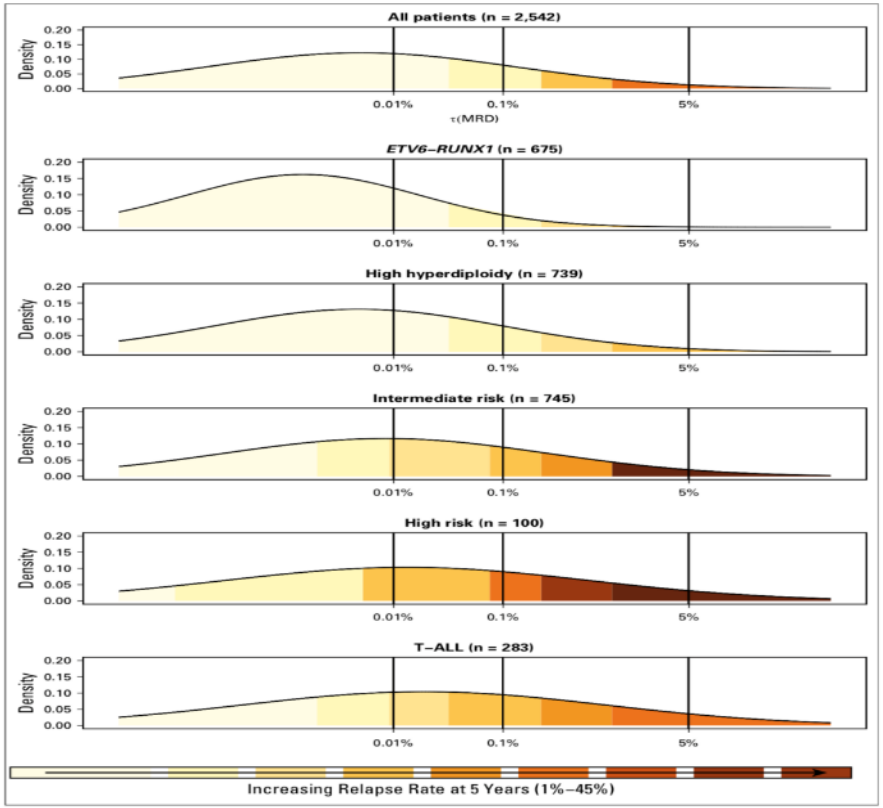
Adapted from Beldjord K, et al. *Blood.* 2014;123:3739-3749.

Value of MRD According to Genetic Subgroups

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

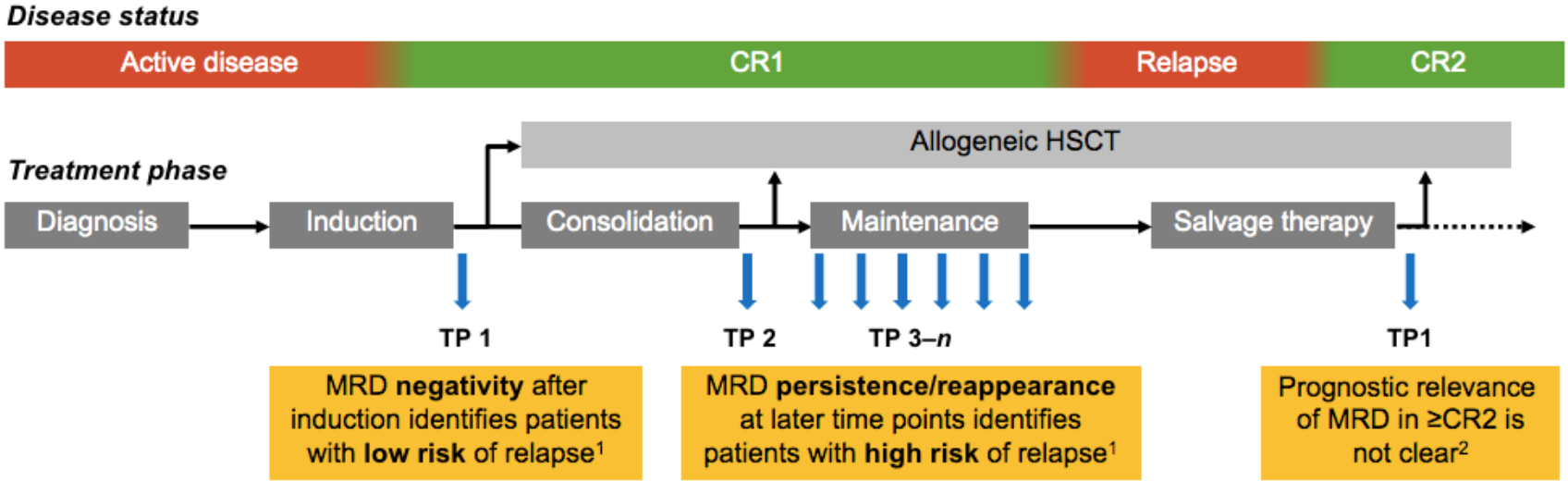
- Pediatric UKALL2003 study
  - The risk of relapse was proportional to the MRD level within each genetic risk group
  - However, absolute relapse rate that was associated with a specific MRD value varied significantly by genetic subtype

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



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

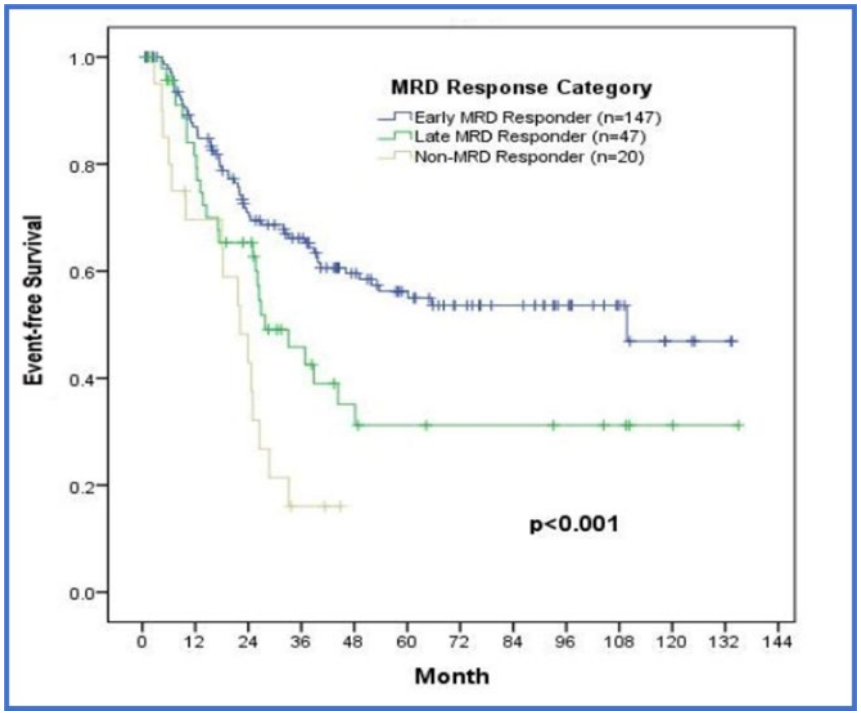
Timepoint to MRD Detection

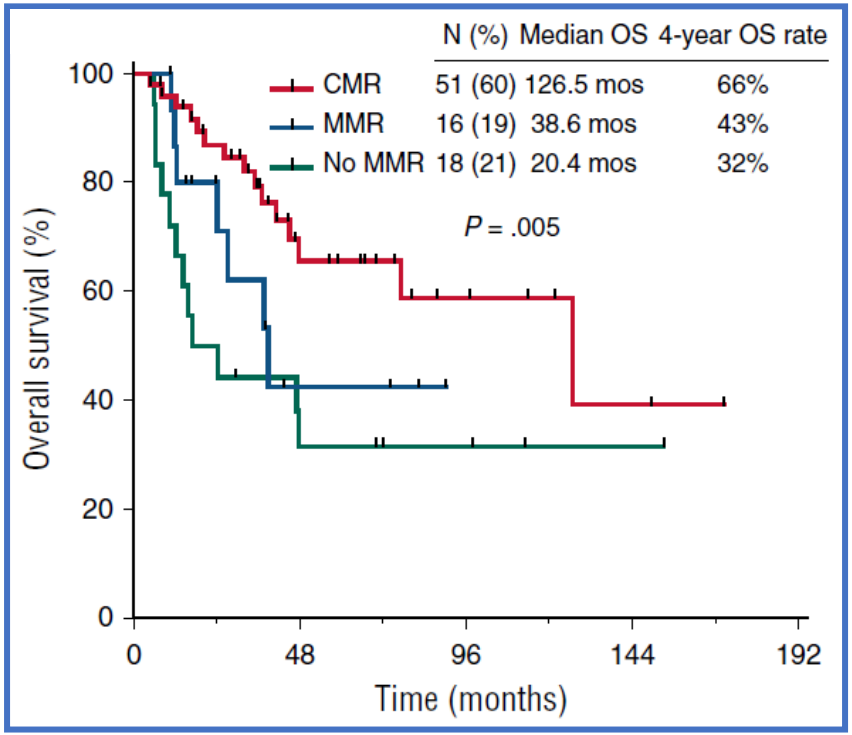


- **Negative** MRD at **TP1**: useful for recognizing patients with **low risk** of relapse
- **Positive** MRD at **TP2**: useful for recognizing patients with **high risk** of relapse

1. Brüggemann M, Kotrova M. *Blood Adv.* 2017;1:2456-2466; 2. Jabbour E, et al. *Cancer.* 2017;123:294-302.

Best Time Point for MRD Assessment: End-Induction for Ph– ALL, 3 Months for Ph+ ALL





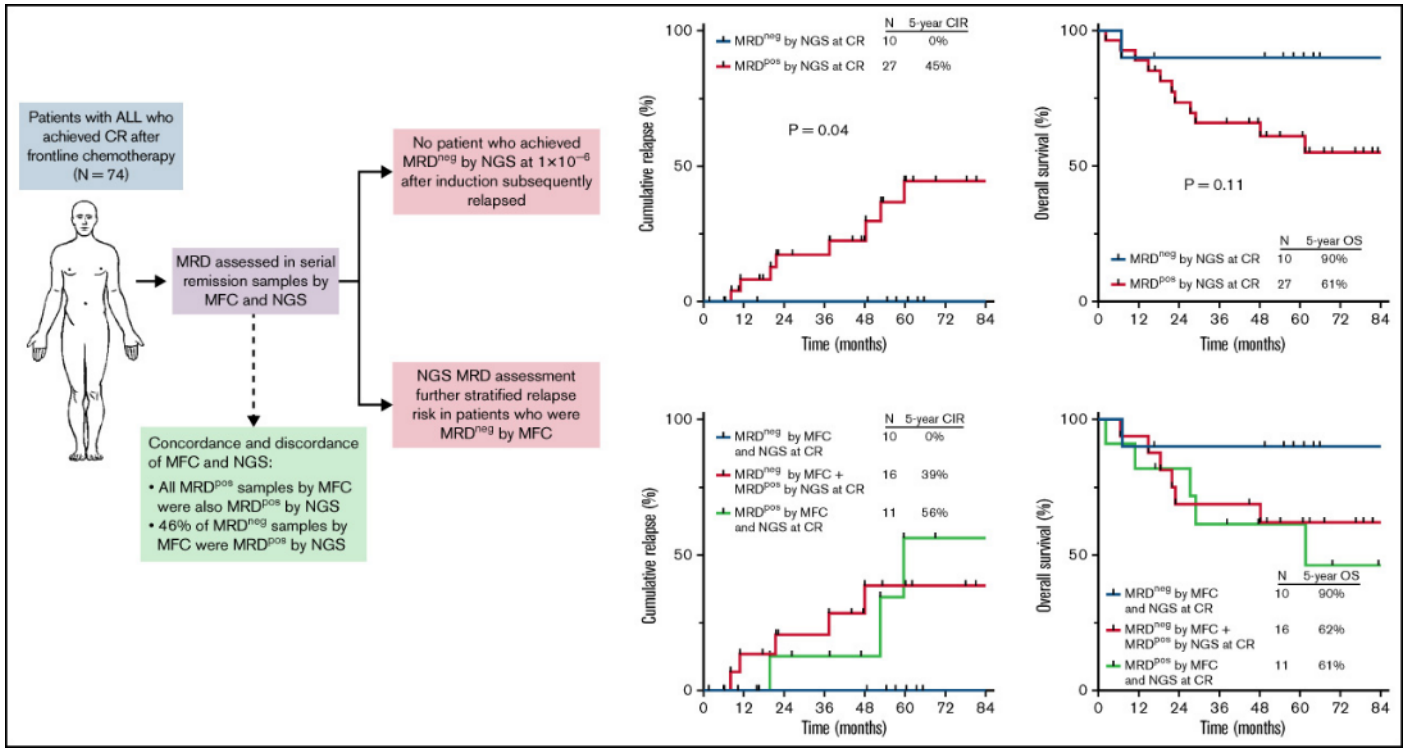
Yilmaz M, et al. *Am J Hematol*. 2020;95:144-150.

Short NJ, et al. *Blood*. 2016;128:504-507.

Impact of Sensitivity of the Method for MRD Assessment on Prognosis

Standard FCM (sensitivity 1 × 10^{-4}) vs ultrasensitive NGS (sensitivity 1 × 10^{-6})

End-induction MRD negative by MFC: 66%, by NGS: 23% of patients

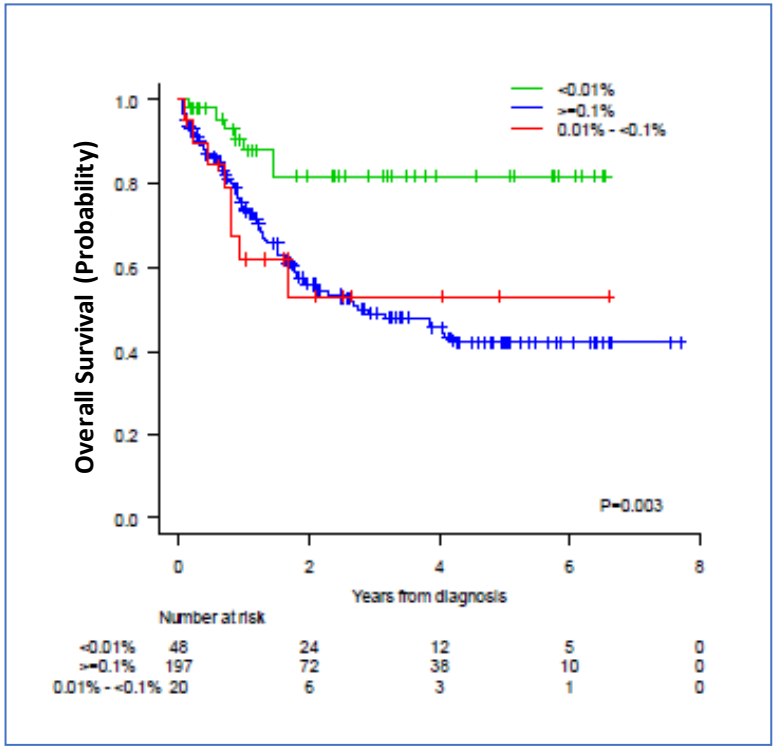


Predictive value of MRD increases with increasing sensitivity!

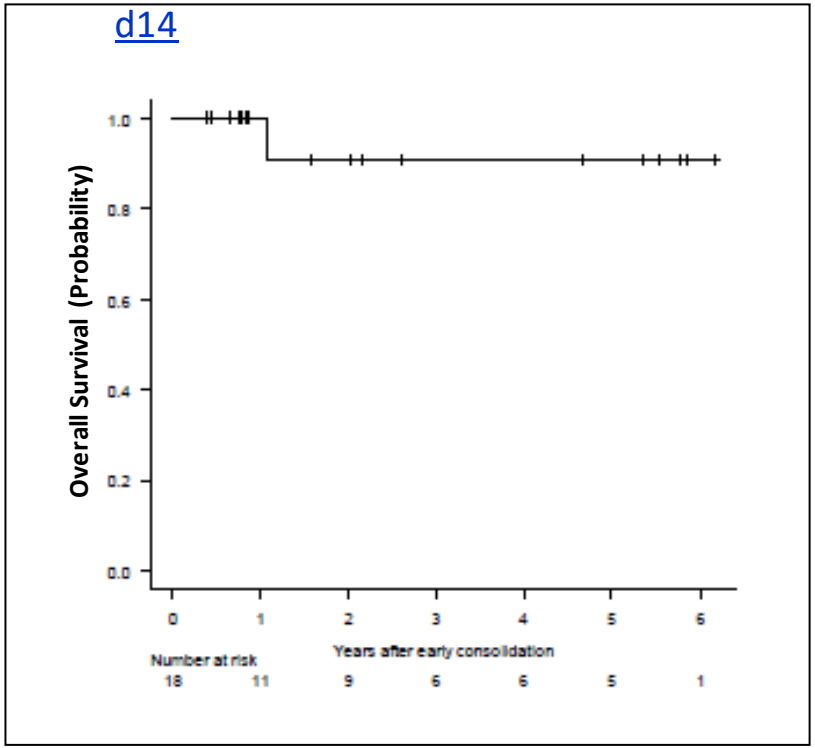
Short N, et al. *Blood Adv*. 2022;6(13):4006-4014.

Outcomes by MRD Assessed by Next-Generation FCM (sensitivity 2×10^{-6})

According to post-induction MRD level



Patients with MRD <0.01% from d14

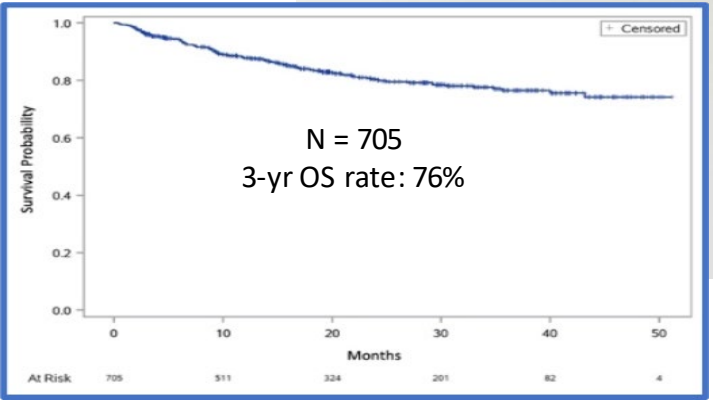


Ribera JM, et al. *Blood.* 2021;137(14):1879-1894.

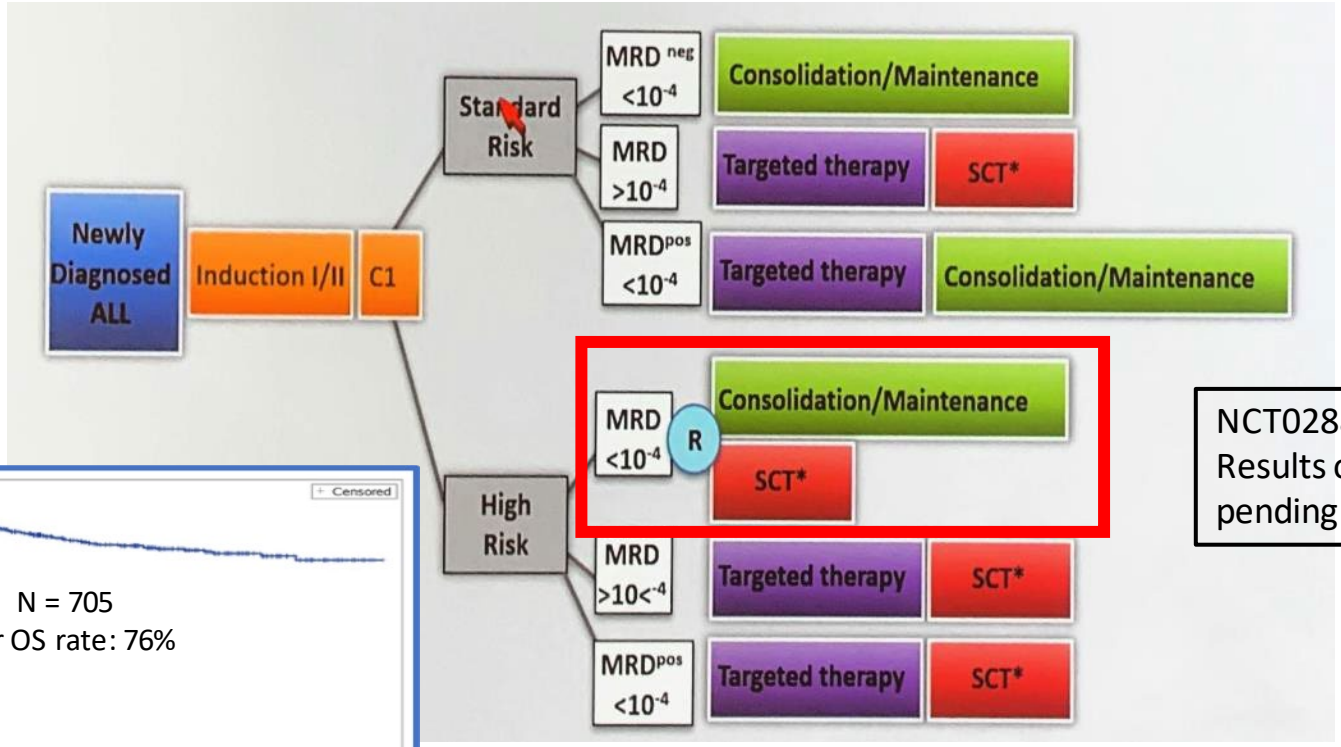
Prospective Studies With Indication for HSCT on the Basis of MRD Data (adult Ph– ALL)

Trial	Risk Groups	MRD Assessment	Randomization Assignment	References
NILG	SR & HR	PCR	• No • Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood.* 2009;113:4153-4162
PETHEMA HR03	HR	4-color flow	• No • AlloHSCT in poor early cytologic responders or MRD+ pts	Ribera JM. *J Clin Oncol.* 2014;32:1595-1604
NILG 10/07	SR & HR	PCR	• No • Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood Cancer J.* 2020;10:119
PETHEMA HR11	HR	8-color flow	• No • AlloHSCT in MRD+ pts	Ribera JM, et al. *Blood*. 2021;137:1879-1894
GMALL 08/2013	SR & HR	PCR	• Yes. AlloHSCT vs chemo in MRD– HR pts • AlloHSCT in MRD+ pts	Ongoing; NCT02881086

Current GMALL Strategy De Novo <55 Years: GMALL Trial 08/2013 — Ph– ALL



N = 705
3-yr OS rate: 76%



NCT02881086
Results of randomization pending

*Dose-reduced conditioning >45 yr.
Gokbuget N, et al. ASH 2021.

How MRD can guide the use of targeted therapies and immunotherapy

Immunotherapy at Early Phases of ALL for Improving the MRD Negativity

Blinatumomab in MRD+ patients in CR: BLAST trial

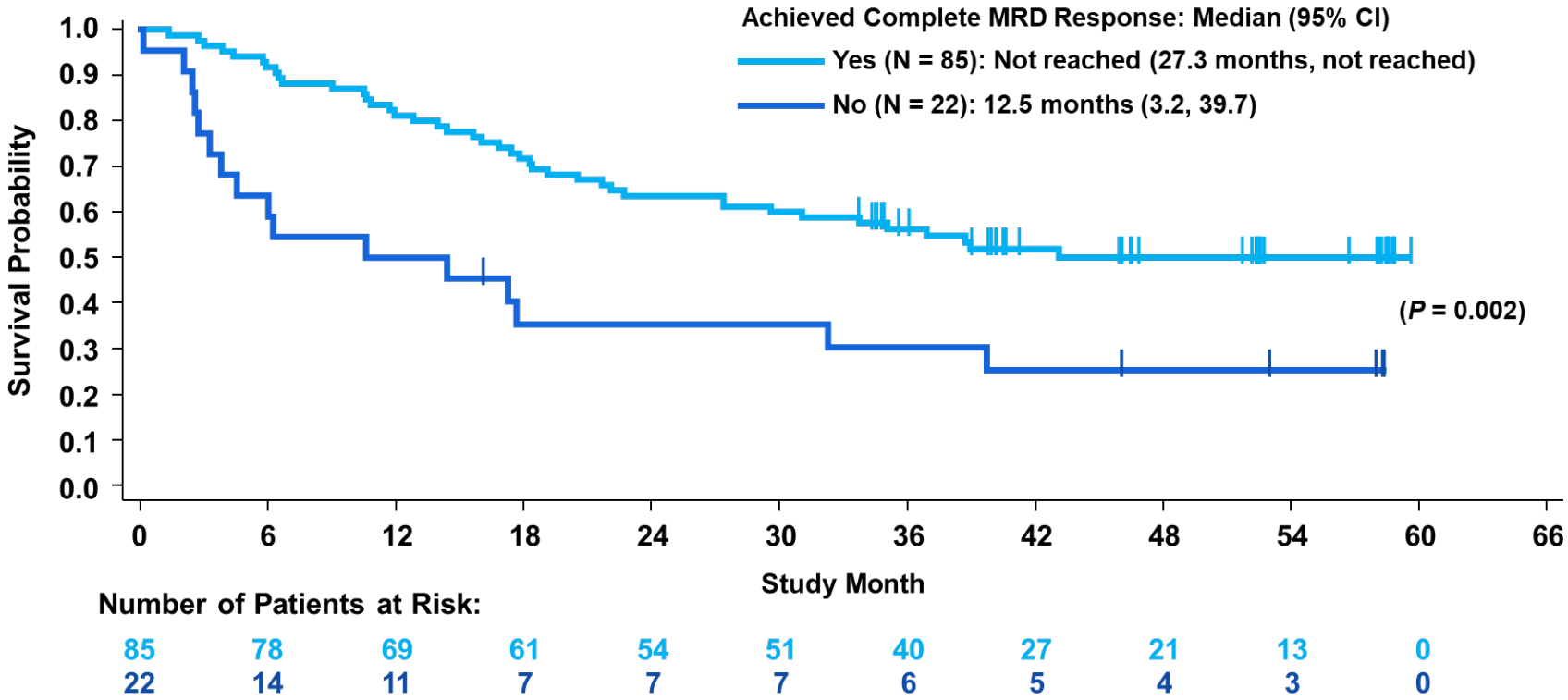
Blinatumomab or inotuzumab with chemotherapy in newly diagnosed Ph– ALL

Blinatumomab or inotuzumab with TKI in newly diagnosed Ph+ ALL

Overall Survival by Complete MRD Response

All Patients Analyzed

BLAST (MT103-203) STUDY



MRD, minimal residual disease.

Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}.

Gökbuget N, et al. ASH 2018. Presentation 554.

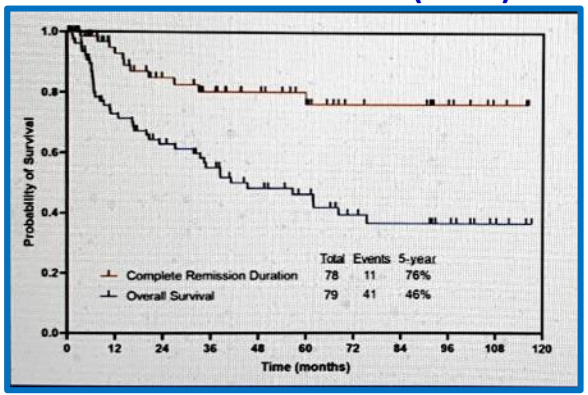
Immunotherapy in Early Phases of Ph– ALL: Results From Phase II Trials

Group	Chemotherapy	MoAb	N pts	Median age (range)	CR after induction	MRD– after induction	OS (y)
MDACC[1]	Mini-HCVD	Ino ± Blin	78	68 (60–87)	86%	80%	46% (5y)
EWALL[2]	EWALL backbone	Ino	90	69 (55–84)	88.8%	73%	78.5% (1y)
GMALL[3]	EWALL backbone (in consolidation)	Ino (single-drug induction)	43	64 (56–80)	100%	74%	77% (2y)
SWOG[4]	POMP (maintenance only)	Blin (single-drug induction)	29	75 (66–84)	65.5%	NA	37% (3y)
GRAALL[5]	Standard induction + consolidation	Blin	94	35 (18–60)	NR	74%	92% (1y)
GMALL[6]	EWALL backbone	Blin	33	65 (56–76)	83%	69%	84% (1y)
MDACC[7]	HyperCVAD	Blin	38	37 (17–59)	81%	85%	83% (3y)

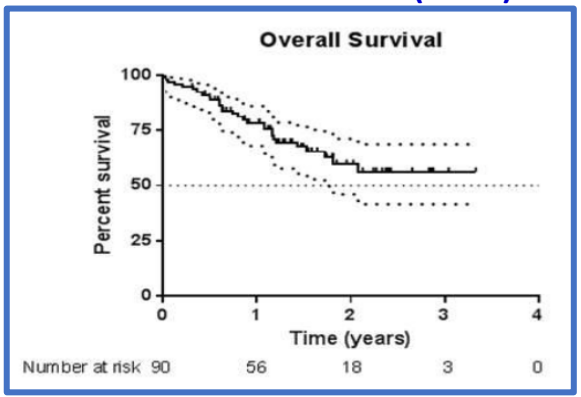
1. Short N, et al. ASH 2021. Abstract 3400; 2. Chevalier P, et al. ASH 2021. Abstract 511; 3. Stelljes M, et al. ASH 2021. Abstract 2300; 4. Advani A, et al. *J Clin Oncol.* 2022 DOI: 10.1200/JCO.21.01766; 5. Boissel N, et al. ASH 2021. Abstract 1232; 6. Gokbuget N, et al. ASH 2021. Abstract 3399; 7. Short N, et al. ASH 2021. Abstract 1233.

Immunotherapy in First-Line ALL: Phase II Trials

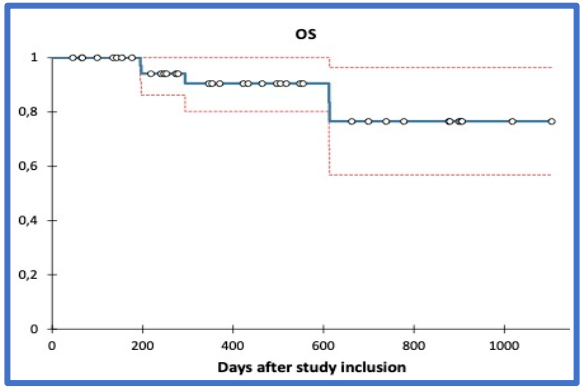
Mini-HCVD + Ino ± Blin (older)[1]



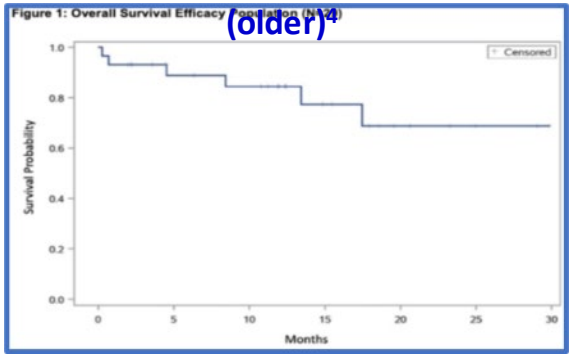
Ino + low induction CHT (older)[2]



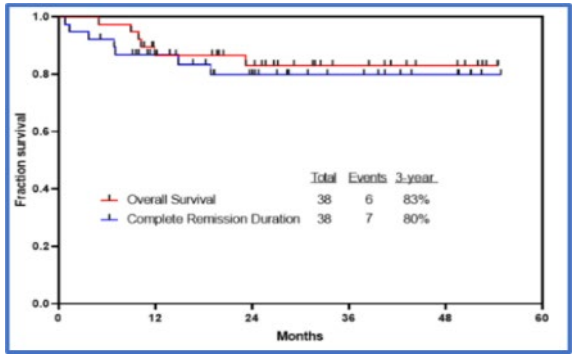
Ino induction + CHT consol (older)[3]



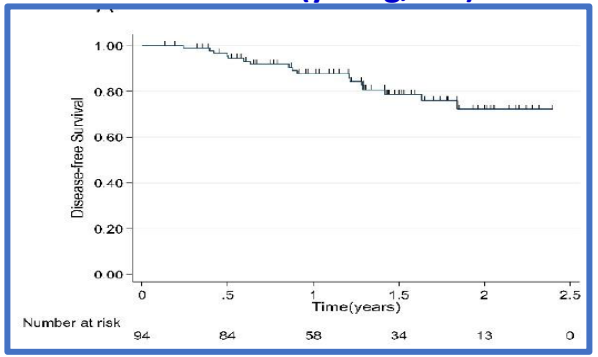
Low induction + Blin consol (older)[4]



Hyper-CVD + Blin (young)[5]



Std CHT + Blin (young, HR)[6]



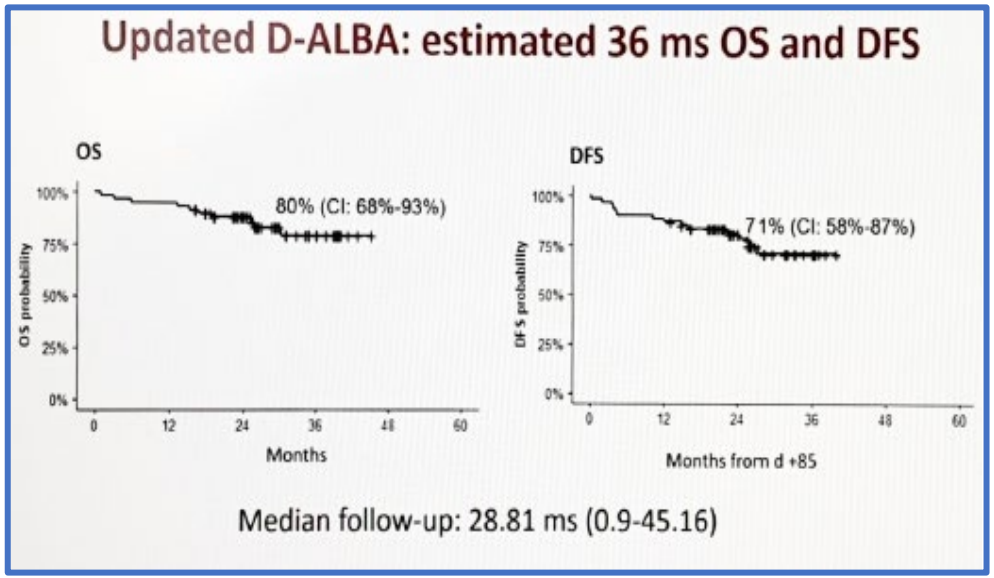
1. Short N, et al. ASH 2021. Abstract 3400; 2. Chevalier P, et al. ASH 2021. Abstract 511; 3. Stelljes M, et al. ASH 2021. Abstract 2300; 4. Gokbuget N, et al. ASH 2021. Abstract 3399; 5. Short N, et al. ASH 2021. Abstract 1233; 6. Boissel N, et al. ASH 2021. Abstract 1232.

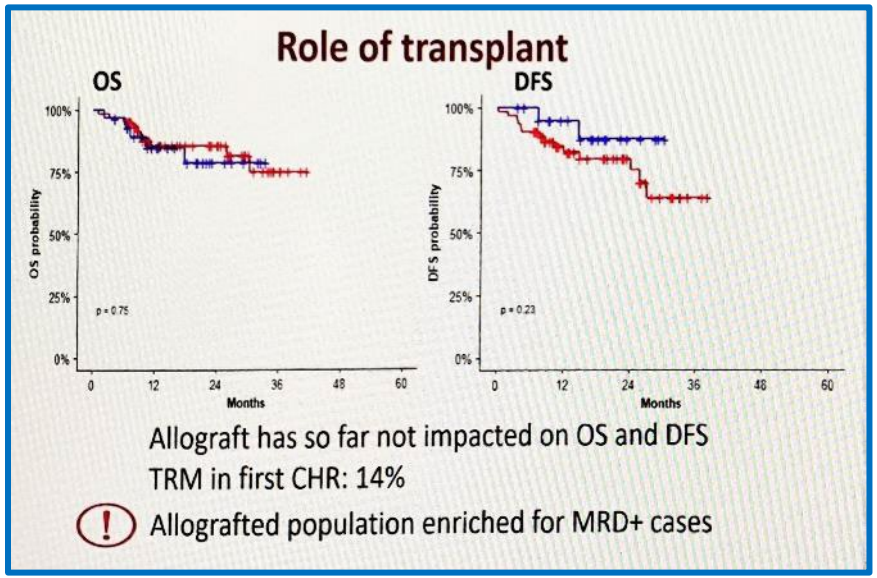
Immunotherapy in Early Phases of Ph+ ALL: Results From Phase II Trials

Reference	TKI	Immunotherapy	N	Median age (range)	CR, %	CMR, %	OS, % (95% CI) years
Foa et al[1]	Dasatinib	Blinatumomab	63	54 (24–82)	98	29 (ponatinib) 60 (blinatumomab)	80 (68–93) 2-yr
Short et al[2]	Ponatinib	Blinatumomab	30	62 (34–83)	94	81 (CMR + MMR)	93 2-yr
Advani et al[3]	Dasatinib	Blinatumomab	24	73 (62–87)	92	31	85 (58–95) 3-yr

1. Foa R, et al. *N Engl J Med.* 2020;383:1613-1623; 2. Short N, et al. *Blood.* 2021;138(suppl 1): abstract 2299; 3. Advani A, et al. *Blood.* 2021; 138(suppl 1): abstract 3397.

Dasatinib + Blinatumomab (updated)





alloHSCT in 50% of patients

Chiaretti S, et al. EHA 2021. Abstract S112.

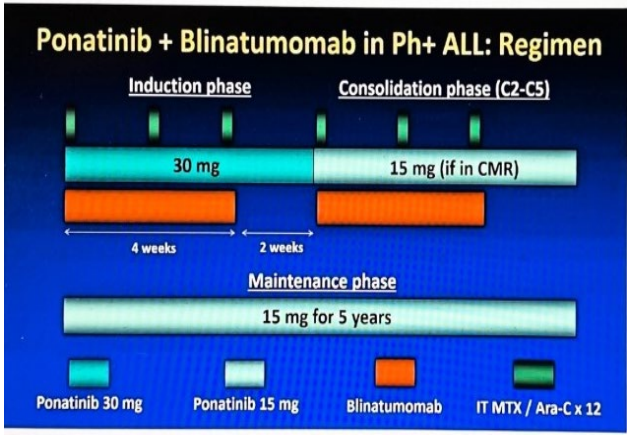
Ponatinib and Blinatumomab for Patients With Ph+ ALL

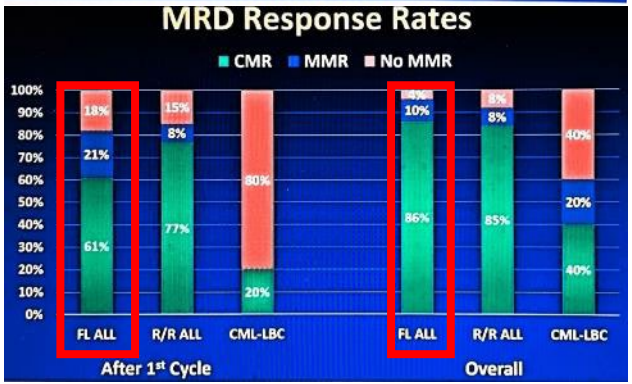
Short N, et al. ASH 2021, #2298

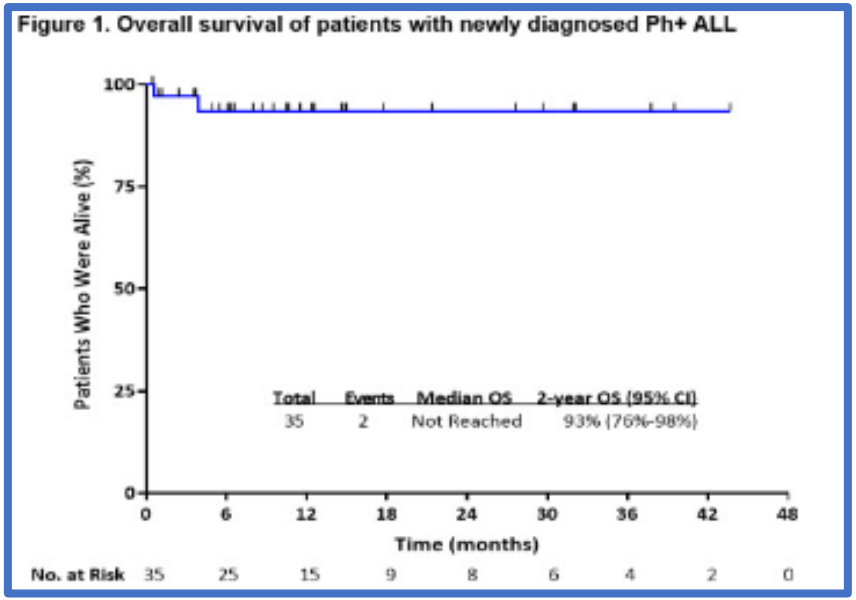
median age, 62 years; range, 34 to 83

Phase II study: newly diagnosed (ND) Ph+ ALL, R/R Ph+ ALL, or CML-LBP

Treatment: Up to 5 cycles of blina. Ponatinib 30 mg/d during cycle 1, 15 mg/d once CMR. Ponatinib at least 5 yr. IT ×12





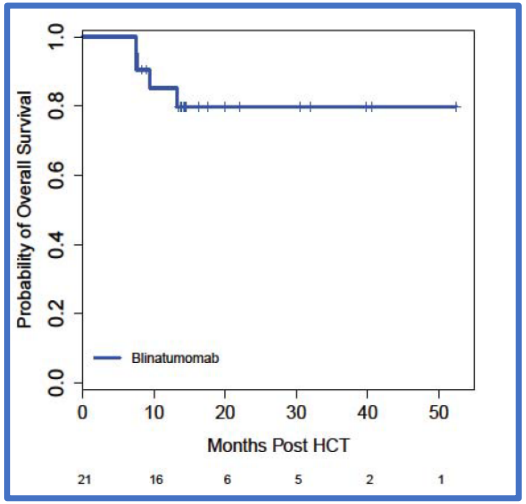


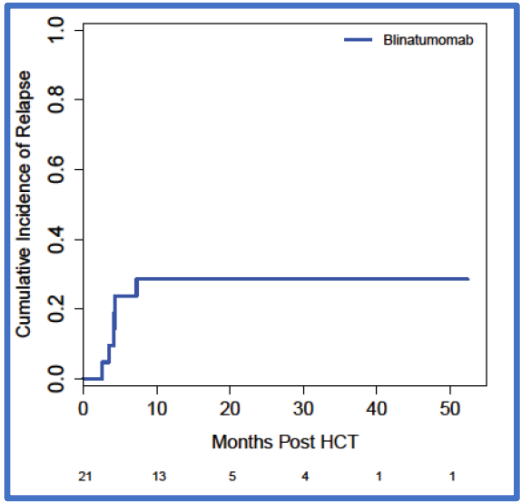
Only 1 HSCT!

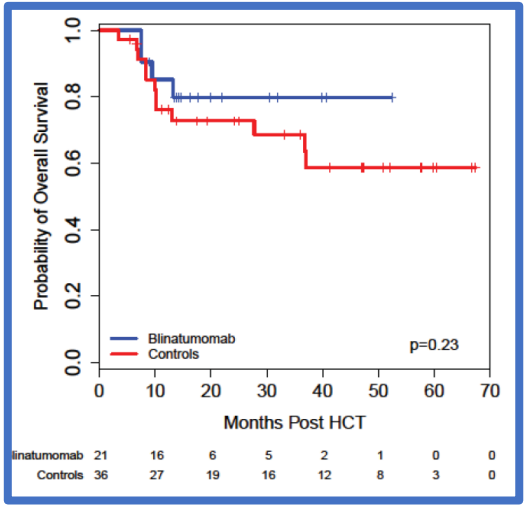
Short N, et al. EHA 2021. Abstract S113.

Prophylactic Use of Immunotherapy After HSCT

- Phase II, adult ALL at HR of relapse after HSCT
- 4 cycles Blina every 3 months during the first yr after HSCT
- N = 21 pts, 12 completed the 4 cycles
- G1 CRS 5%, G2 neurotoxicity 5%
- 1-year OS, PFS, and NRM: 85%, 71%, and 0%, respectively. Responders had higher proportions of effector memory CD8 T-cell subsets
- Non-responders were T-cell deficient and expressed more inhibitory checkpoint molecules
- Blinatumomab post-allogeneic HCT, benefit dependent on the immune milieu







Gaballa M, et al. *Blood.* 2022;139:1908-1919.

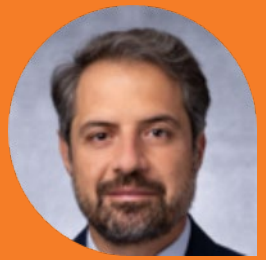
Conclusions

- Prognostic significance at any time point (after induction, consolidation, before and after HSCT)
- Limited predictive value. Possible additional influence of oncogenetic factors
- Importance of the sensitivity of the method
- Early interventions with targeted therapies and immunotherapy to decrease the MRD level
  - Immunotherapy with mAb (blinatumomab, inotuzumab)(Ph–ALL)
  - Combination of mAb with targeted therapy (Ph+ ALL)

Global Leukemia Academy

How to Optimally Sequence CD19-Targeted Approaches in ALL

Elias Jabbour



APTITUDE HEALTH

Incorporation of Antibodies Into the Management of ALL: Upfront and Relapsed Disease

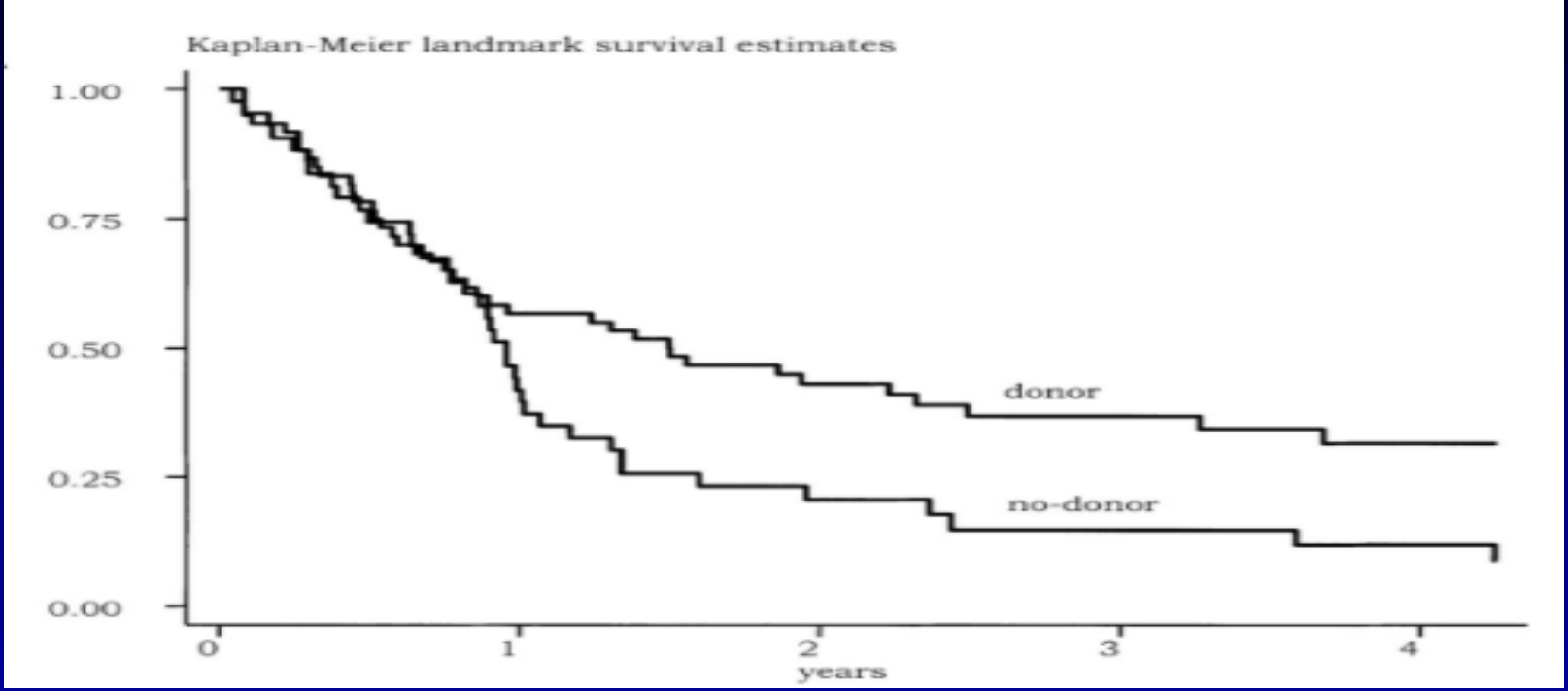
Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

2022

Conflict of Interest Disclosure

- Research Grants
  - Pfizer, Takeda, Amgen, AbbVie, Novartis
- Consultancy and advisory roles
  - Pfizer, Takeda, Amgen, AbbVie, BMS

SCT for Ph+ ALL: Pre-TKI



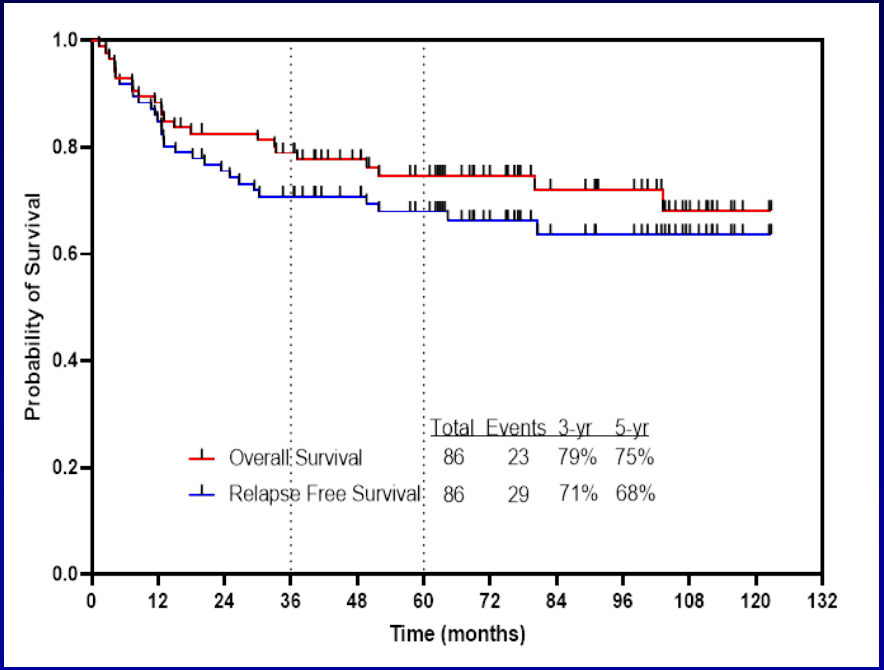
- Donor (n = 60) – 3-year OS: 37%
- No donor (n = 43) – 3-year OS: 12%

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

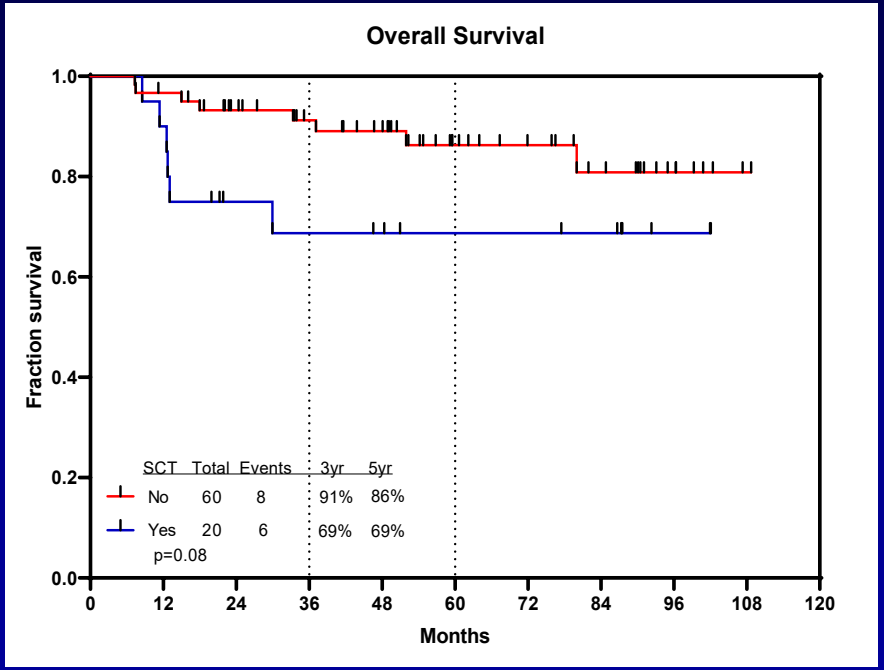
HyperCVAD + Ponatinib in Ph+ ALL

- 86 pts Rx; median age 47 yrs (39–61); median FU 75 mos (16–123)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); CMR 84%; 3/5-yr OS 79/75%, EFS 71/68%

Relapse-Free and Overall Survival



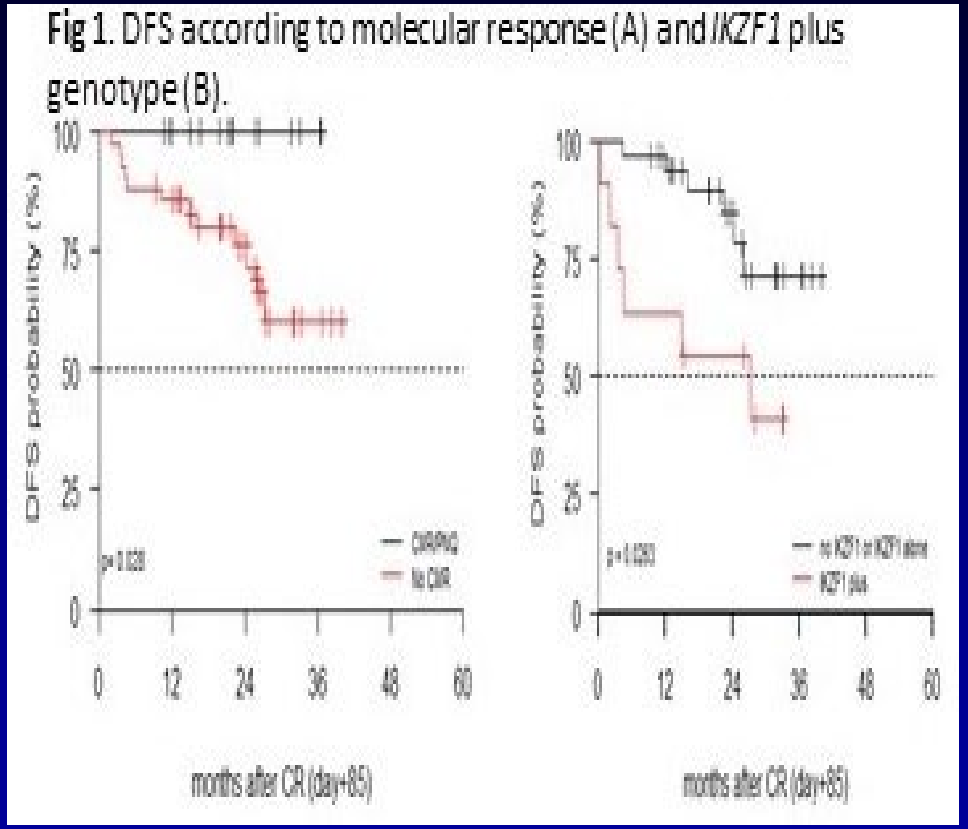
6-Month Landmark



Jabbour E, et al. *Lancet Hematol.* 2018;618:(and update April 2022); Short et al. *Blood.* 2019;134:Abstract 283.

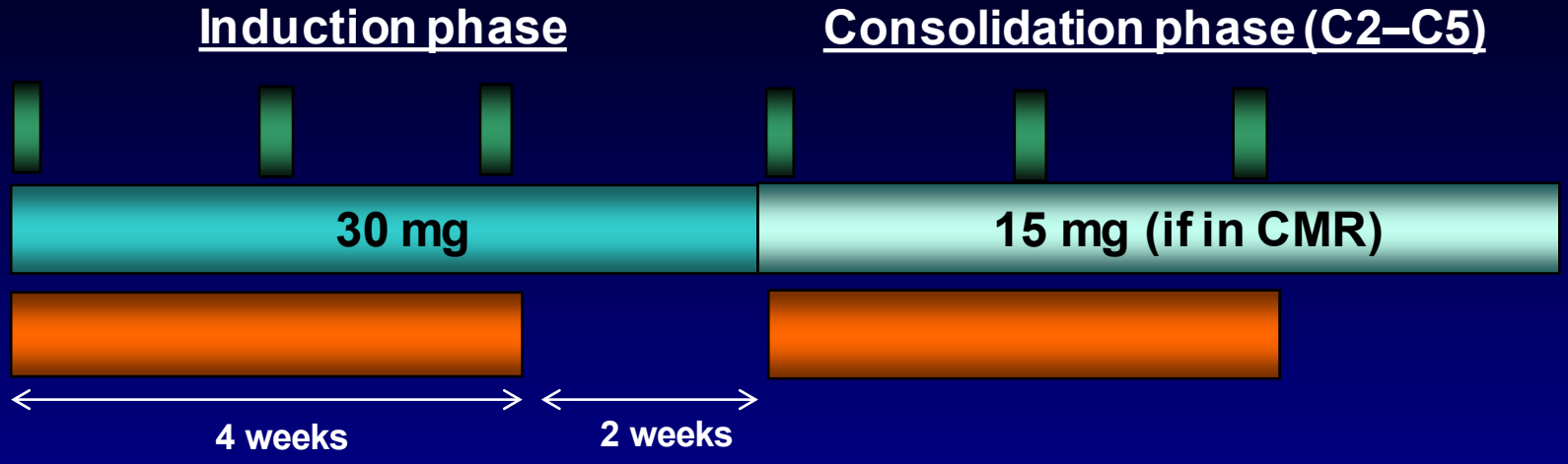
Dasatinib + Blinatumomab (D-ALBA) in Newly-Dx Ph+ ALL – Update

- 63 pts Rx; median age 54 yrs (24–82). Median FU 40 mos
- Molecular response (32/53 = 60%)
  - 22 CMR (41%)
- 29/58 (50%) who started blina have SCT – 6 in CR2
- SCT did not impact OS or DFS, but SCT "enriched" by 23 pts who did not have molecular response
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 48-mos OS 78%, DFS 75%



Chiaretti et al. EHA 2022. Abstract P353.

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Maintenance phase

15 mg for 5 years

Ponatinib 30 mg

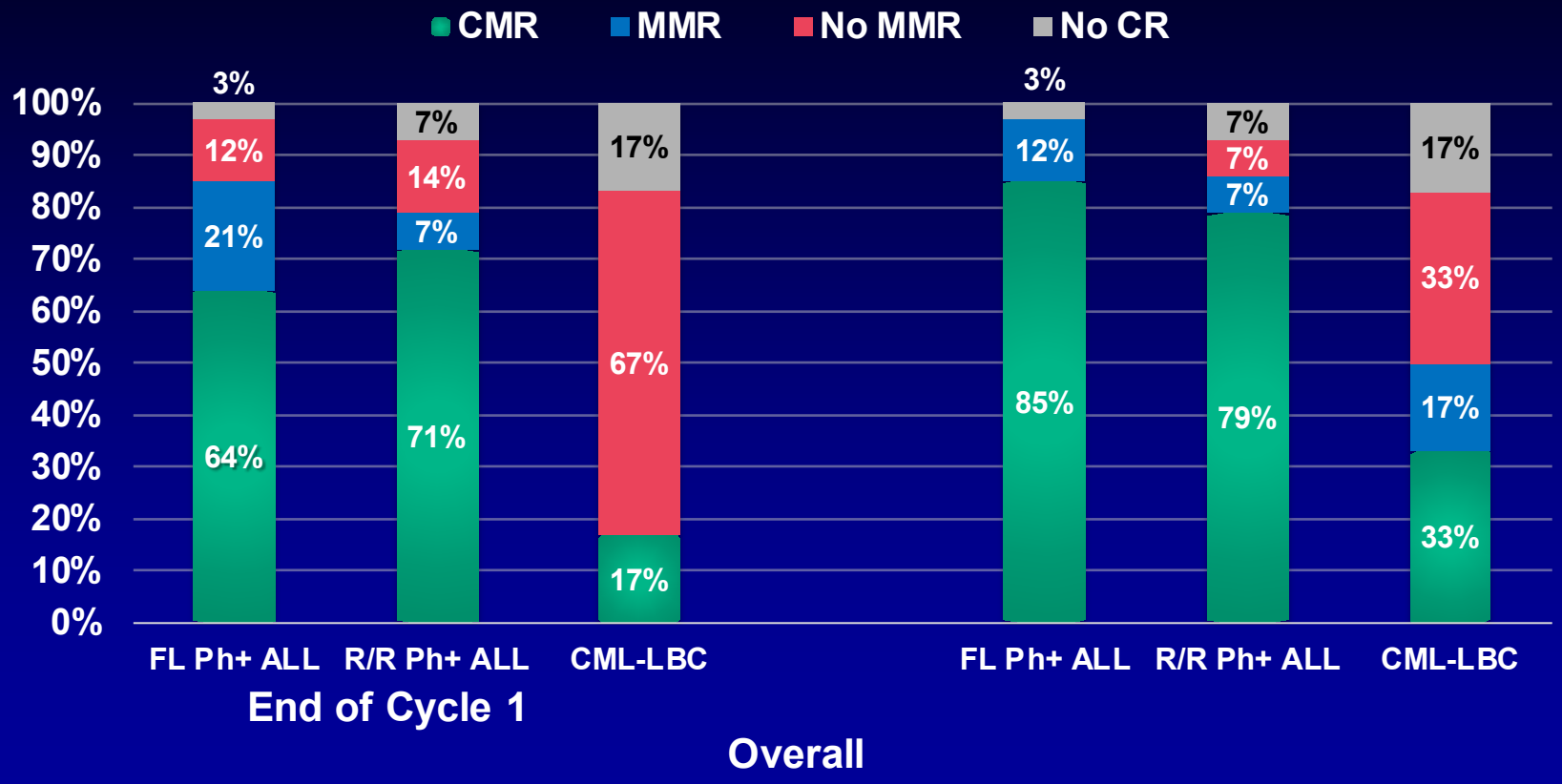
Ponatinib 15 mg

Blinatumomab

IT MTX, Ara-C × 12

Short NJ, et al. EHA 2022. Abstract S114.

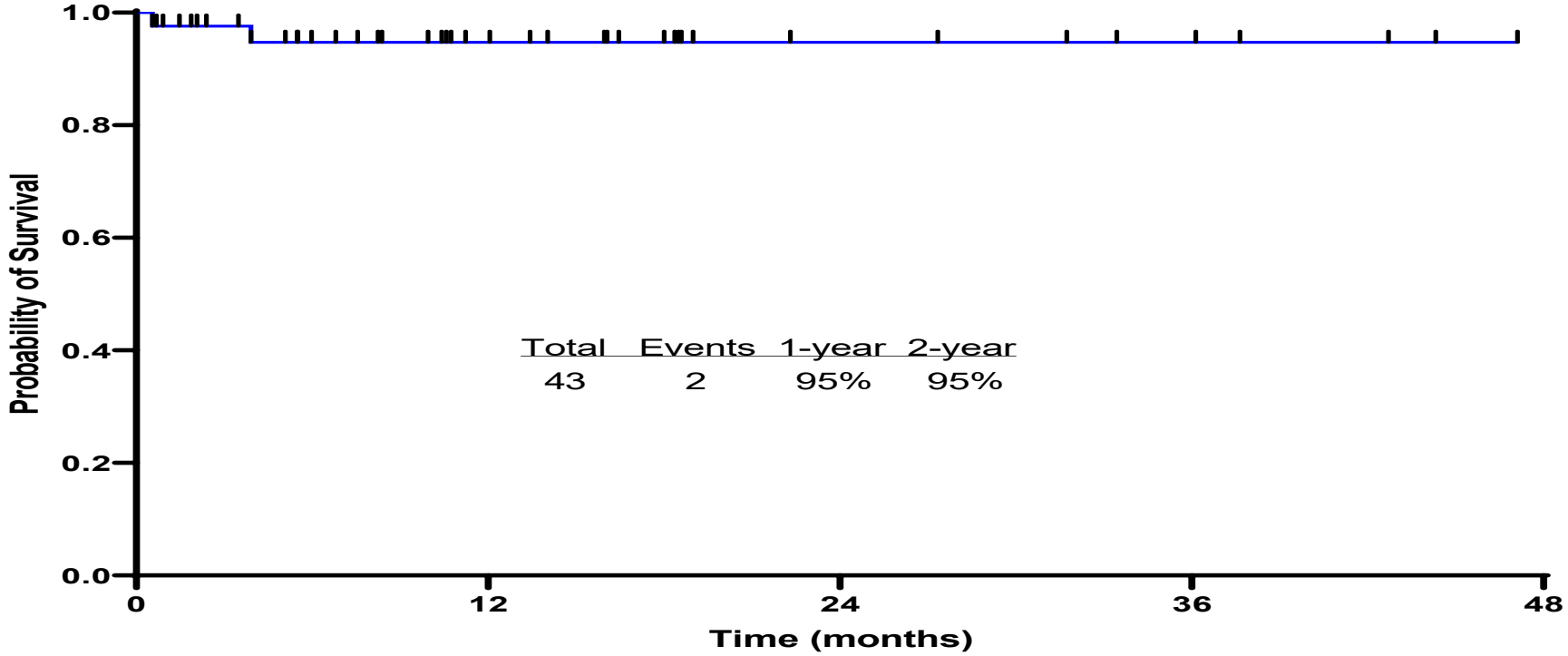
Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates



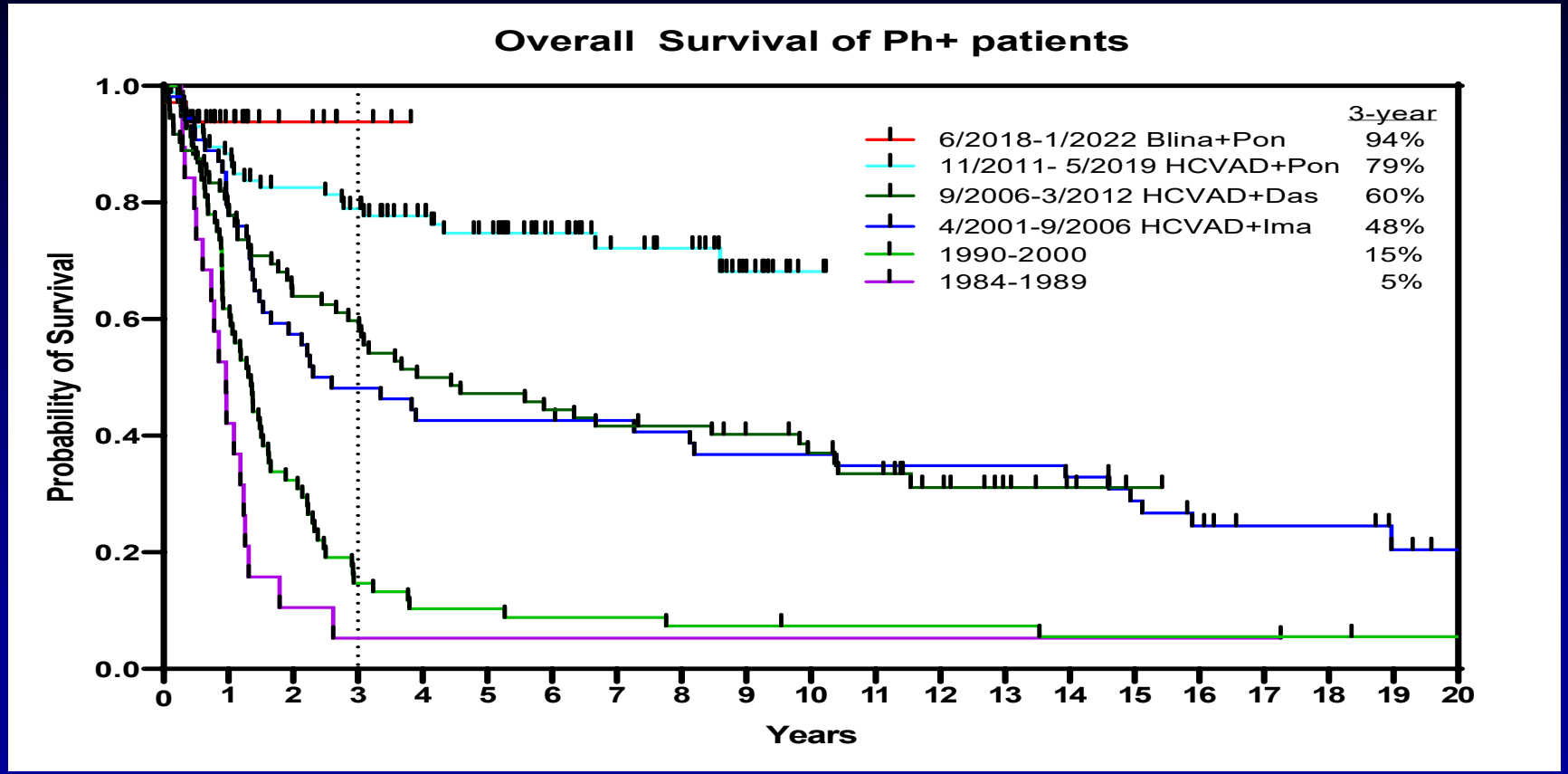
Short NJ, et al. EHA 2022. Abstract S114.

Ponatinib + Blinatumomab in Ph+ ALL. Survival Outcomes for Frontline Cohort

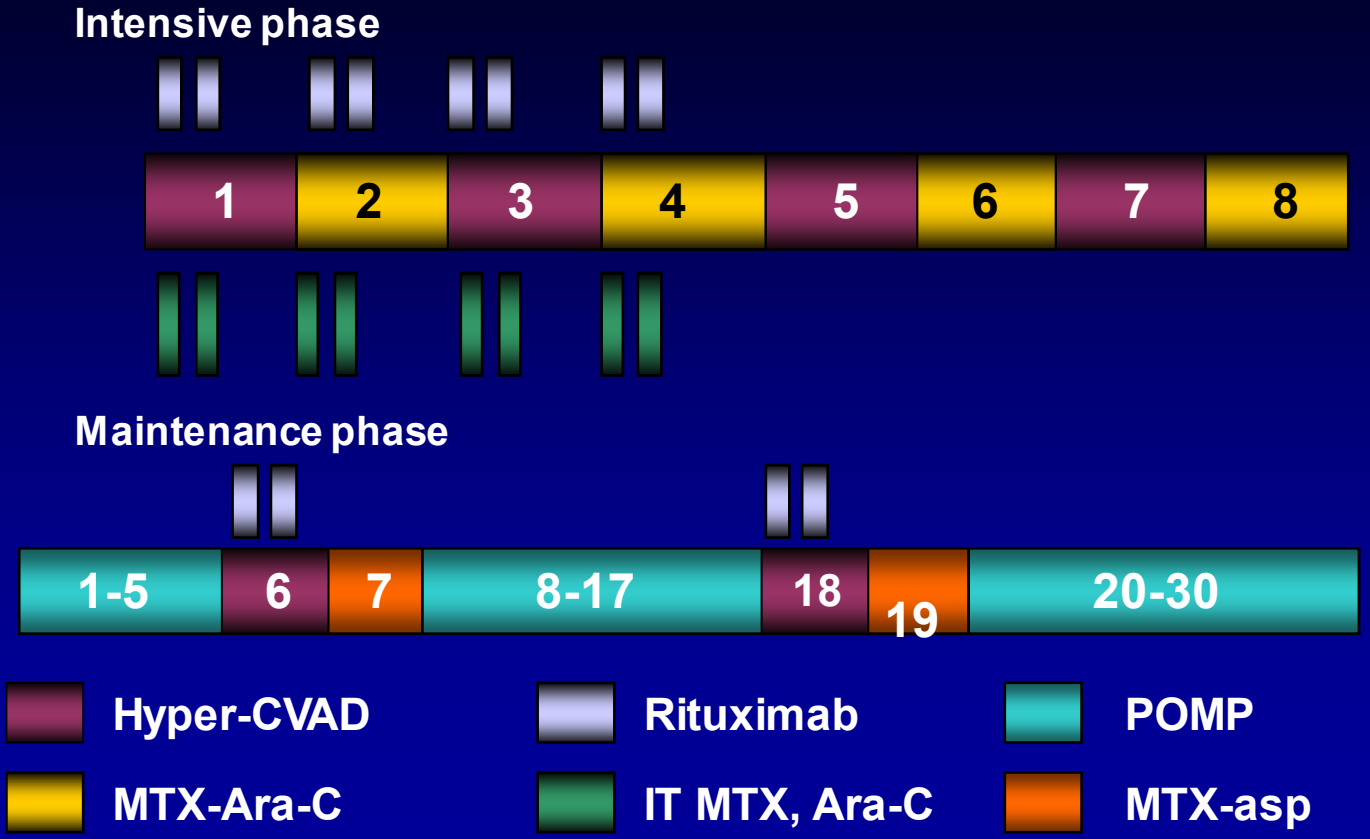
Median follow-up: 14 months (range, <1-51)



ALL: Survival by Decade (MDACC 1985–2022)



Hyper-CVAD + Rituximab in Precursor B-ALL

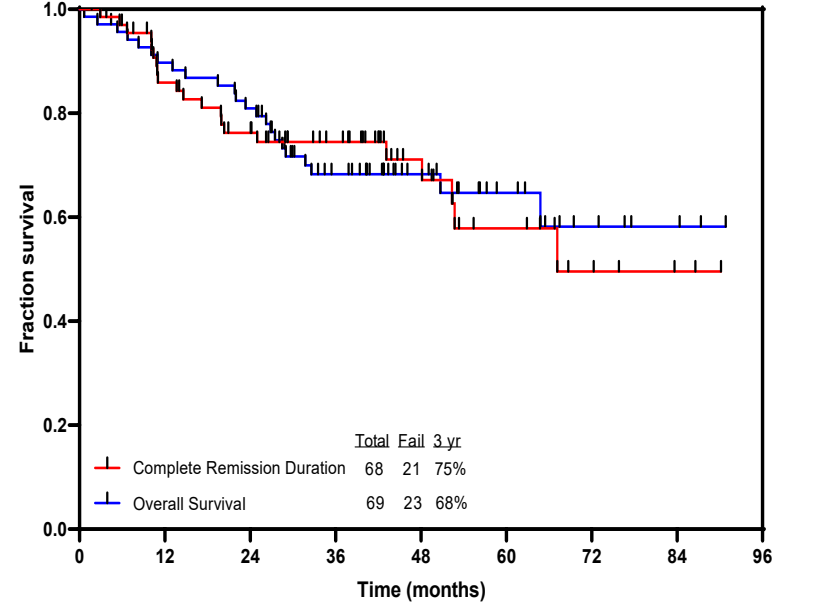


Thomas. *J Clin Oncol.* 2010;28:3880-3889.

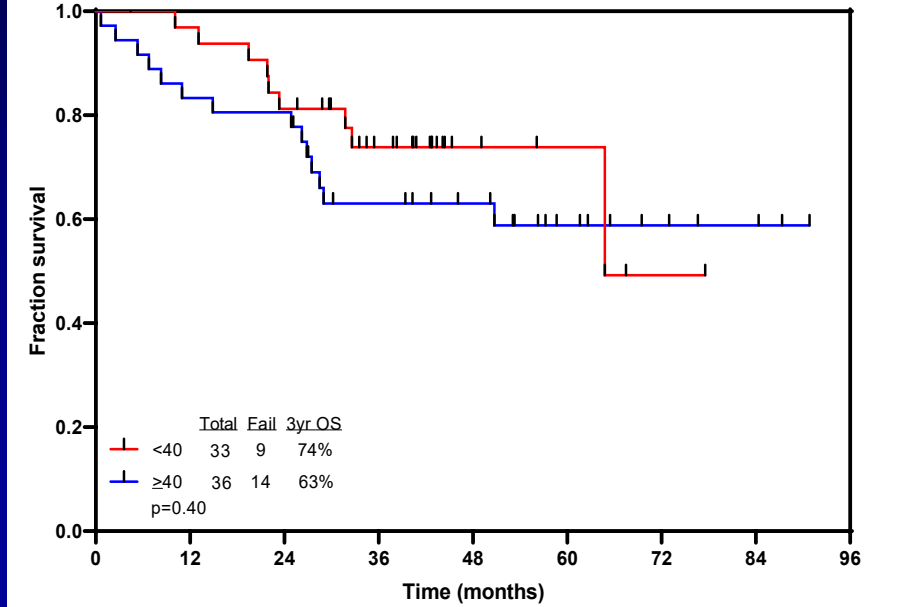
HCVAD + Ofatumumab: Outcomes (N = 69)

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

CRD and OS Overall

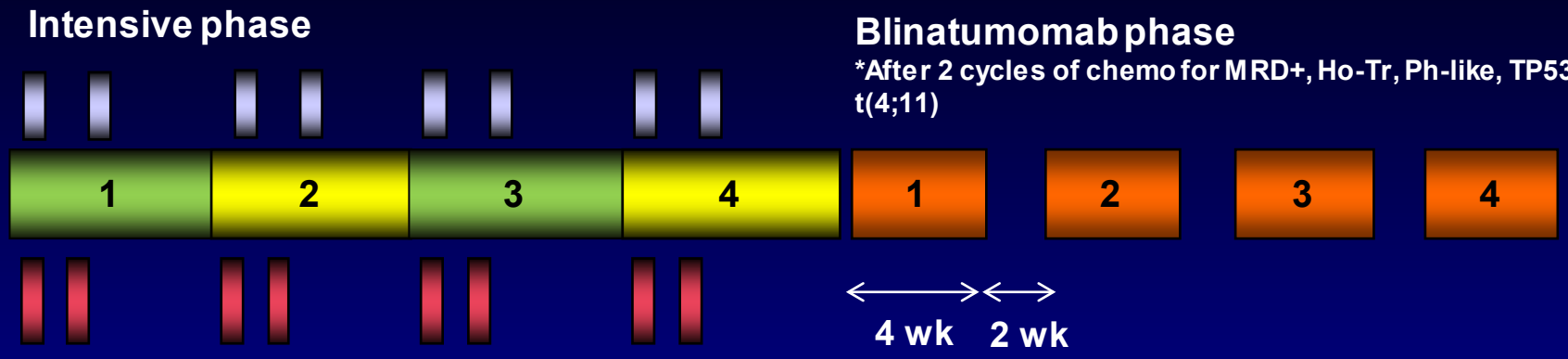


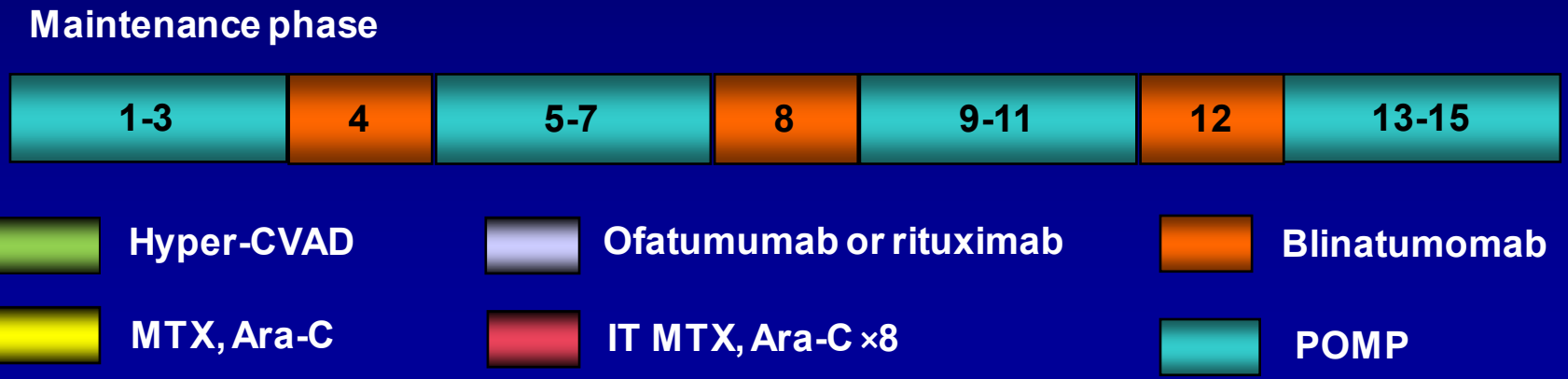
OS by Age



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

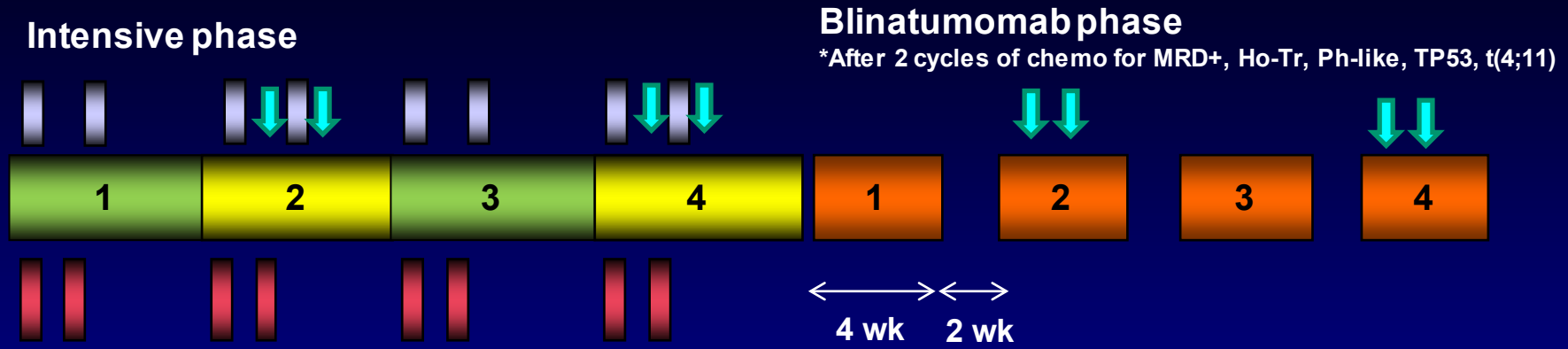
Hyper-CVAD + Blinatumomab in B-ALL: Regimen (1st cohort; N = 38)





Short NJ, et al. EHA 2022. Abstract P371.

Hyper-CVAD + Blina + InO in B-ALL: Regimen (2nd cohort)



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX (500 mg/m^2) + Ara-C (1 g/m^2)

IT MTX, Ara-C ×8

POMP

Inotuzumab 0.3 mg/m^2 on D1 and D8

Short NJ, et al. EHA 2022. Abstract P371.

Hyper-CVAD + Blina + InO in B-ALL. Patient Characteristics (N=63)

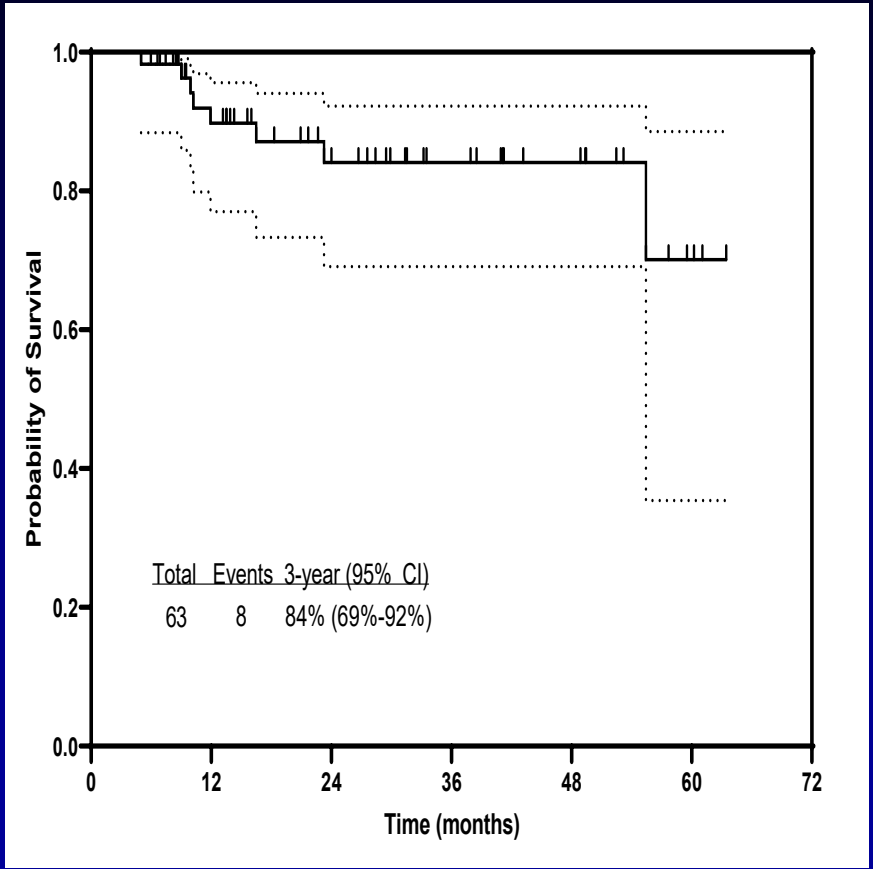
Characteristic (N=58)		Overall (n=63)	Cohort 1 (n=38)	Cohort 2 (n=25)
Age (years, range)		33 [18-59]	37 [18-59]	24 [18-54]
Sex	Male	44 (70)	26 (68)	18 (72)
PS (ECOG)	0-1	52 (83)	30 (79)	22 (88)
WBC (x 10^9/L)		4.3 [0.5-553]	3.12 [0.5-360.9]	8.6 [1.2-553]
CNS disease		6 (10)	4 (11)	2 (8)
CD19 ≥ 50 %		52/53 (98)	31/32 (97)	21/21 (100)
CD20 ≥ 20 %		28/54 (52)	17/33 (52)	11/21 (52)
TP53 mutation		14/58 (24)	10/37 (27)	4/21 (19)
CRLF2+		9/53 (17)	6/33 (18)	3/20 (15)
JAK2+		4/58 (7)	2/37 (5)	2/21 (10)
Cytogenetics	Diploid	21 (33)	11 (29)	10 (40)
	Low hypodiploidy / Near triploidy	8 (13)	6 (16)	2 (8)
	Complex (≥ 5 anomalies)	4 (6)	3 (8)	1 (4)
	High hyperdiploidy	5 (8)	3 (8)	2 (8)
	KMT2A rearrangement	5 (8)	3 (8)	2 (8)
	Other	20 (32)	12 (32)	8 (32)

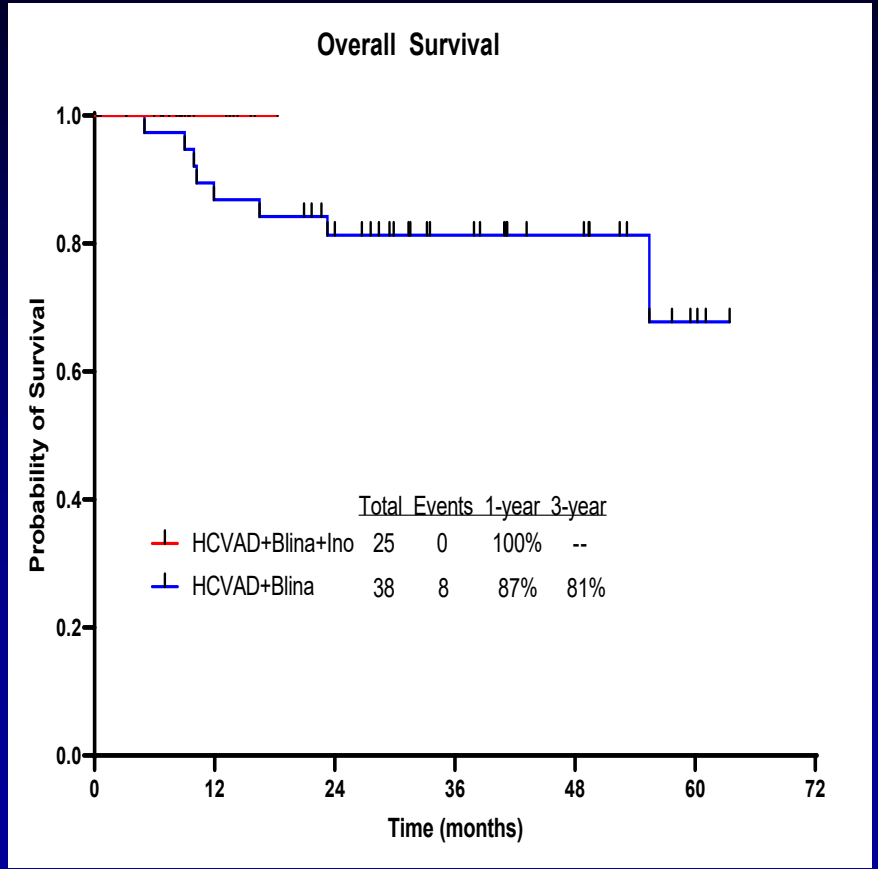
Hyper-CVAD + Blina + InO in B-ALL. Response Rates

Response assessment	Overall N (%) (n=63)	Cohort 1 (n=38)	Cohort 2 (n=25)
CR after induction	38/47 (81)	26/32 (81)	12/15 (80)
CR at any time	47/47 (100)	32/32 (100)	15/15 (100)
MRD negativity after induction	33/44 (75)	22/26 (85)	11/18 (61)
MRD negativity at any time	58/61 (95)	37/38 (97)	21/23 (91)
NGS MRD negativity at any time	12/20 (60)	1/2 (50)	11/18 (61)
Early death (30-day)	0	0	0

- 6 are CR at start (Cohort 1); 8 are CR at start (Cohort 2); 2 are too early
- Median time to MRD negativity : 20 days

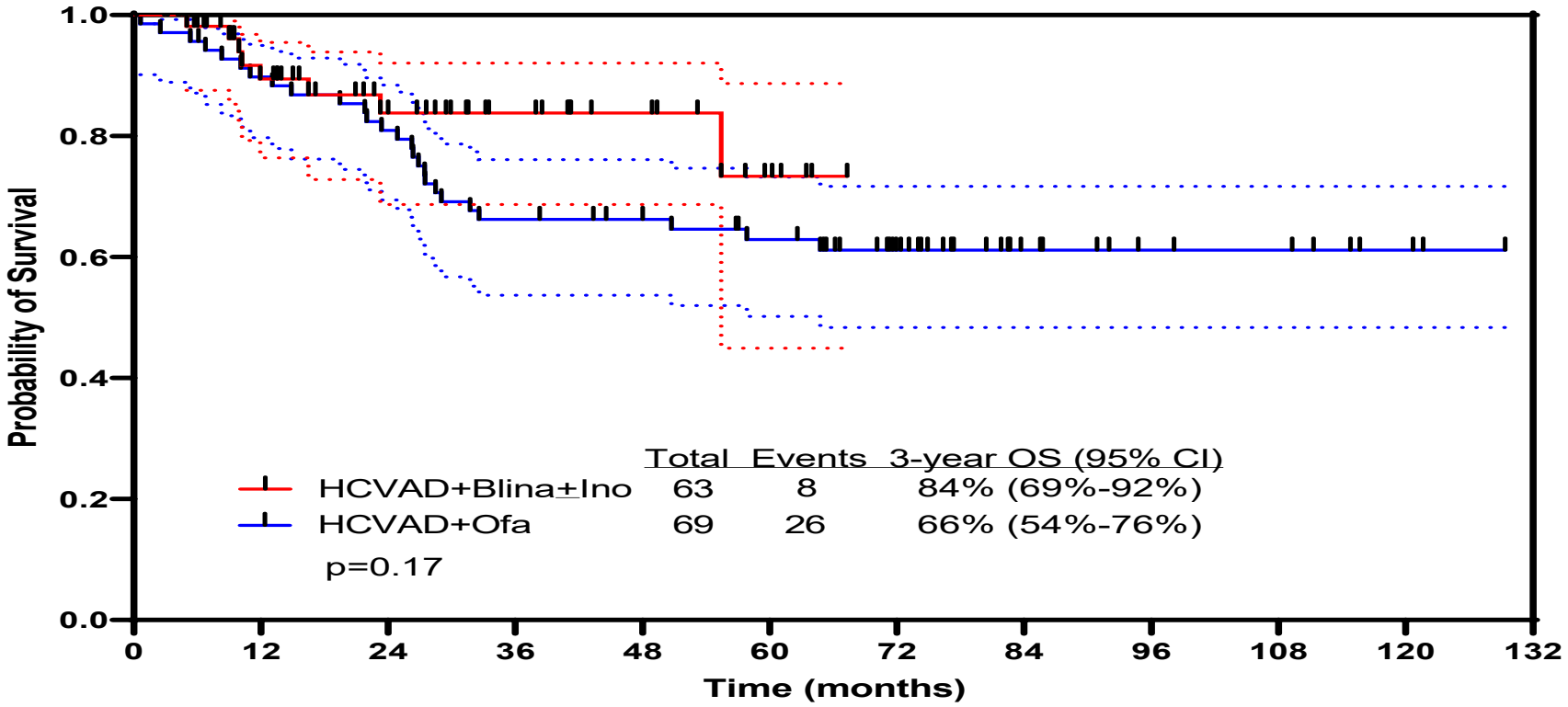
Hyper-CVAD + Blina + InO in B-ALL: Outcomes





Short NJ, et al. EHA 2022. Abstract P371.

Hyper-CVAD + Blina + InO in B-ALL: Outcome vs Historical Control



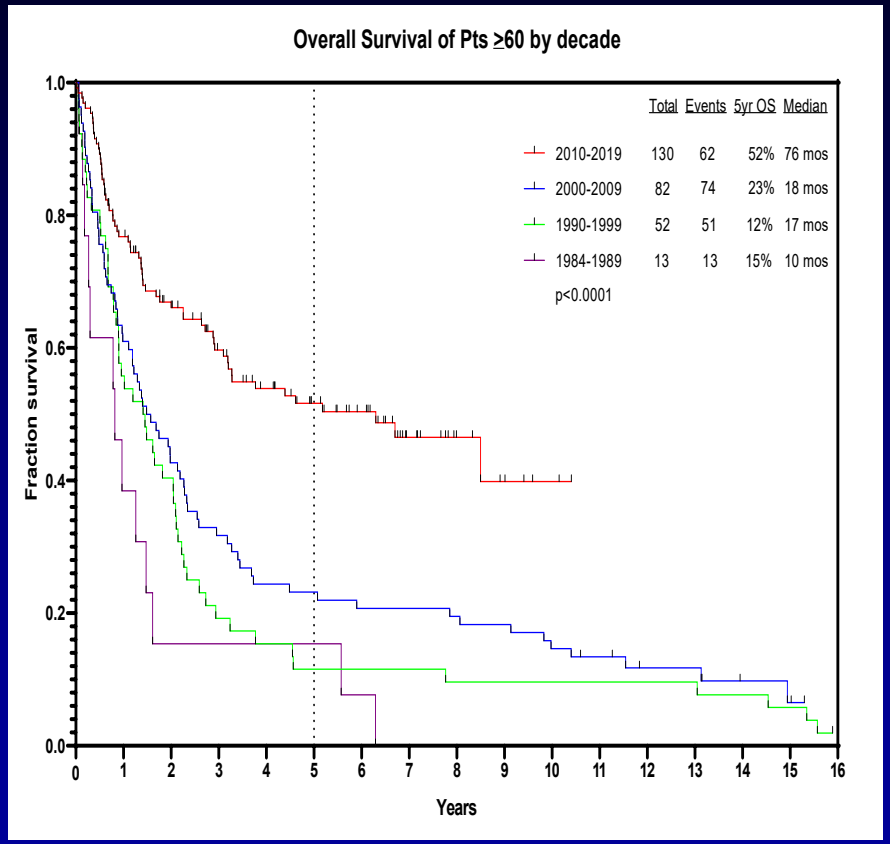
Short NJ, et al. EHA 2022. Abstract P371.

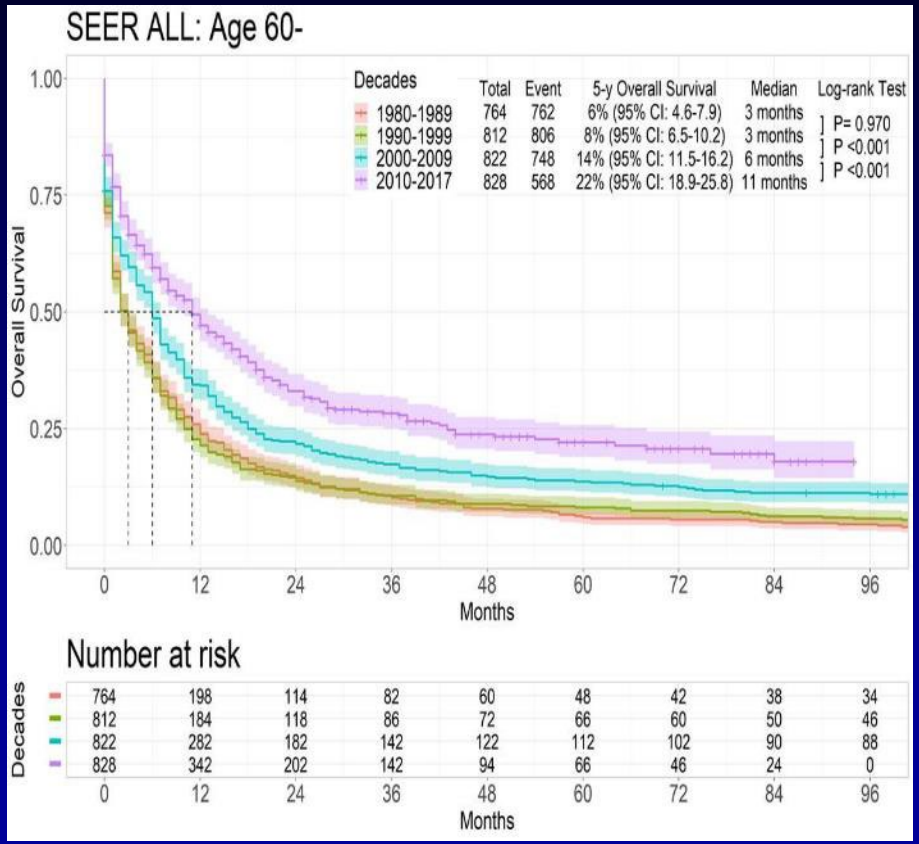
Frontline Blina and Ino Combinations in Adults with Newly Dx ALL

	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
HCVAD-Blina	Blinatumomab	38	37 (17-59)	100	97	81 (3-yr)
HCVAD-blina-inotuzumab	Blinatumomab and Inotuzumab	25	24 (18-47)	100	91	100 (1-yr)
GIMEMA LAL1913	Blinatumomab	149	41 (18-65)	90	96	84 (1-yr)
GRAALL-2014-Quest	Blinatumomab	95	35 (18-60)	NA	74	92 (1.5 yr)
Low-intensity-Blinatumomab	Blinatumomab	30	52 (39-66)	100	73	69 (2-yr)

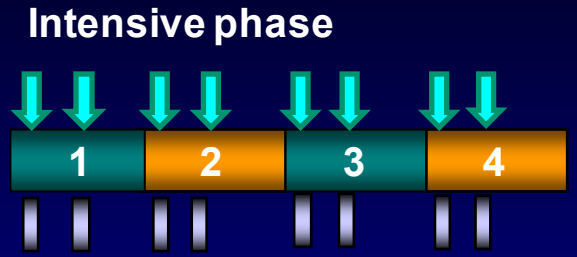
Short. Blood 138:1223; 2021. Bassan. EHA: S114; 2021. Boissel. Blood 140: abst 1232; 2021. Fleming. Blood 138:1224; 2021

MDACC ALL: Survival by Decades for ≥60 Years





Mini-HCVD + INO ± Blina in Older ALL: Modified Design



Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

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

Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

Haddad F, et al. EHA 2022. Abstract P355.

Mini-HCVD + INO ± Blina in Older ALL. (N=80)

Characteristic	Category	N (%) / median [range]
Age (years)		68 [60-87]
	≥70	30 (38)
Performance status	≥2	10 (13)
WBC (x10^9/L)		3.1 [0.3-111.0]
Karyotype	Diploid	26 (33)
	HeH	5 (6)
	Ho-Tr	12 (15)
	Tetraploidy	3 (4)
	Complex	3 (4)
	t(4;11)	1 (1)
	Misc	15 (19)
	IM/ND	15 (19)
CNS disease at diagnosis		4 (5)
CD19 expression (%)		99.5 [26-100]
CD22 expression (%)		96.9 [27-100]
CD20 expression	≥ 20%	44/73 (60)
Ph-like ALL		9/47 (19)
TP53 mutation		24/61 (39)

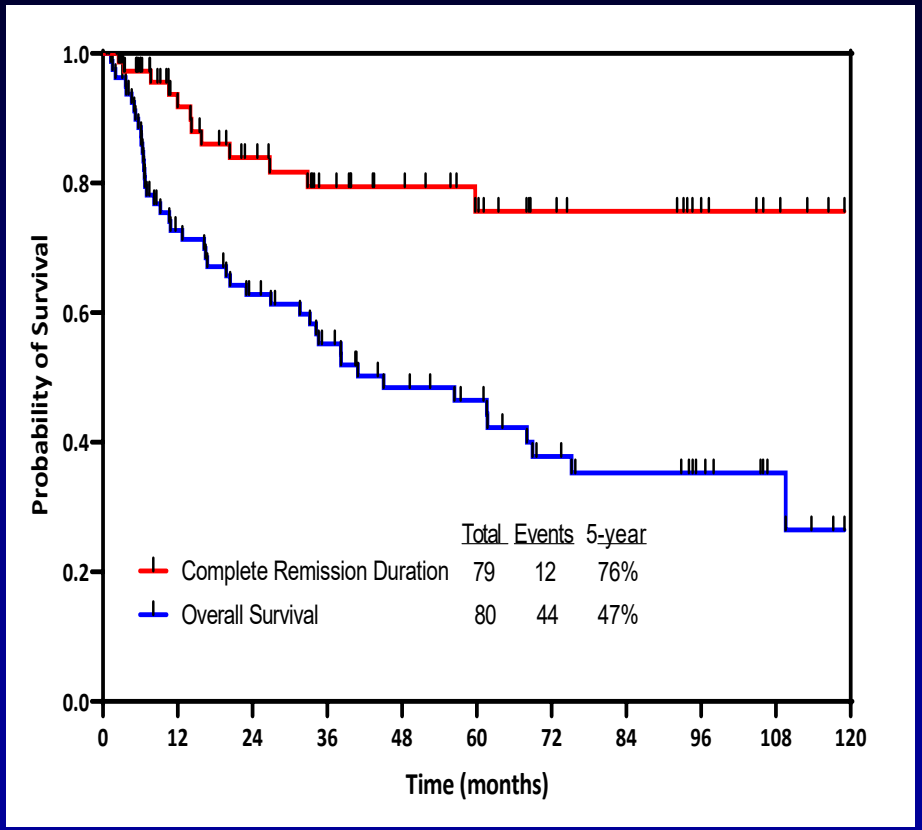
Response (N=74*)	N (%)
ORR	73 (99)
CR	66 (89)
CRp	6 (8)
CRi	1 (1)
No response	1 (1)
Early death	0

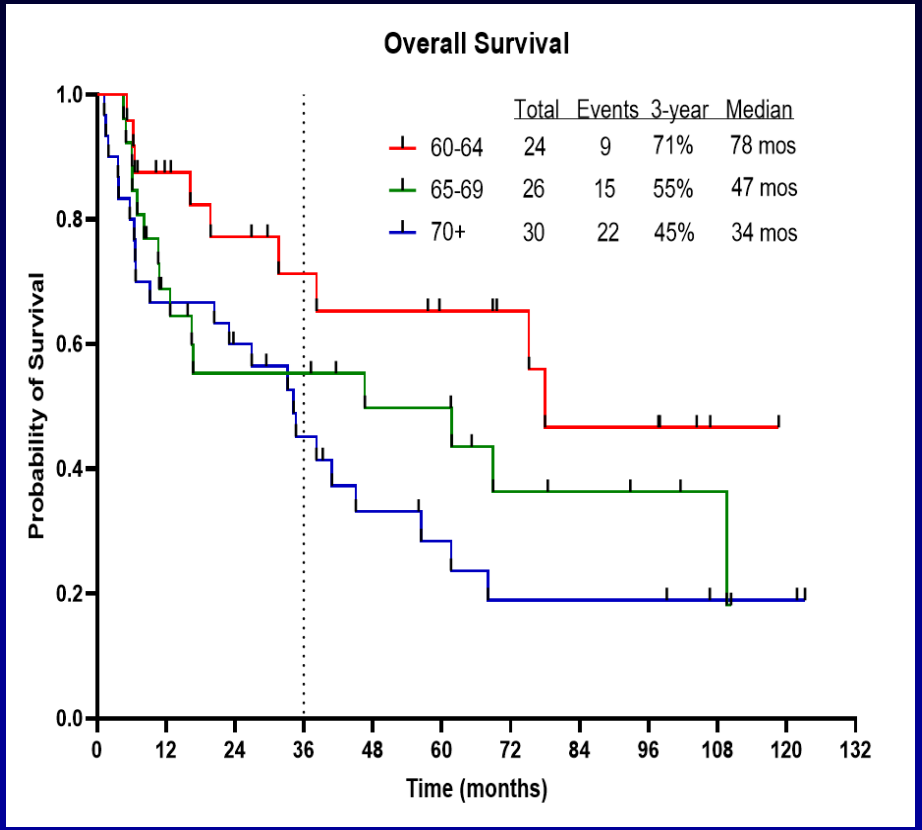
Flow MRD response	N (%)
Cycle 1, Day 21	61/76 (80)
Overall	74/79 (94)

* 6 pts were enrolled in CR

Haddad F et al. EHA abstract #P355, 2022

Mini-HCVD + INO ± Blina in Older ALL: Outcomes

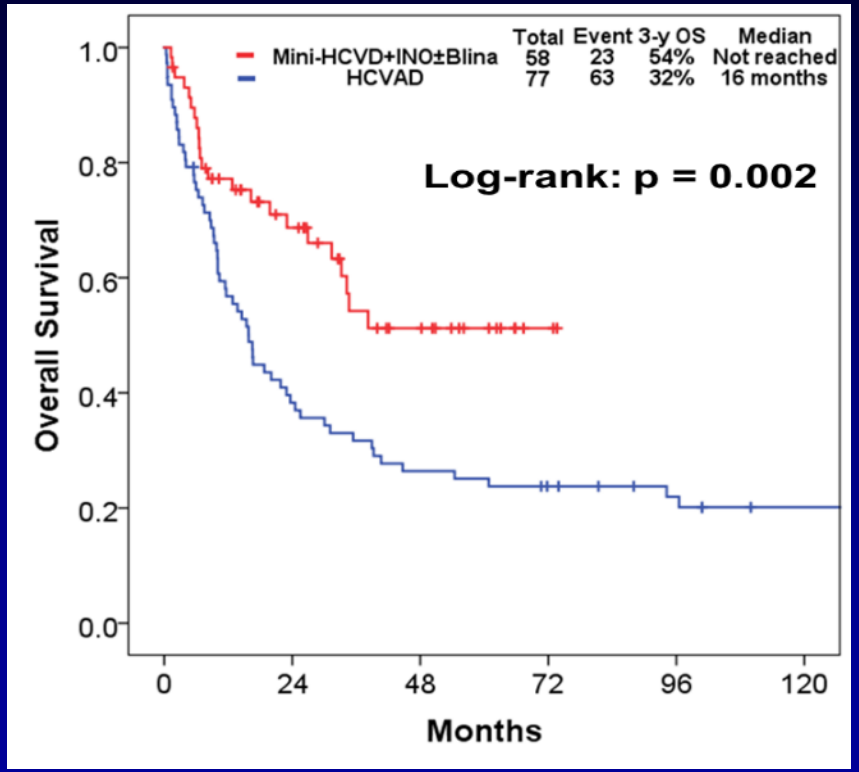




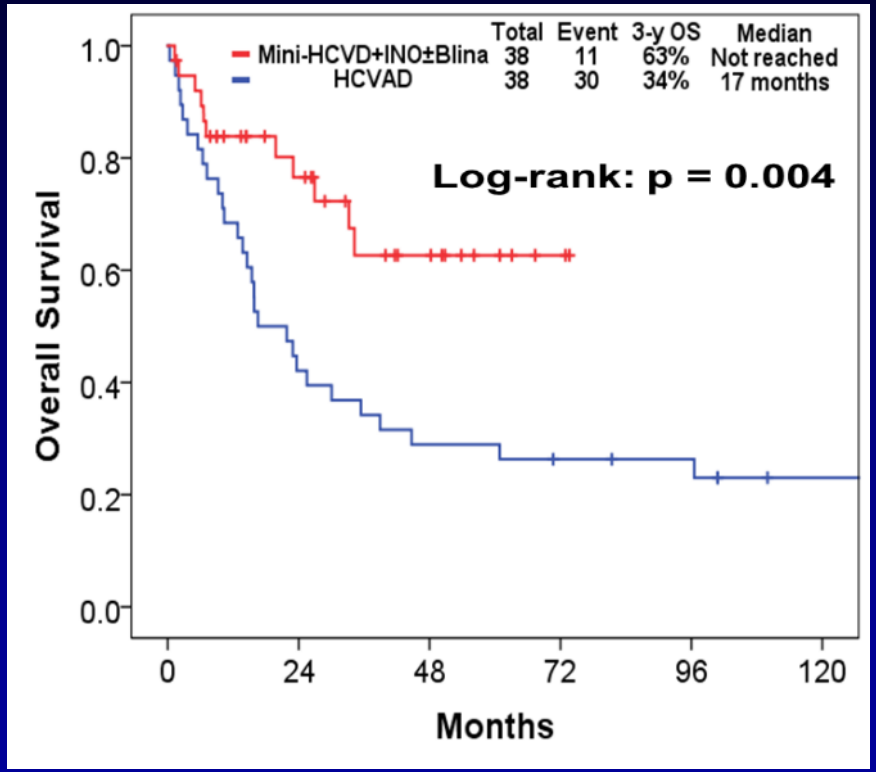
Haddad F, et al. EHA 2022. Abstract P355.

Mini-HCVD + INO ± Blina vs HCVAD in Older ALL: Overall Survival

Pre-matched

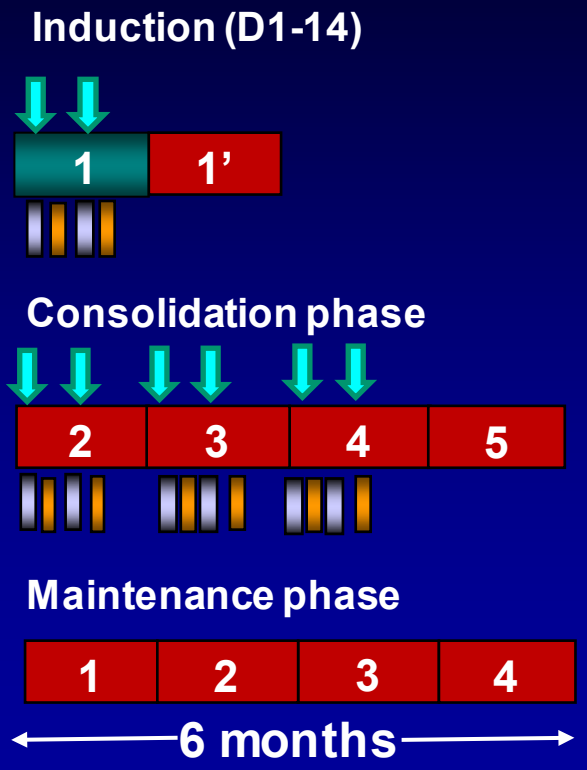


Matched



Jabbour E, et al. *Cancer.* 2019;125(15):2579-2586.

INO + Blina in Older ALL: Amended Design (pts ≥70 years)



Dexa 20 mg D1–4 and VCR 1 mg D4

Blinatumomab

IT MTX, Ara-C Rituximab if CD20+

1' Blinatumomab for 2 weeks

INO*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D1, 0.3 D8
C2–C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

Frontline Blina and Inotuzumab Combinations in Newly Dx Older ALL

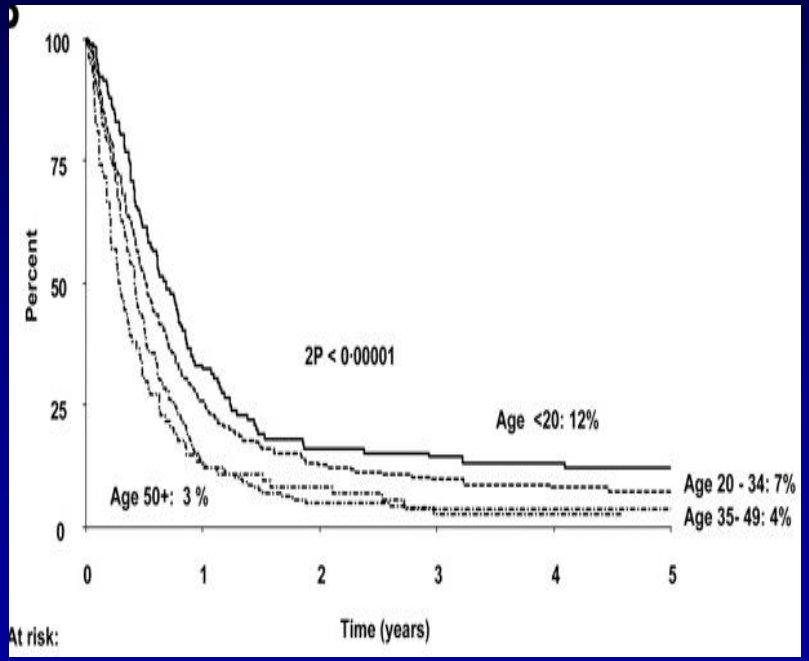
	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
Mini-HCVD-Inotuzumab-blinatumomab	Blinatumomab and Inotuzumab	80	68 (60-87)	89	94	47 (8-yr)
SWOG-1318	Blinatumomab	31	73 (66-86)	66	92	37 (3-yr)
EWALL-INO	Inotuzumab	115	69 (55-84)	88	73	78 (1-yr)
GMALL Bold	Blinatumomab	34	65 (56-76)	76	69	89 (1-yr)
INITIAL-1	Inotuzumab	45	65 (56-80)	100	74	77 (2-yr)

Short. Blood 138:3400; 2021. Advani. JCO 2022: Feb 14. Chevallier. Blood 140: abst 511; 2021. Goekbuget. Blood 140: abst 3399; 2021. Stelljes. Blood 140: Abst 2300; 2021

ALL – Historical Survival Rates After First Relapse

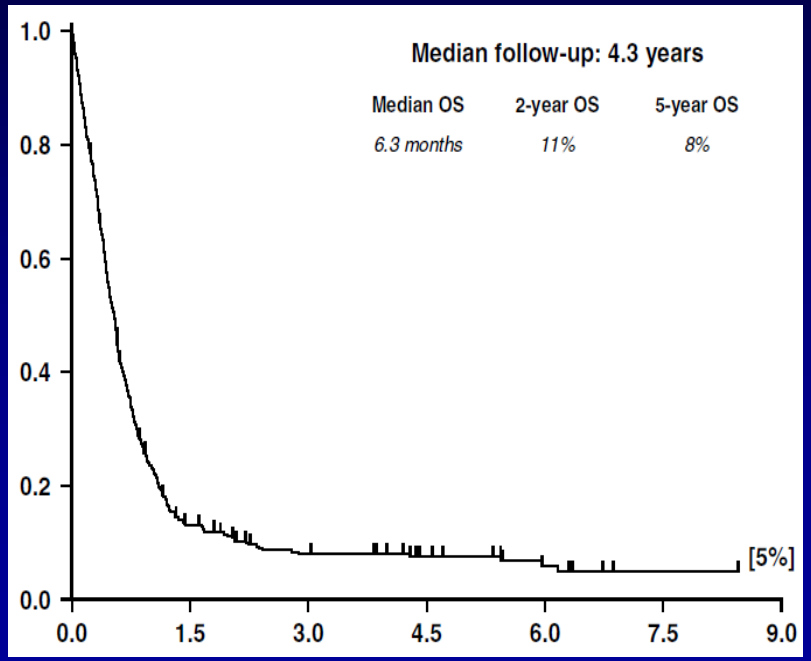
MRC UKALL2/ ECOG2993 Study (n = 609)

Outcome of patients after 1st relapse
5-yr OS: 7%



LALA-94 Study (n = 421)

Outcome of patients after 1st relapse
2-yr OS: 11% and 5-yr OS: 8%

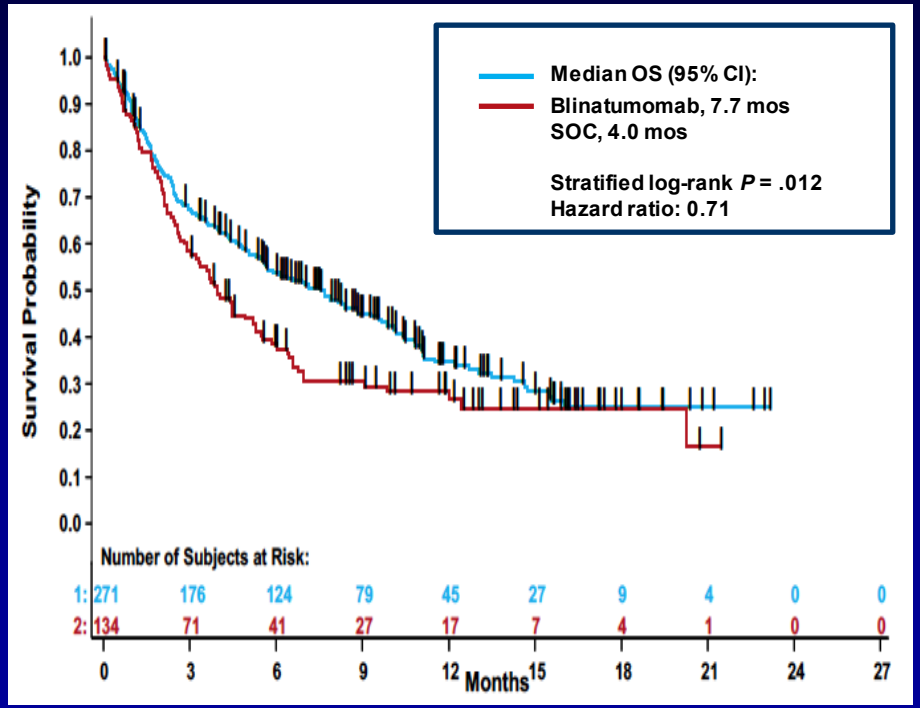


Fielding et al. *Blood.* 2007;109:944-950; Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

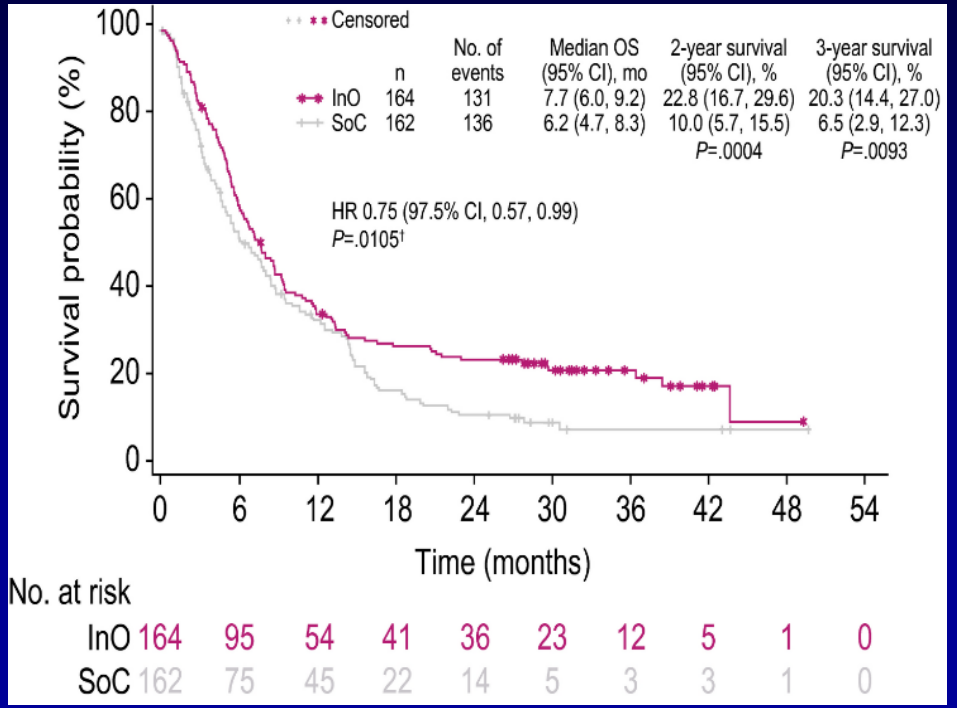
- **Marrow CR**

Blina vs SOC: 44% vs 25%



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

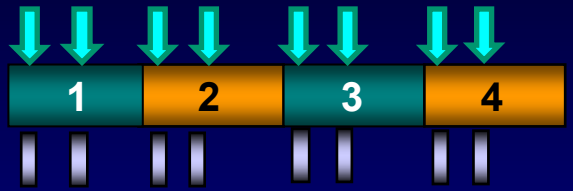
Ino vs SOC: 74% vs 31%



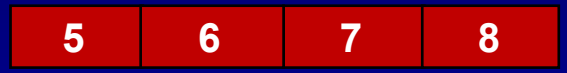
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

Mini-HCVD + INO ± Blina in R/R ALL

Intensive phase



Consolidation phase



Maintenance phase

Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

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

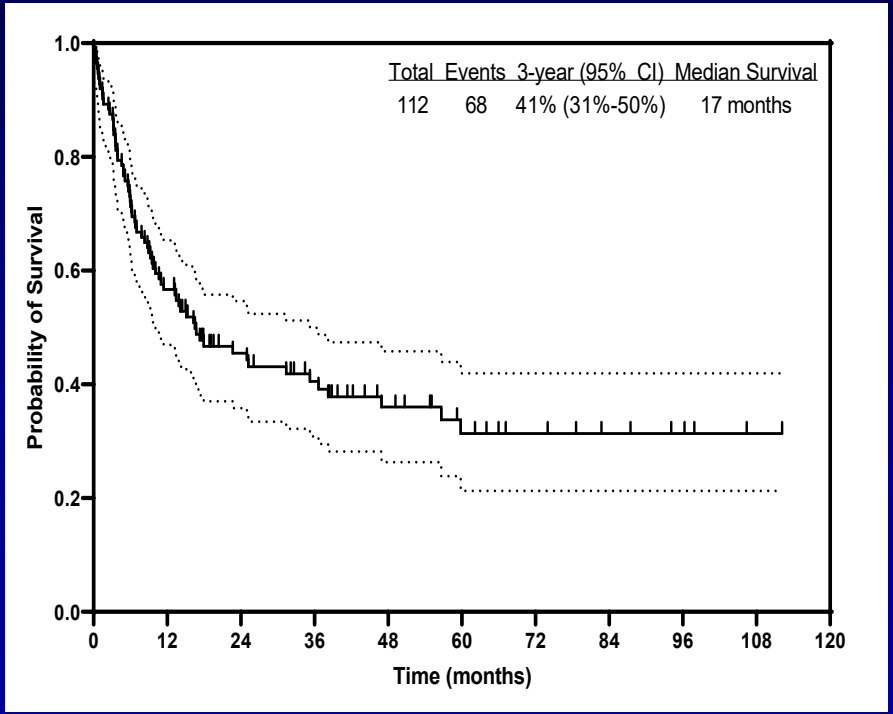
Total INO dose = 2.7 mg/m^2

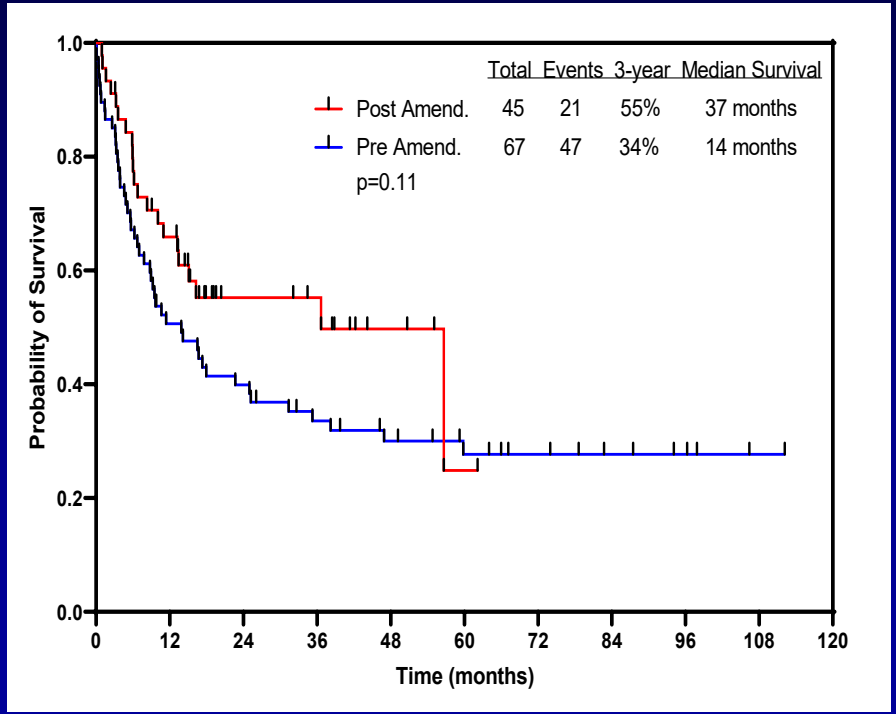
*Ursodiol 300 mg tid for VOD prophylaxis

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

ALL Salvage – MiniCVD-Inotuzumab ± Blinatumomab

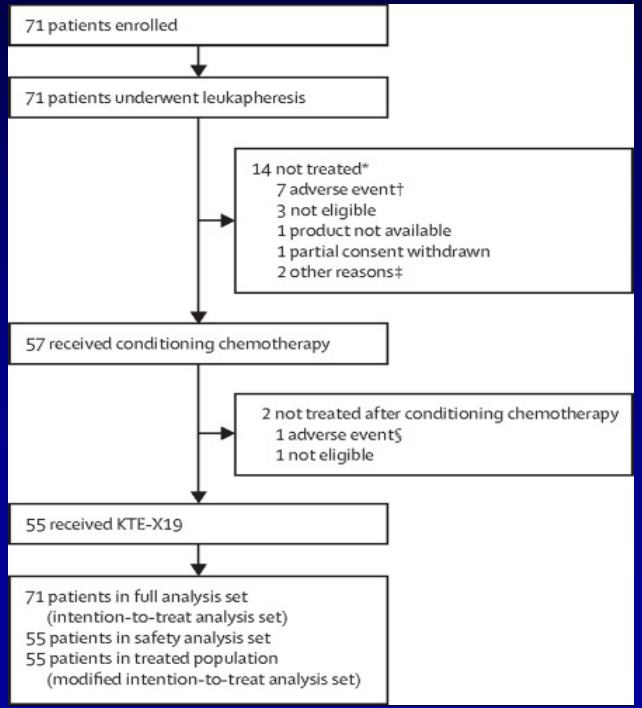
- 112 pts Rx for R/R ALL: 80 in S1; 32 in S2+
- CR 70/112 = 62%; ORR 93/112 = 83%. MRD-neg 76/91 = 83%. VOD 10/112 = 9%; 1% post amendment

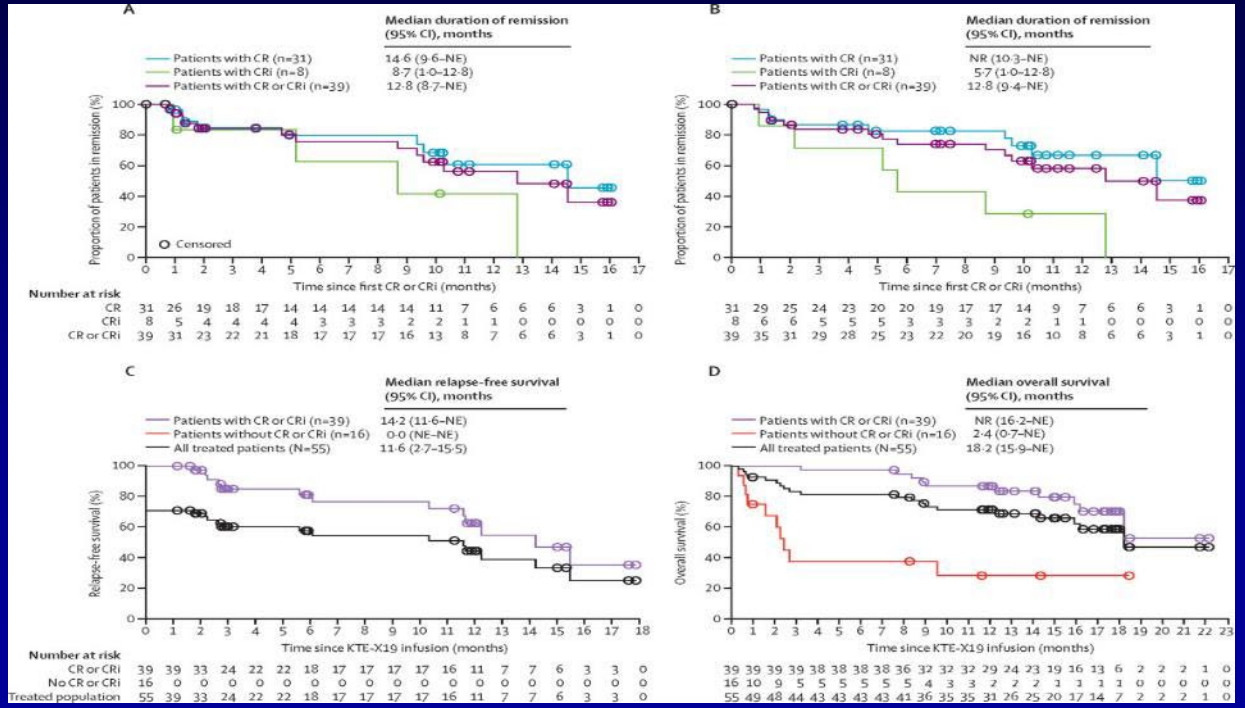




KTE-X19 Anti-CD19 CAR T Cells RX (Kite) in R/R ALL: Phase II (ZUMA-3)

- 71 enrolled, 55 infused; median age 40 yrs (28–52)
- CR/CRi 39/55 (71%, CR 56%); ITT (39/71; 55% – CR 44%); MRD– response 76% (97% among responders); 10 pts (18% Rx ASCT)
- mDOR 12.8 mos; mRFS 11.6 mos; mOS 18.2 mos
- Grade ≥3: CRS 24%; NE 25%

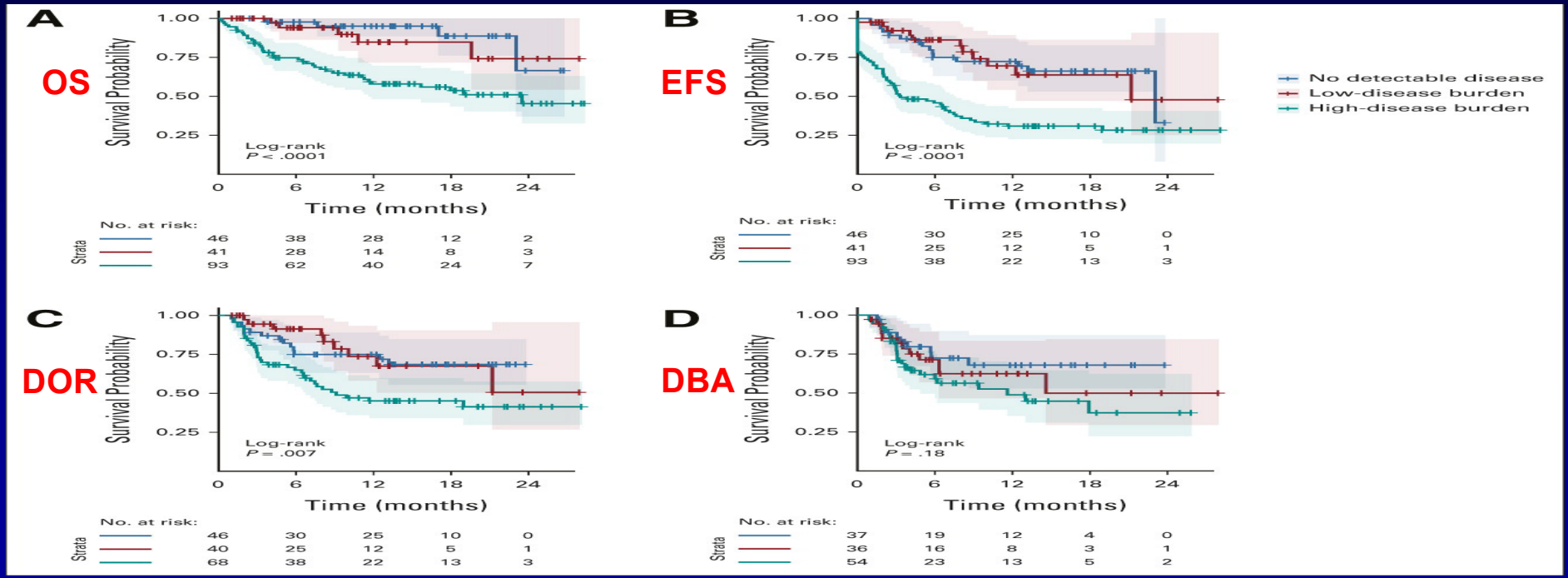




Shah et al. *Lancet.* 2021;S0140-6736.

Real Word CAR Consortium and Disease Burden

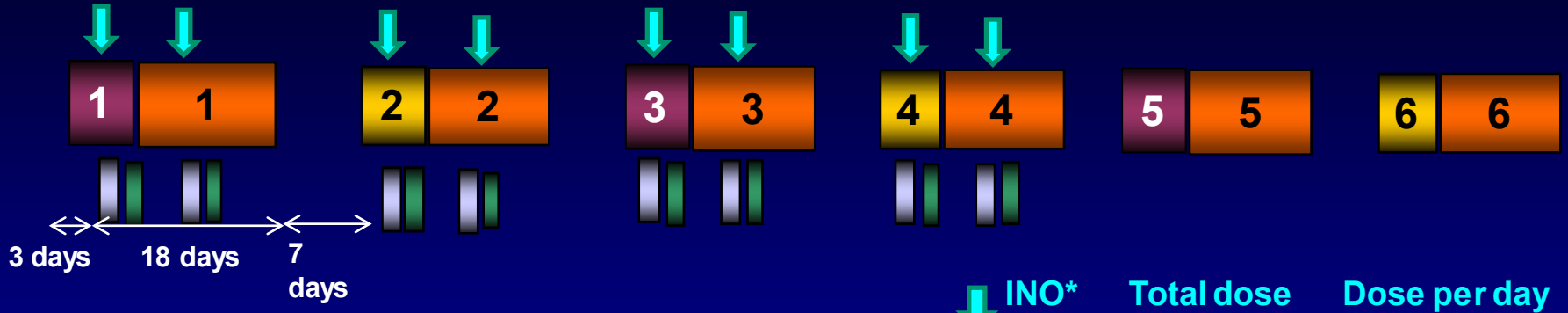
- 200 pts (185 pts infused); median age 12 yrs (0-26 yrs); CR=85%
- HBD n=94 (47%); LBD n=60 (30%); ND n=46 (23%)
- 12-mos EFS=50%, 12 mos OS=72%
- G3 CRS=21% (35% in HBD); G3 NE=7% (9% in HBD)



Schultz. J Clin Oncol. 2022;40:945-955

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

Induction phase: C1–C6



Consolidation phase

CAR T Consolidation

INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2–C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Mini-Hyper-CVD

Mini-MTX-Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

Thank You

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Global Leukemia Academy

Hot Topics and Regional Challenges of ALL Management

All faculty

APTITUDE HEALTH

Global Leukemia Academy

BREAK

Day 2 – 24 September

Pediatric ALL Session 10.00 – 12.45 CEST
Adult ALL Session 11.00 – 13.45 CEST
Adult AML Session 14.30 – 17.15 CEST

APTITUDE HEALTH

Global Leukemia Academy

AML Session

Gail J. Roboz and Naval Daver

APTITUDE HEALTH

Global Leukemia Academy

What's New in AML? Recent Developments in Research and Management

Naval Daver

APTITUDE HEALTH

What's New in AML? Recent Developments in Research and Management

Overview of recent data in AML

SEPT 2022

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Associate Professor
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Disclosures

Naval Daver, MD

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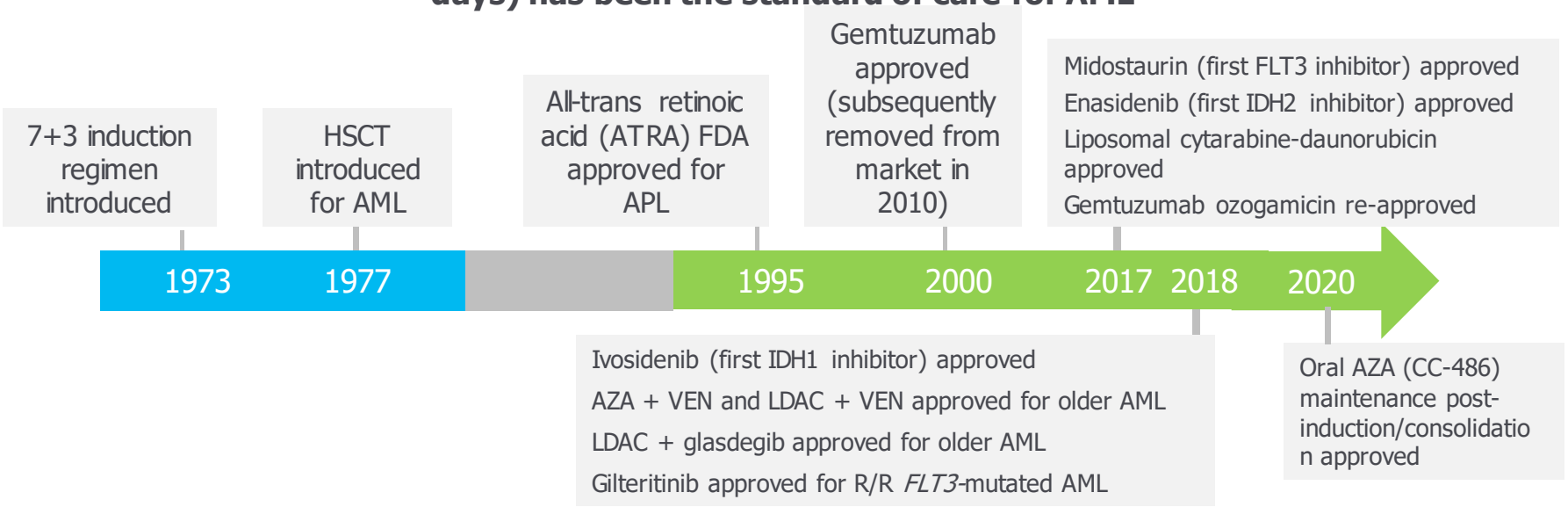
Disclaimer: Data will include medications not yet approved or with indications still under clinical study

Treatment of AML (Accelerated Progress 2017–2020): History

Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML



Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; FDA, United States Food & Drug Administration; HSCT, hematopoietic stem cell transplantation; R/R, relapsed/refractory.

Emerging Targeted Molecular Therapies in AML

***FLT3*-ITD mutations:** Add FLT3 inhibitor (gilteritinib, midostaurin, sorafenib), consider allo HSCT and post-HSCT FLT3i

***IDH1/2* mutations:** Add IDH inhibitor – enasidenib (*IDH2)* or ivosidenib (*IDH1*)

***NPM1* mutation** in diploid cytogenetics: cytarabine sensitivity; Menin inhibitors

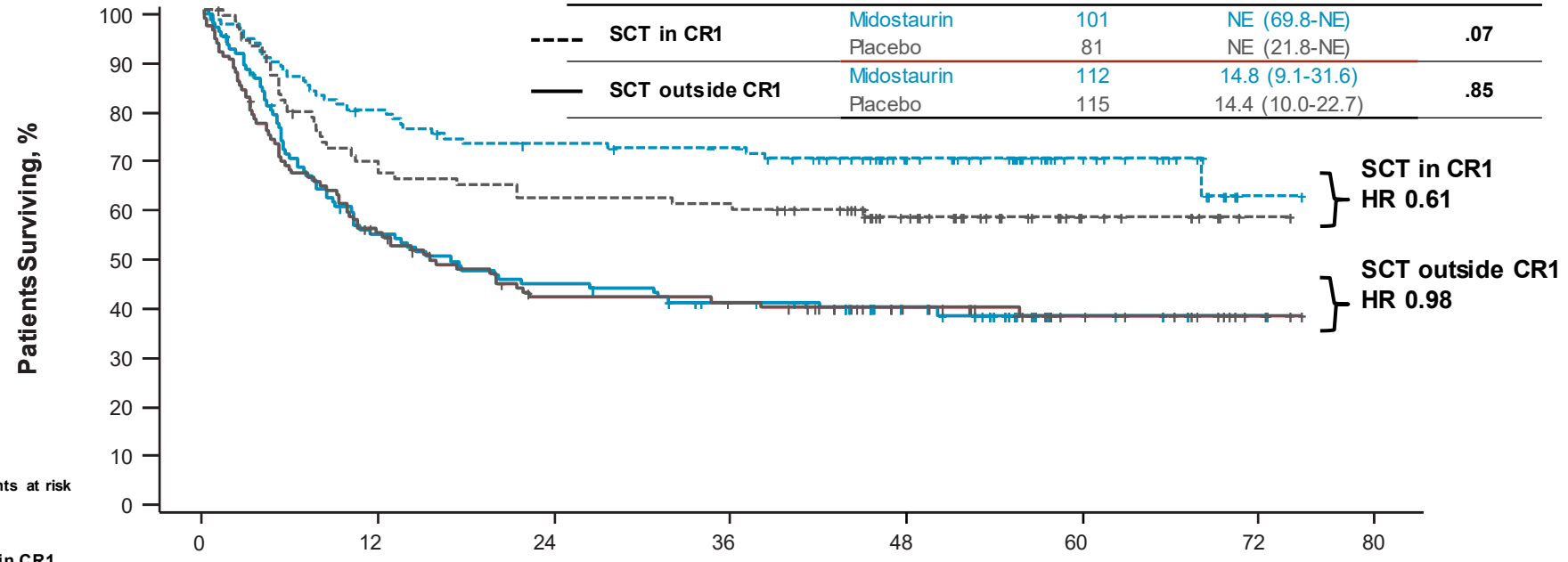
***TP53* mutation:** Consider decitabine 10 days ± others (GO, venetoclax); refer to allo HSCT; role of anti-CD47 (magrolimab)

***MLL*-rearranged AML; t(11q23;---):** Menin inhibitors

1. Targeting *FLT3* Mutations

OS, Posttransplant With 3+7 Plus Mido vs 3+7 Plus Placebo

		Patients, n	Median (95% CI), months	*P* Value[a]
SCT in CR1	Midostaurin	101	NE (69.8-NE)	.07
	Placebo	81	NE (21.8-NE)	
SCT outside CR1	Midostaurin	112	14.8 (9.1-31.6)	.85
	Placebo	115	14.4 (10.0-22.7)	



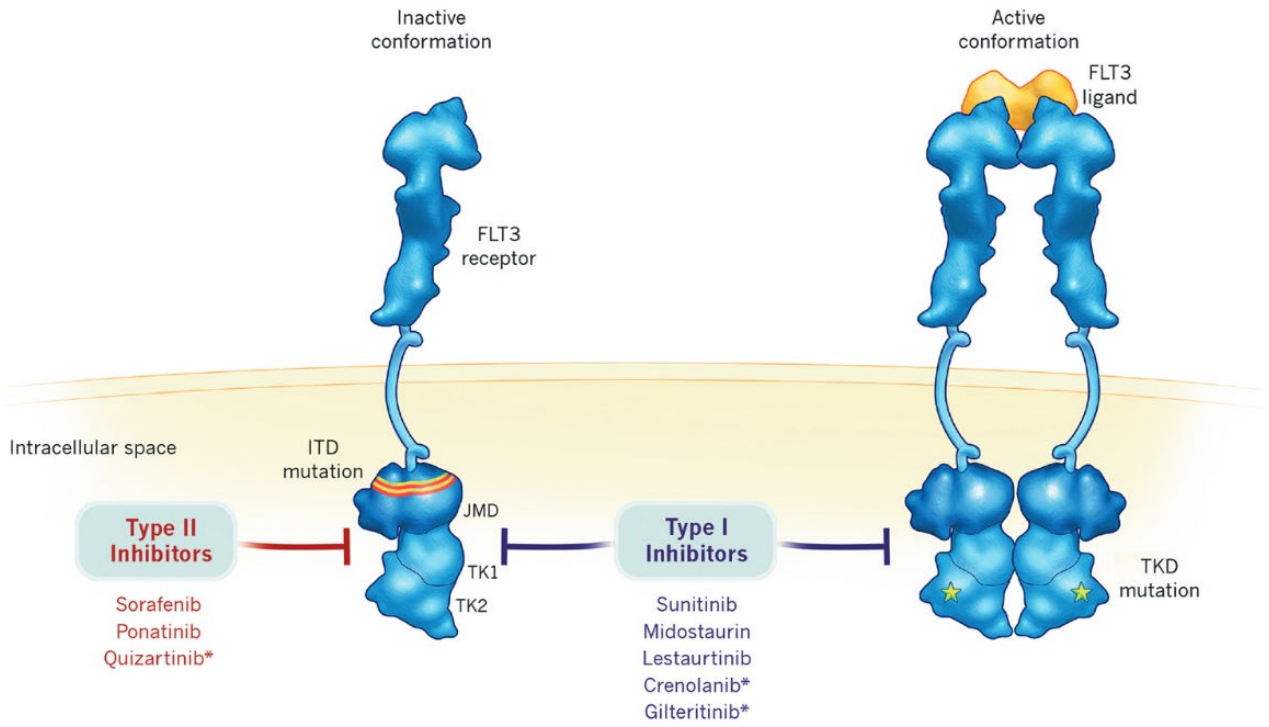
*Stratified on *FLT3* subtype; two-sided, long-rank *P* value.

Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

FLT3-Mutated AML
Types of FLT3 Inhibitors

Type I: Bind receptor "active" conformation near ATP pocket or activation loop; ITD and TKD

Type II: Bind receptor "inactive" conformation near ATP pocket; ITD only



*Second-generation FLT3 inhibitors.

Daver N et al, Leukemia. 2019;33:299-312.

QuANTUM-First Phase 3 Trial (NCT02668653): Quizartinib Plus Standard Induction Chemotherapy and Consolidation Followed by Single-Agent Quizartinib

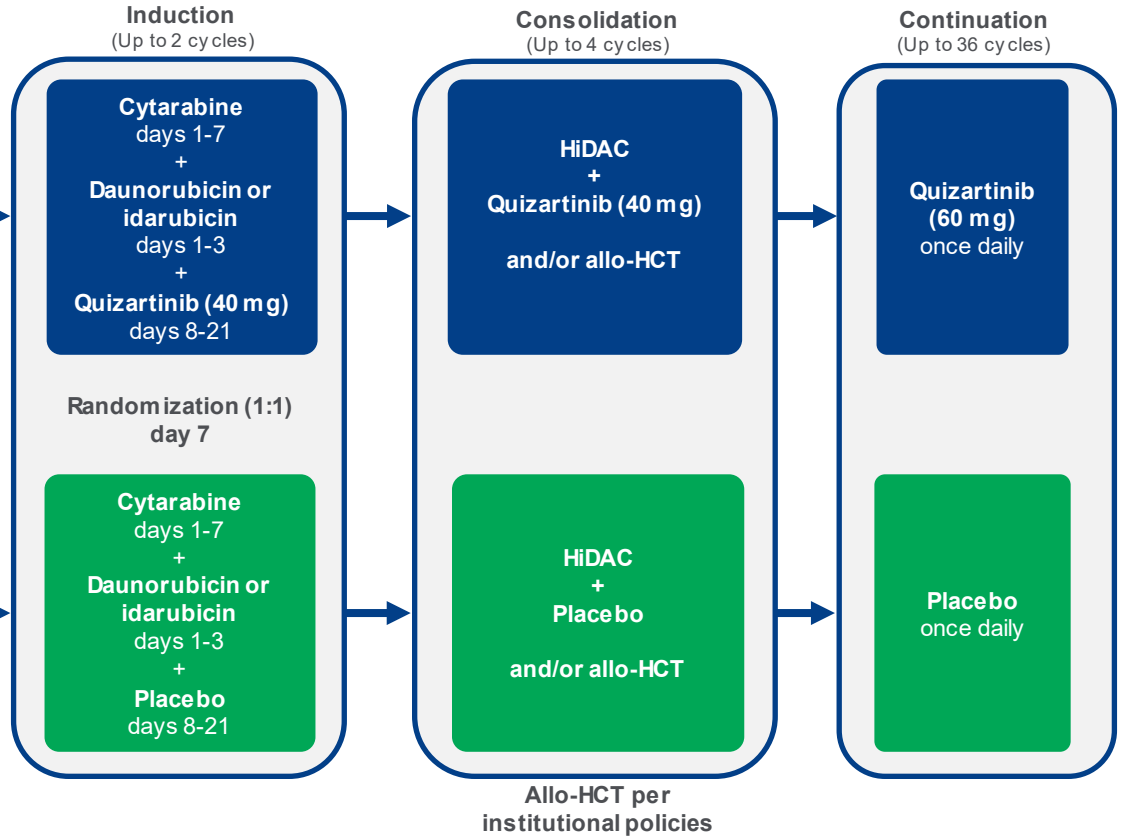
Enrollment dates: September 2016 to August 2019
Data cutoff: August 13, 2021

Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: <40×10^9/L, ≥40×10^9/L

- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

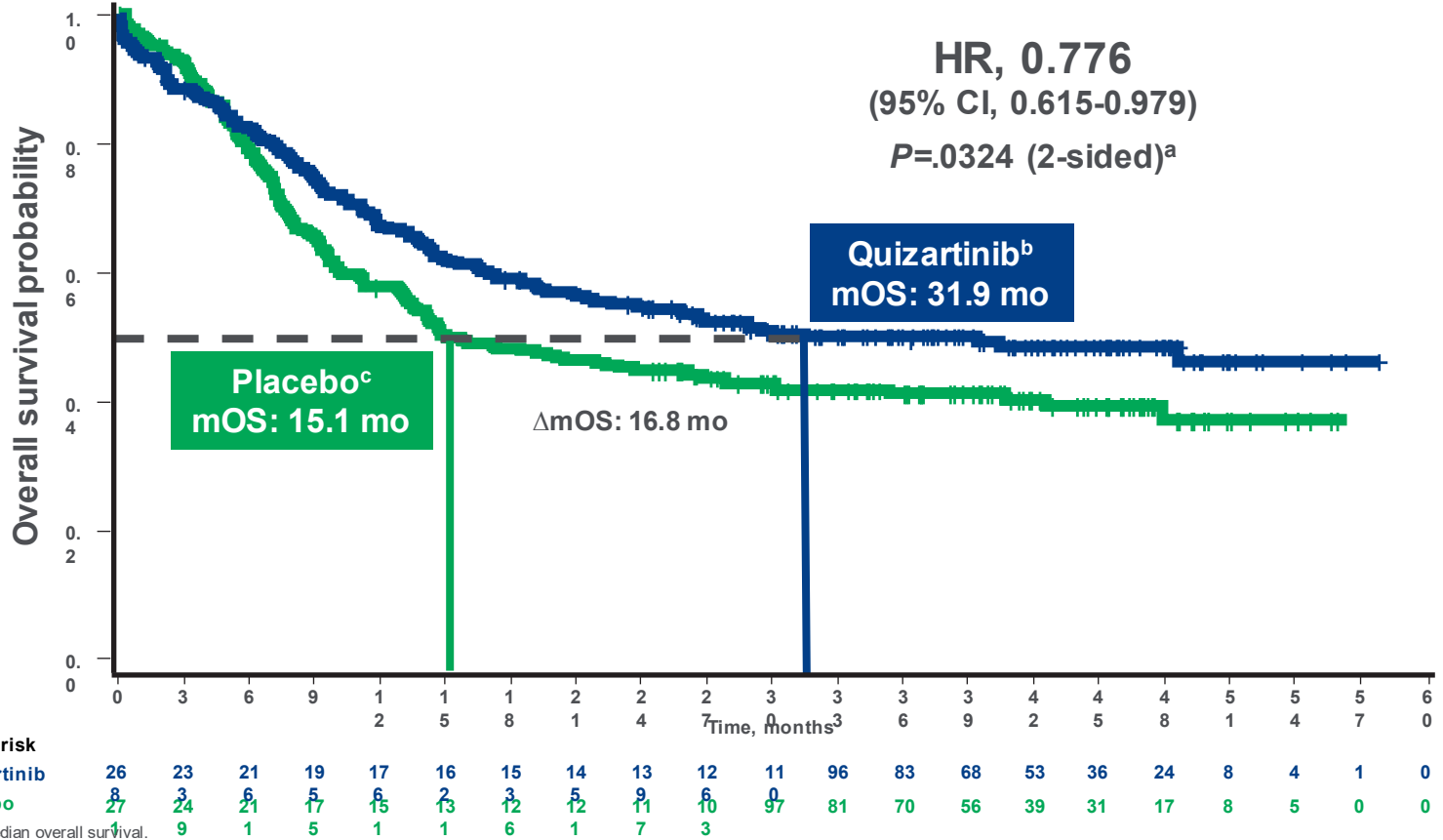
Selected endpoints
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR/CRc, Safety
- **Exploratory endpoints**: RFS, DoCR

A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR and CRc.



AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, Europe; HiDAC, high-dose cytarabine; NA, North America, OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.
[a] WBC count was measured at the time of AML diagnosis.

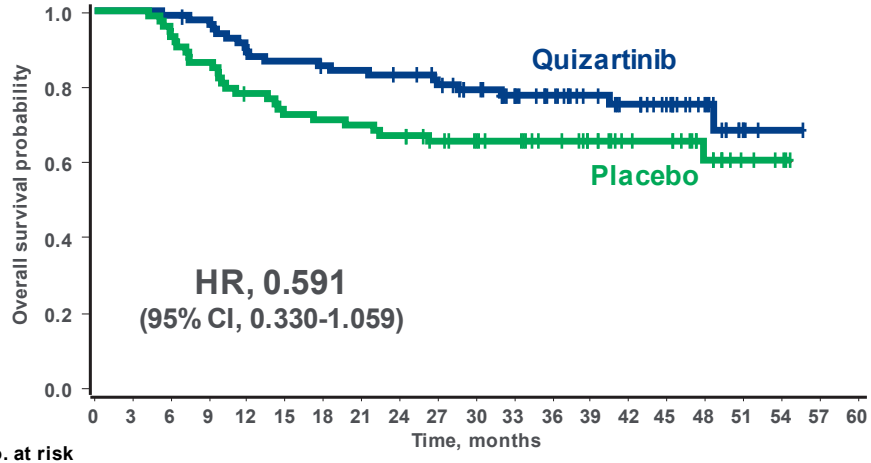
Primary Endpoint: Overall Survival



HR, hazard ratio; mOS, median overall survival.
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 39.2 months. [c] Median follow-up time for placebo arm, 39.2 months.

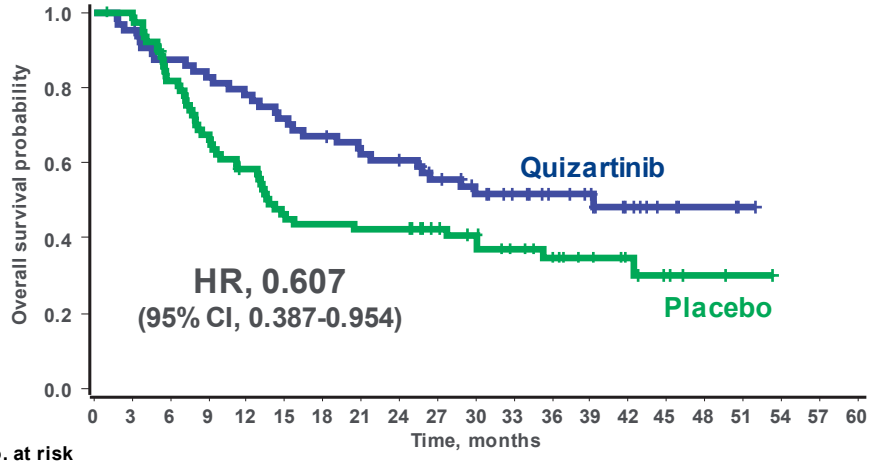
Post-hoc Analysis: OS in Patients Who Achieved CR[a]

OS – Patients With CR Who Received Allo-HCT in CR1



No. at risk																				
Quizartinib	84	84	83	81	74	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0	0
Placebo	73	73	68	63	56	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0	0

OS – Patients With CR NOT Receiving Allo-HCT in CR1

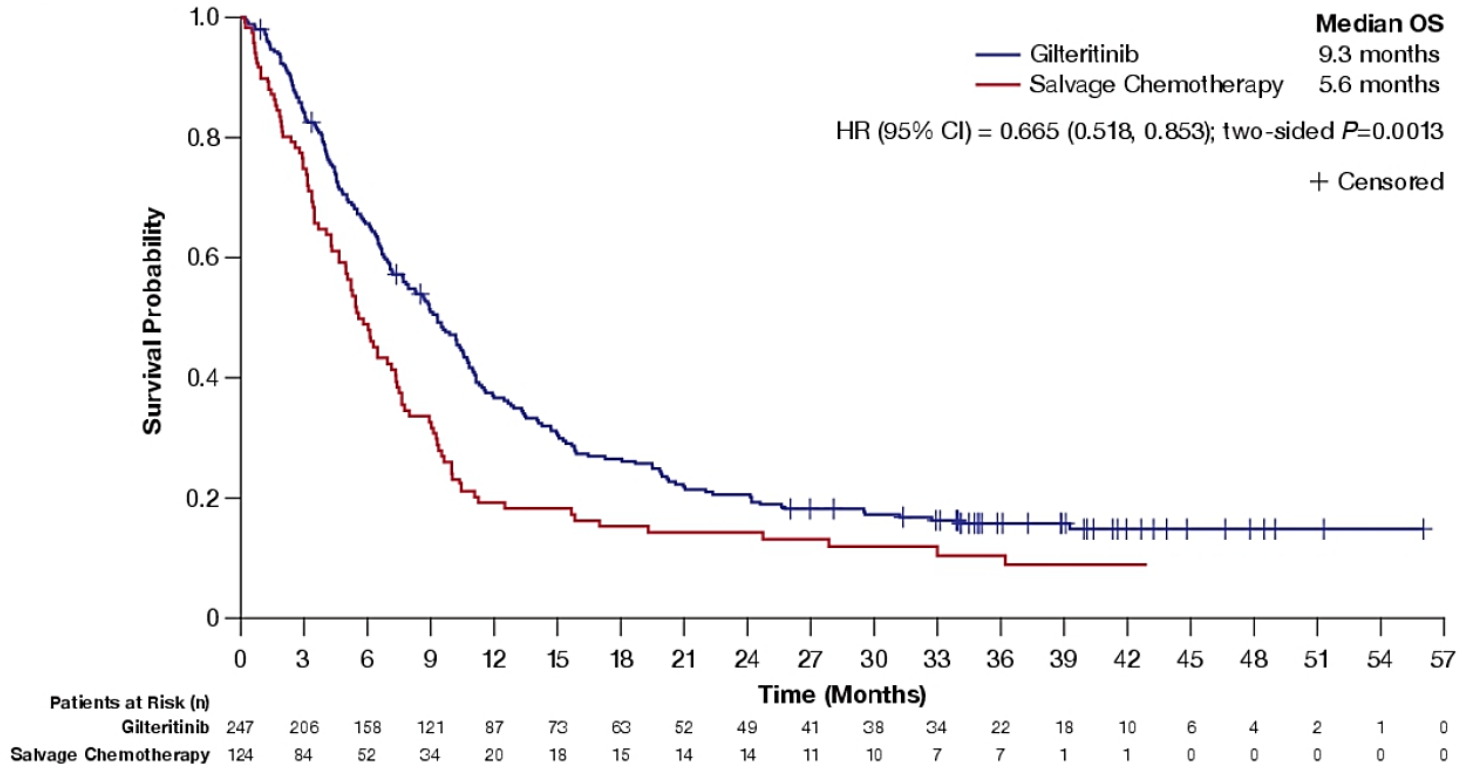


No. at risk																				
Quizartinib	63	60	54	51	48	44	41	37	35	30	25	21	17	15	9	5	3	1	0	0	0
Placebo	77	76	61	50	42	33	31	30	30	25	22	17	14	10	7	4	2	1	0	0	0

- Subgroup analysis for descriptive purposes only

Allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; HR, hazard ratio; IRC, independent review committee; OS, overall survival.
[a] By end of induction by IRC.

ADMIRAL: Longer Follow-Up Confirms OS Benefit With Gilteritinib in R/R *FLT3* Mutant AML



Perl AE, et al. Blood. 2022;139:3366-3375.

Gilteritinib
Clinical Activity in Patients With Prior TKI Exposure

- Multicenter retrospective review[a]
  - 11 US centers; 113 patients with prior TKI exposure who received gilteritinib for R/R *FLT3*-mutated AML
  - **The CRc rate for patients treated with gilteritinib who received prior 7+3 and midostaurin ± consolidation was 58%, with a median survival of 7.8 months**

- Combined responses of 303 patients receiving gilteritinib 120 mg in CHRYSALIS and ADMIRAL trials[b]

Response Parameter, n (%)	With Prior TKI (n = 48)	Without Prior TKI (n = 255)
CR	7 (15)	52 (20)
CRi	13 (27)	67 (26)
CRp	5 (10)	16 (6)
PR	6 (13)	31 (12)
NR	14 (29)	75 (29)
NE	3 (6)	14 (5)
CRc*	**25 (52)**	**135 (53)**

CR, complete remission; CRc, composite complete remission; CRi*, complete remission with incomplete neutrophil count recovery; CRp, complete remission with incomplete platelet recovery; NE, not evaluable; NR, no response; PR, partial remission; TKI, tyrosine kinase inhibitors.

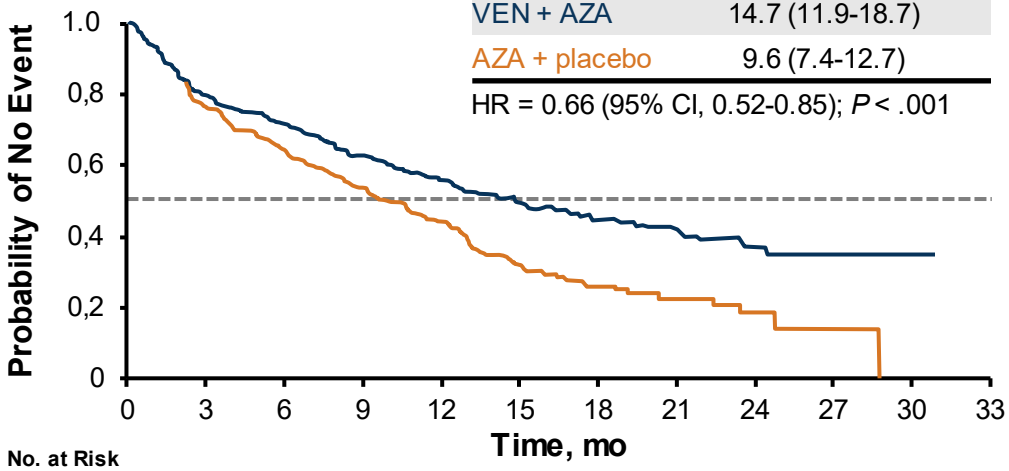
a. Numan Y, et al. Am J Hematol. 2022;97:322-328; b. Perl AE, et al. Blood Cancer J. 2022;12:84.

VIALE-A Established VEN + AZA as a Standard Upfront Regimen in AML Care

VEN + AZA led to statistically significant and clinically meaningful improvement in response rates and OS compared with AZA[1]

	Median OS, mo (95% CI)
VEN + AZA	14.7 (11.9-18.7)
AZA + placebo	9.6 (7.4-12.7)

HR = 0.66 (95% CI, 0.52-0.85); *P* < .001



No. at Risk												
VEN + AZA	286	219	198	168	143	117	101	54	23	5	3	0
AZA + placebo	145	109	92	74	59	35	30	14	5	1	0	0

- CR + CRi rate of 64.4% with VEN + AZA

DiNardo C et al. N Engl J Med. 2020;383:617-629.

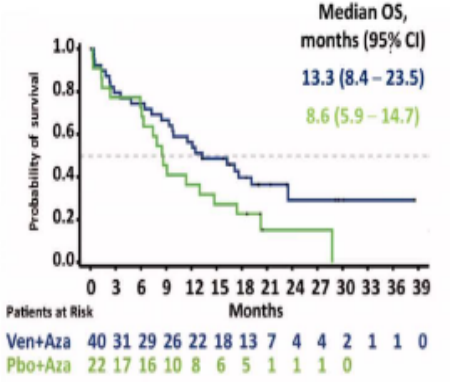
AZA + VEN Improved Responses vs AZA in *FLT3*-Mutated Newly Diagnosed AML, But Median OS Was <12 Months

CR/CRi

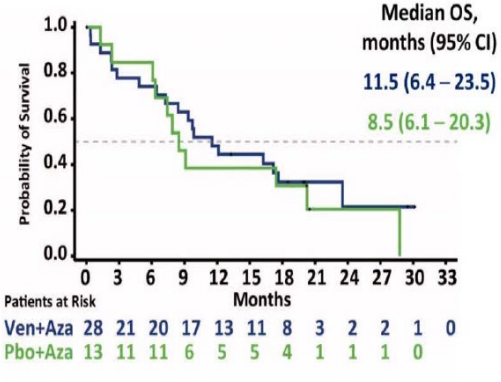
CR + CRi, n/N (%)	VEN + AZA	PBO + AZA
FLT3 mutation	28/40 (70)	8/22 (36)
FLT3 WT	150/227 (66)	21/86 (24)
***FLT3*-ITD**	**19/28 (68)**	**6/13 (46)**
FLT3-ITD AR <0.5	14/19 (74)	4/8 (50)
FLT3-ITD AR ≥0.5	5/9 (56)	2/5 (40)
***FLT3*-TKD**	**10/13 (77)**	**3/10 (30)**
FLT3 and *NPM1* comutation	10/14 (71)	2/7 (29)

Median Duration of CR + CRi	VEN + AZA		PBO + AZA	
	N	Months (95% CI)	N	Months (95% CI)
FLT3 mutation	28	17.3 (10.1-NR)	8	5.0 (1.0-15.9)
FLT3 WT	150	18.2 (14.0-NR)	21	13.4 (5.8-15.6)

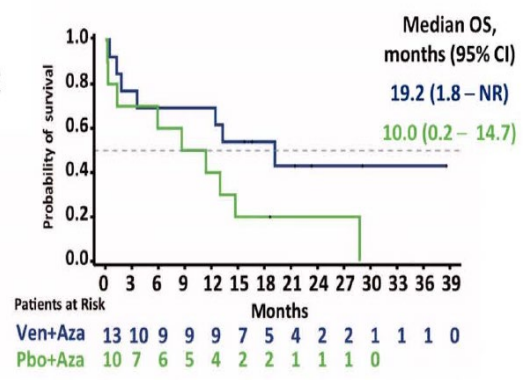
FLT3



FLT3-ITD

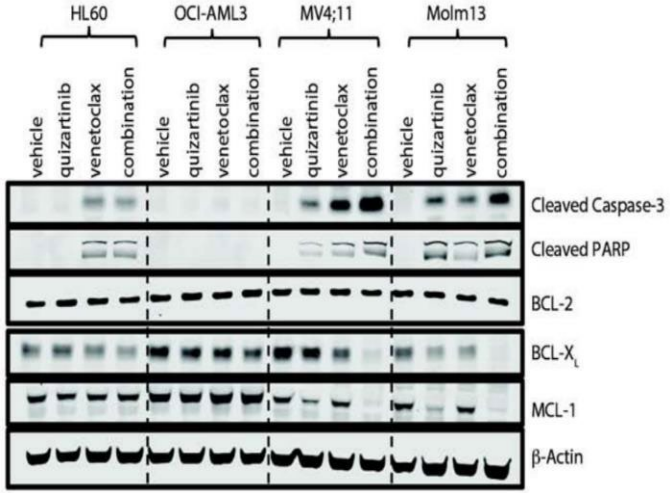


FLT3-TKD

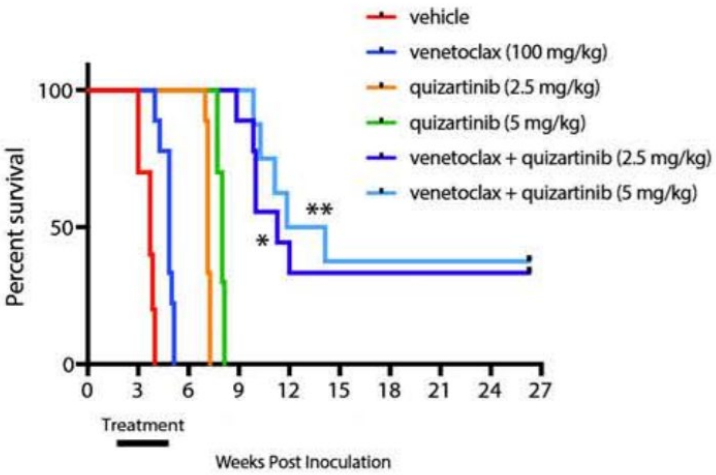


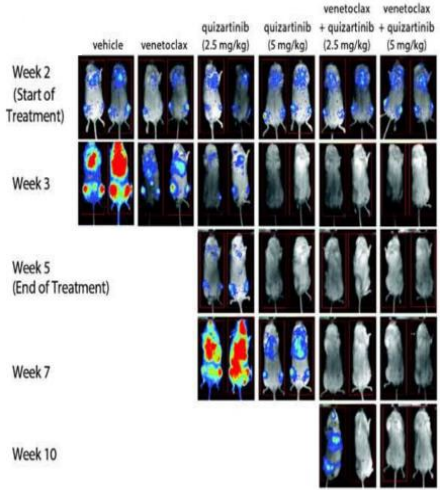
Konopleva M et al. ASH 2020. Abstract 1904.

Venetoclax Combines Synergistically With FLT3i's (Quizartinib)



Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X$_L$

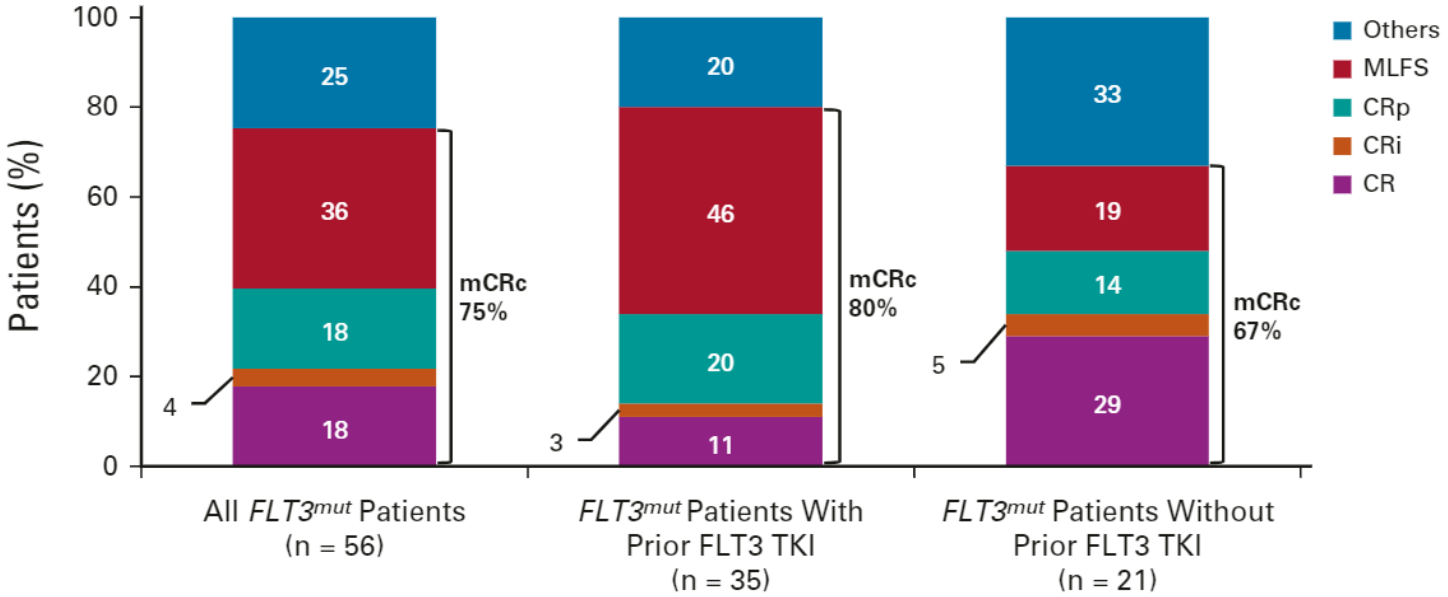




Venetoclax combined with quizartinib prolonged survival and reduced tumor burden in FLT3-ITD+ xenograft models

a. Yilmaz M, et al. Blood. 2021;138: Abstract 370; b. Singh Mali R, et al. Haematologica. 2021;106:1034-1046.

VEN + GILT
Summary of Best Responses



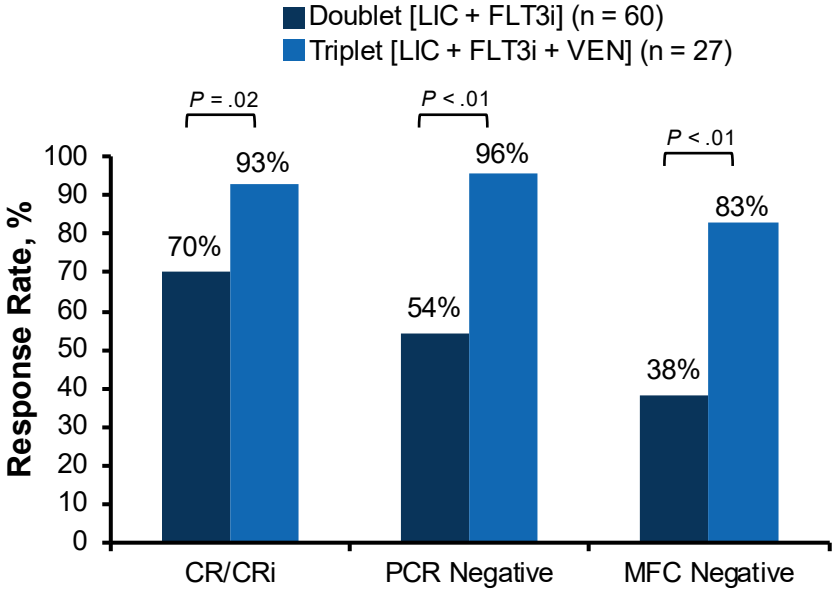
The mCRc rate in this study was **75**%,[a] whereas the CRc rate in the ADMIRAL phase 3 study for single-agent GILT was **54.3%** (using the same response parameters)[b]

mCRc, modified composite complete remission; MLFS, morphologic leukemia-free state.

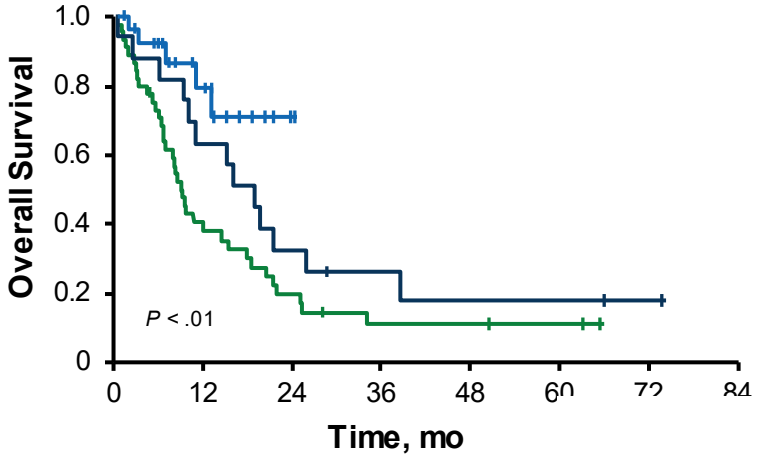
a. Daver N, et al. J Clin Oncol. 2022:JCO2200602; b. Perl AE, et al. New Engl J Med. 2019;381:1728-1740.

Retrospective Pooled Analysis Suggests That Frontline Triplets May Be Highly Active in *FLT3*-Mutant AML[1]

- **First- and second-generation FLT3i-based doublet and triplet regimens in older/unfit adults with newly diagnosed *FLT3*-mutated AML (N = 87)**
  - **Doublets (FLT3i + low-intensity chemotherapy):** CRc: 70%; survival of 9-16 mo
  - **HMA/VEN/FLT3i combination** significantly improved CR/CRi rates, CR rates, *FLT3*-PCR and MFC MRD rates, as well as OS, without increasing 60-day mortality (7% vs 10%)



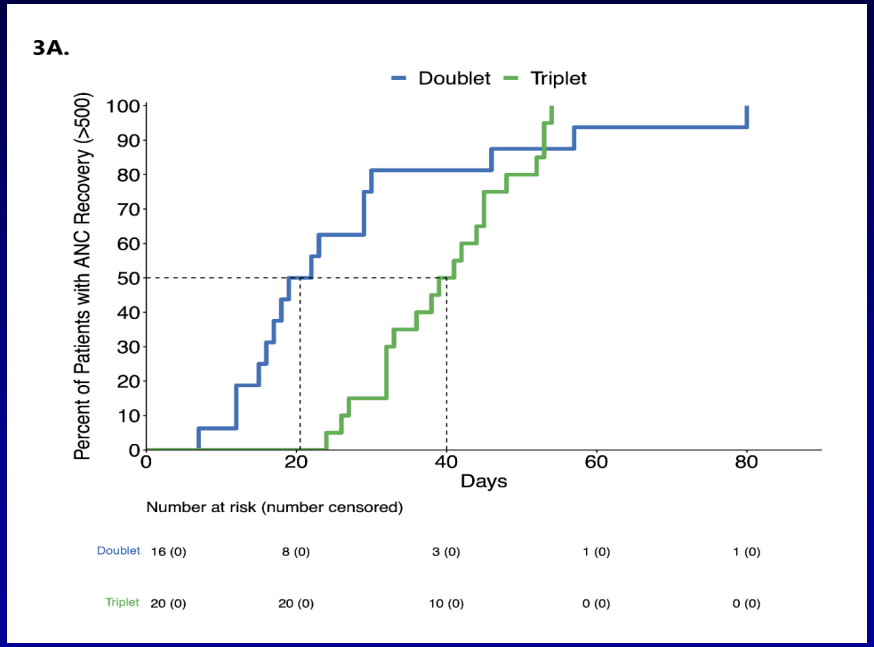
Treatment Regimen	N = 87	Median Age	Median OS, mo
Triplet (LIC + FLT3i + VEN)	27	69 (40-85)	NR
Doublet (LIC + 2nd generation FLT3i)	16	71 (64-83)	15.7
Doublet (LIC + 1st generation FLT3i)	44	70 (51-83)	8.7



Yilmaz M,....., Daver N. Blood Cancer Journal, April 2022

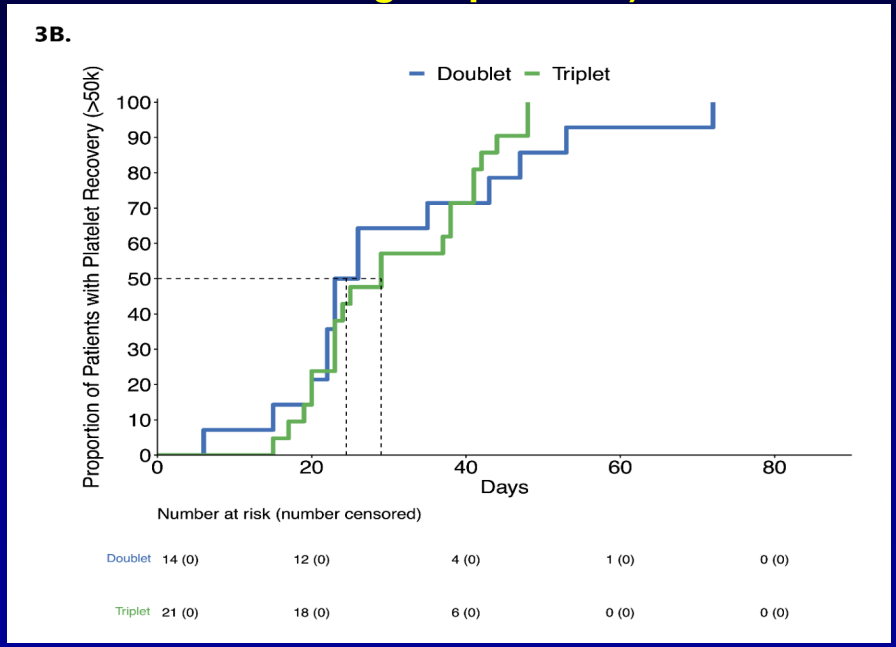
Time to Count Recovery at the End of Cycle 1 – Doublet *vs.* Triplet

ANC >500 (40 vs 21 days among responders)



When all pts considered by C1D42: ANC >0.5 in 14/27 (52%) versus 20/60 (33%) due to higher response in triplet

Platelet count >50K (29 vs 25 days among responders)

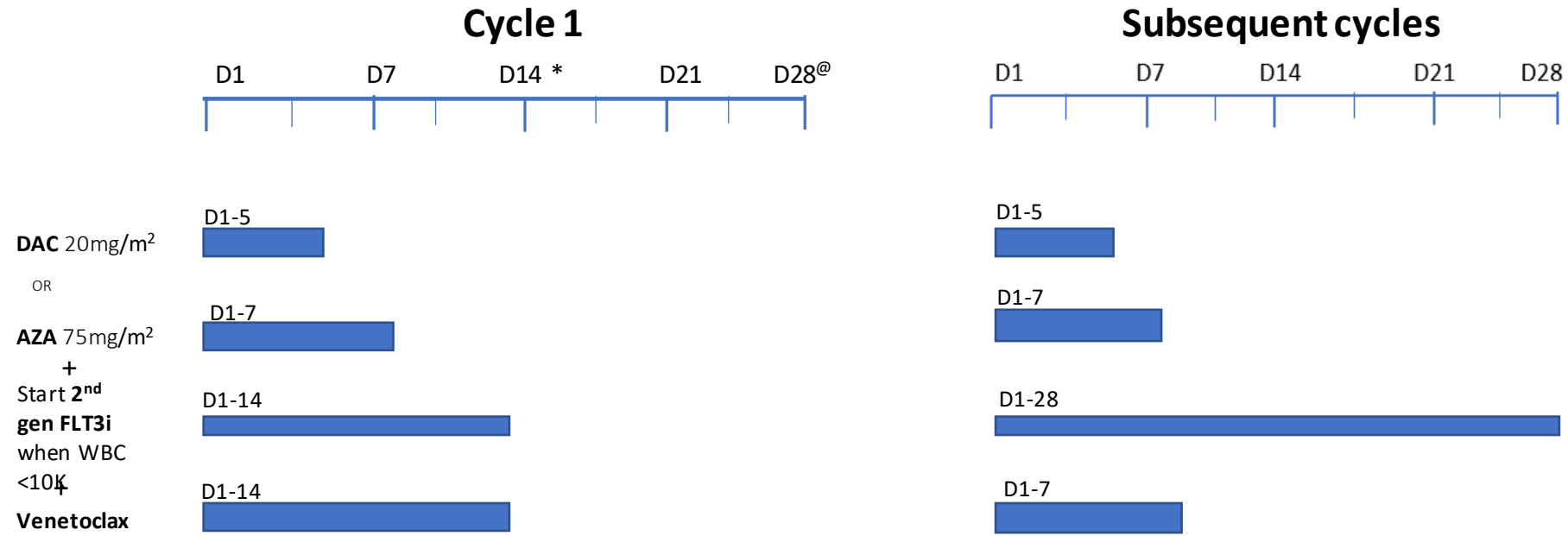


When all pts considered by C1D42: PLT > 50 in 20/27 (74%) versus 17/60 (28%) due to higher response in triplet

Yilmaz M,….., Daver N. Blood Cancer Journal, April 2022

Dosing, duration and response evaluation timing with the FLT3 triplet regimen (Dose optimization critical and ongoing)

Ongoing prospective trial dosing: AZA + VEN + GILT ; PI: Nick Short
DAC + VEN + Quiz; PI: Musa Yilmaz



- *C1 D14: Perform bone marrow biopsy; If bone marrow shows <5% blasts and/or <5% cellularity/insufficient sample --> Stop venetoclax on D14.
- **If the C1 D14 bone marrow show >5% blasts --> continue venetoclax till C1 D21
- @ Repeat a C1 D28 bone marrow on all patients to confirm remission. If C1 D28 marrow confirms remission and ANC<0.5 and/or platelet<50K consider interrupting FLT3i and using neupogen to enhance count recovery.

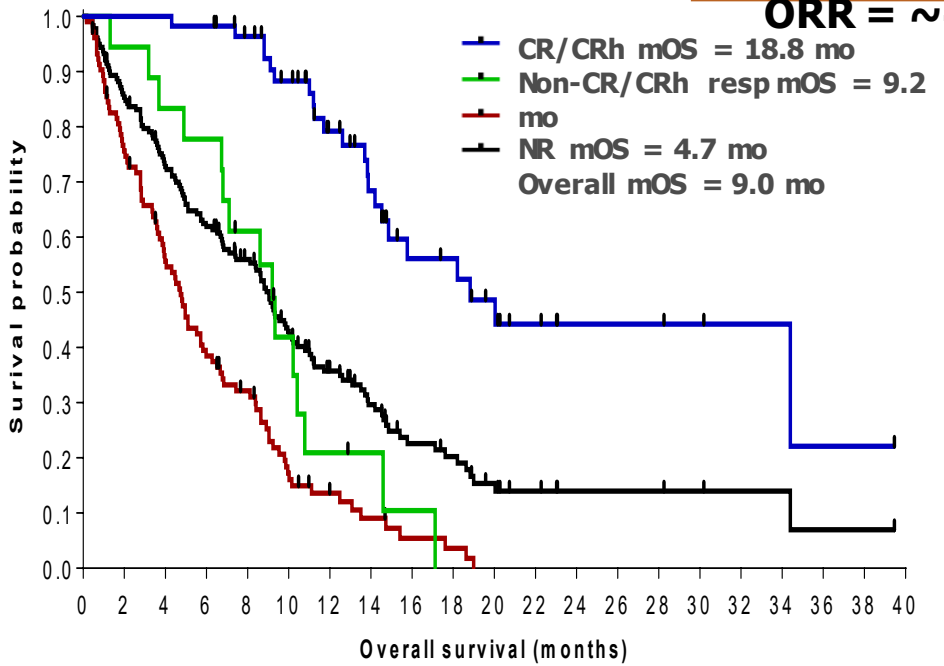
Daver N et al . Blood Cancer Journal, May 2021

2. Targeting *IDH1* and *IDH2* Mutations

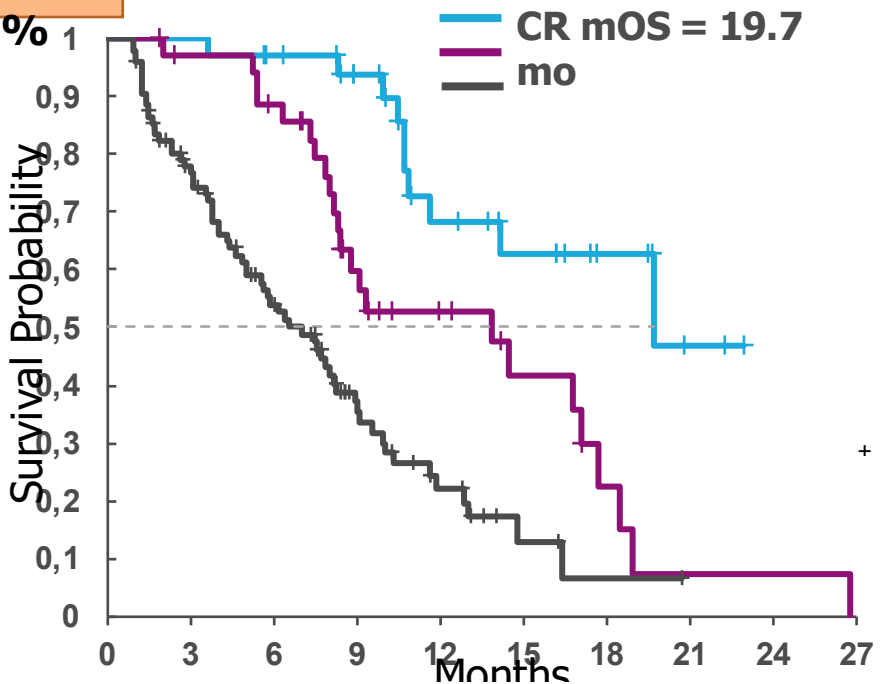
IDH1 or IDH2 Inhibitor Monotherapy

CR rate = ~20%
CR/CRh rate = ~30%
ORR = ~40%

Ivosidenib (IDH1 inhibitor)[a]

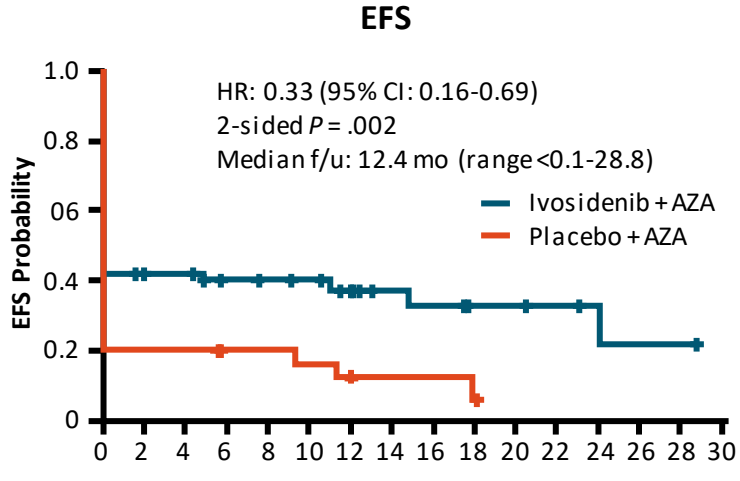


Enasidenib (IDH2 Inhibitor)[b]

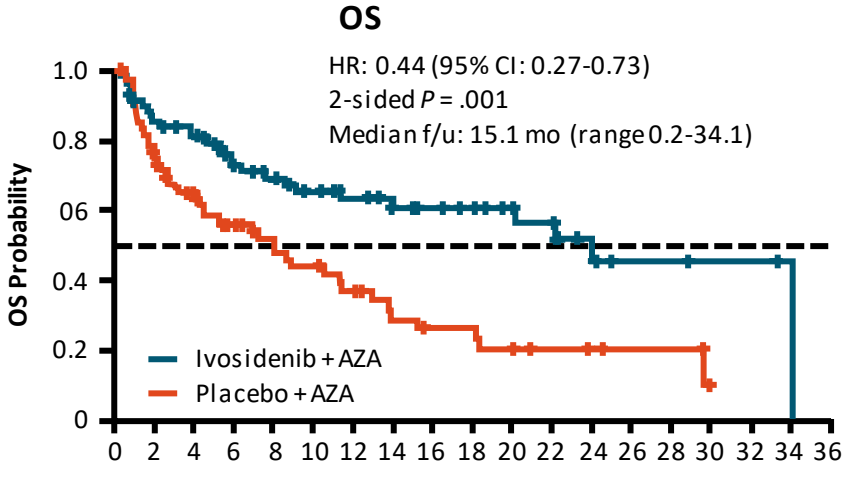


a. Pollyea DA, et al. J Clin Oncol. 2018;36: Abstract 7000; b. Stein EM, et al. Blood. 2017;130:722-731.

AGILE: EFS and OS in Intention-to-Treat Population



Patients at Risk, n																
IVO + AZA	72	26	25	20	19	17	13	9	8	5	5	4	2	2	2	0
PBO + AZA	74	8	8	5	5	4	3	2	2	1	0					



Patients at Risk, n																	
IVO + AZA	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1
PBO + AZA	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		

Montesinos. NEJM. 2022;386:1519.

Slide credit: clinicaloptions.com

3. Targeting MLLr and NPM1 mutated AML

Leukemias with *KMT2Ar* or mutated *NPM1*

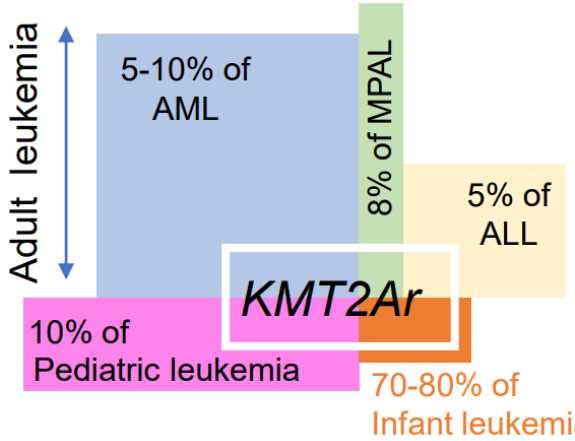
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

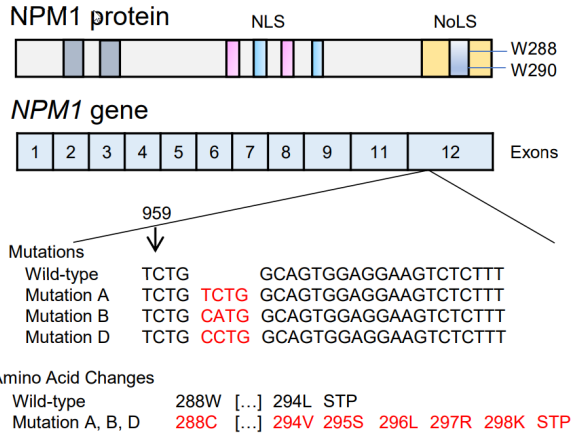
KMT2Ar

~ 10% of Acute Leukemias

15% of t-AML

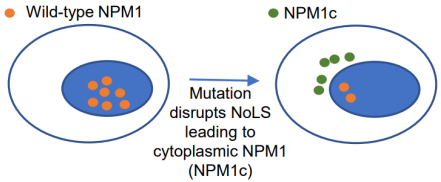
70% of t-AML 1-2 years following topo II Inh

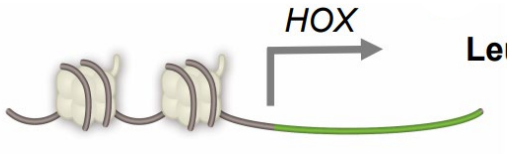




NPM1c

25-30% of AML

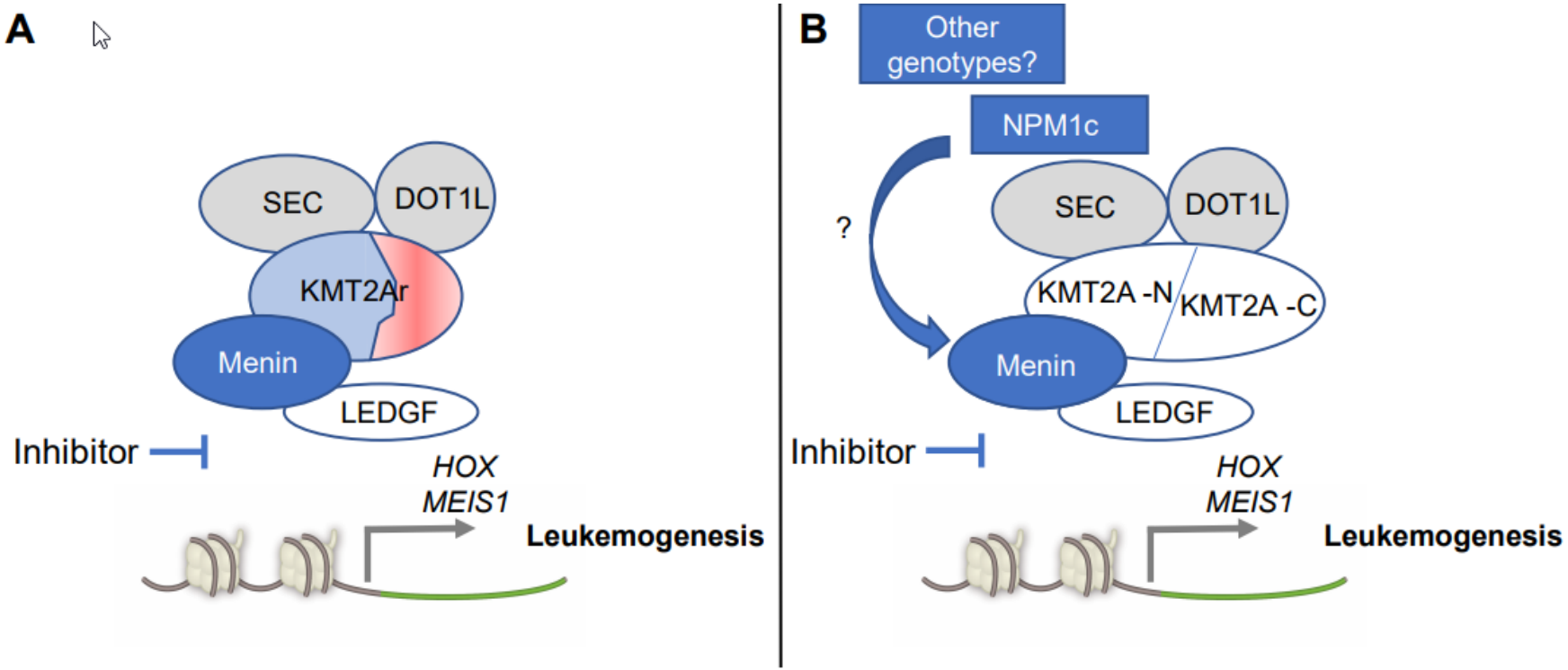




Leukemogenesis

Issa GC et al. Leukemia 2021. 2021 Sep;35(9):2482-2495.

Menin Inhibition – MOA in Leukemia



Phase 1 AUGMENT 101: Menin Inhibitor Revumenib (SNDX-5613) for *MLL*-Rearranged and *NPM1*-Mutated AML

Currently being evaluated in the phase 1/2 AUGMENT-101 study (N = 54)

Median age was 49 years

- 82% (n = 44) of patients had AML
- 65% (n = 35) had *MLL*-rearranged leukemia
- 19% (n = 10) had *NPM1*-mutated leukemia

Two parallel dose-escalation cohorts

- Arm A: patients not taking strong CYP3A4 inhibitors
- Arm B: patients taking strong CYP3A4 inhibitors
- Revumenib dosing: orally every 12 hours in continuous 28-day cycles

MTD was 276 mg every 12 hours in arm A and 163 mg every 12 hours in arm B

Best Overall Response	Overall (N = 54), n (%)
CRc (CR + CRh + CRp + CRi/MLFS)	20 (44.4)
CR + CRh	10 (22.2)
CR	7 (15.6)
CRh	3 (6.7)
CRp	3 (6.7)
CRi/MLFS	7 (15.6)

CRh, CR with partial hematologic recovery; MLFS, morphological leukemia-free state; MTD, maximum tolerated dose.
Stein EM, et al. Blood. 2021;138: Abstract 699.

AUGMENT 101: Revumenib
Safety and Tolerability

- The frequency of grade 3 prolonged QTc at these doses was 8% (3/38)
- No ventricular arrhythmias were reported, and no patients discontinued 5613 due to a treatment-related event

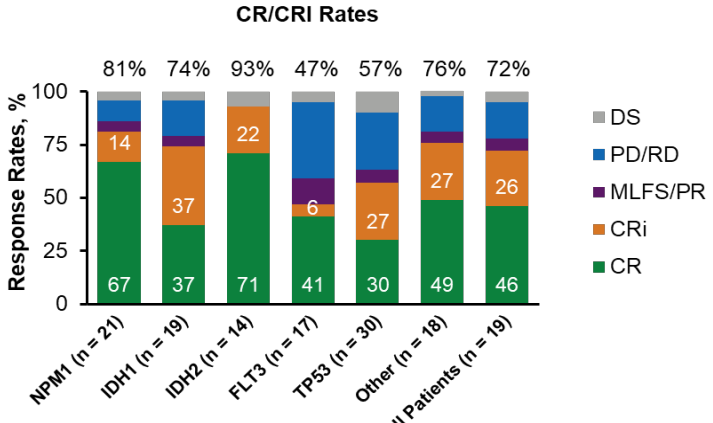
	Arm A Overall (n = 25), n (%)	Arm B Overall (n = 29), n (%)	Overall (N = 54), n (%)
Subjects with ≥1 grade 3 or greater related TEAE	5 (20)	5 (17.2)	10 (18.5)
ECG QT prolonged	4 (16)	3 (10.3)	7 (13)
Anemia	0	1 (3.4)	1 (1.9)
Asthenia	0	1 (3.4)	1 (1.9)
Diarrhea	0	1 (3.4)	1 (1.9)
Fatigue	0	1 (3.4)	1 (1.9)
Hypokalemia	0	1 (3.4)	1 (1.9)
Neutropenia	0	1 (3.4)	1 (1.9)
Thrombocytopenia	0	1 (3.4)	1 (1.9)
Tumor lysis syndrome	1 (4.0)	0	1 (1.9)

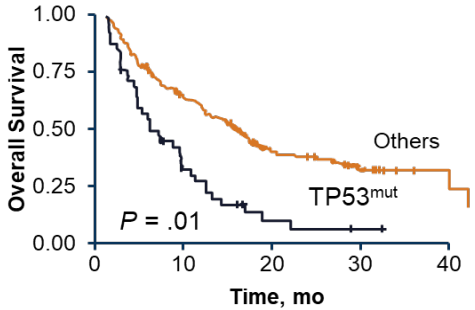
Stein E, et al. Blood. 2021;138:699.

4. TP53 mutation directed therapies and Immune Therapies in AML

Poor Outcomes in *TP53* Mutant AML, Even With Venetoclax-Based Treatment

Venetoclax + LDAC or HMA (Phase IB study)[1]

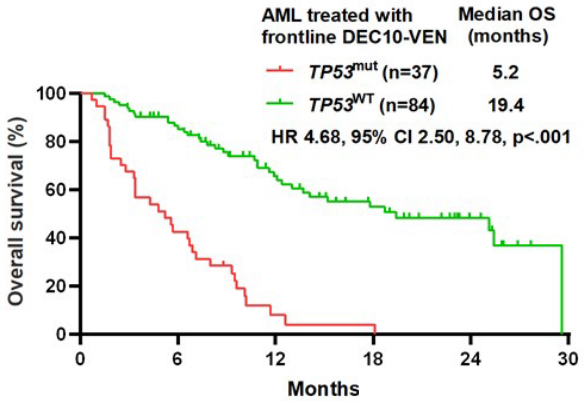




Median OS = 6.4 months

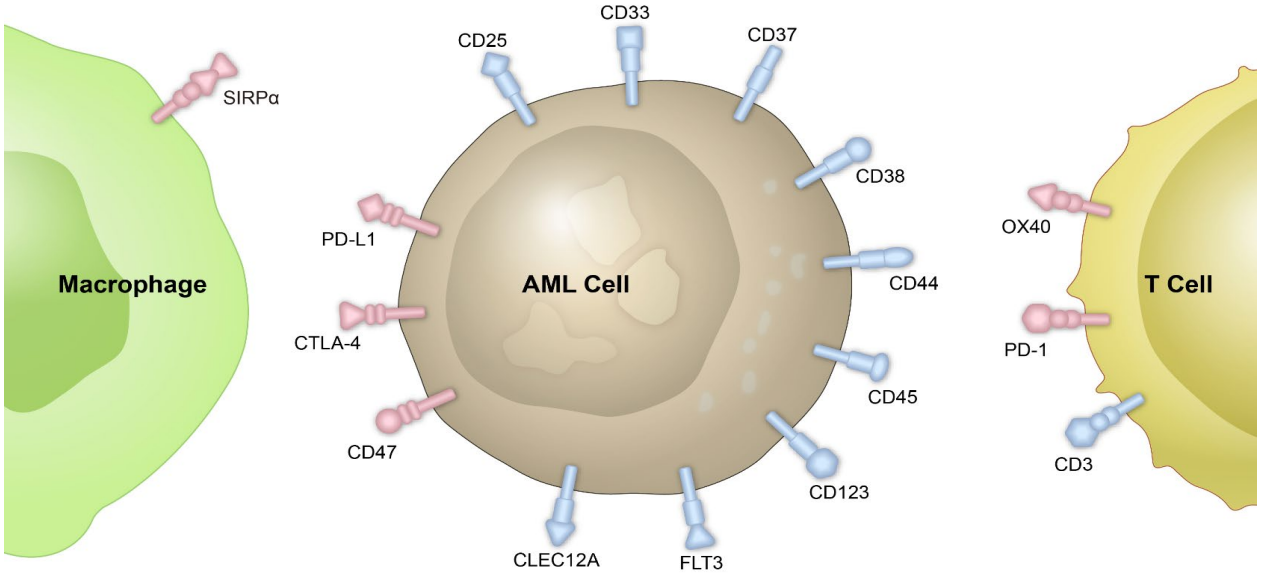
N = 121 patients with newly diagnosed AML receiving decitabine + venetoclax[2]

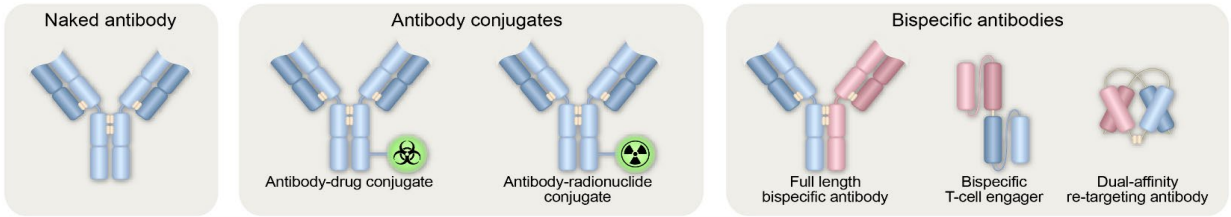
- **Those with *TP53*^{mut} (N=35) had a lower rate of CR at 35% vs 57% in pts with *TP53*^{WT} (N=83) (P = 0.026)**
- Lower rate of CR/CRi (54% vs. 76%; *P* .015),



1. Chyla BJ et al. ASH 2019. Abstract 546. 2. Kim K, et al. ASH 2020. Abstract 693.

Immune Based Approaches in AML: Maybe well suited for triplets with HMA-VEN backbone?





Two major approaches:

1. **<u>Antibody drug conjugates</u> (CD33, CD123, CLL1)**
2. **<u>Adaptive or Innate immune</u> system harnessing therapies:**

a. **Bi-specific antibodies (CD3 x AML antigen; CD47 x CD3, others)**

b. **Immune checkpoint based approaches: T-cell and macrophage checkpoints**

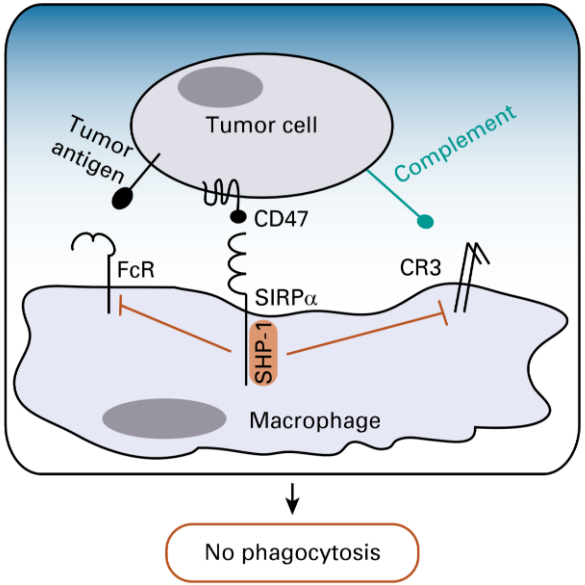
c. **CART, CAR NK, High volume hn-NK cells**

d. **Vaccines**

Short N….Daver N, et al, Cancer Discovery 2020

CD47 Is a Major Macrophage Immune Checkpoint & "Do Not Eat Me" Signal in Myeloid Malignancies, Including AML

- CD47 is a "do not eat me" signal in cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients



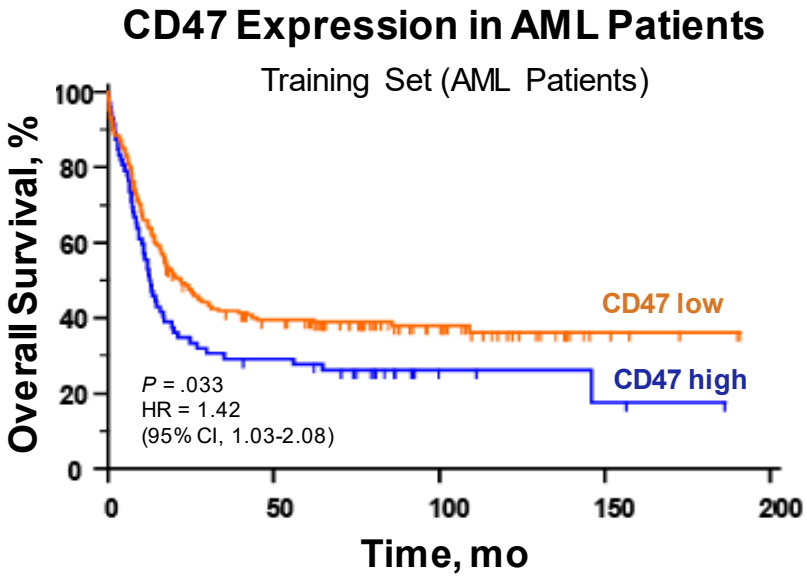
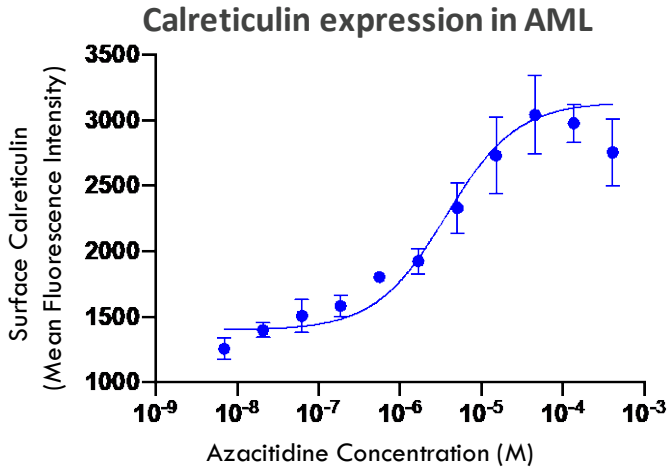
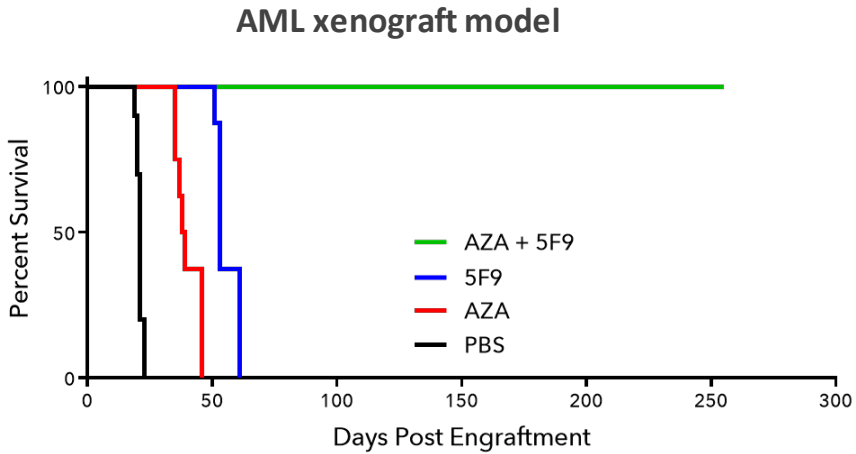


Figure at left adapted from Veillette A, Tang Z. *J Clin Onc*. 2019;37:1012-1014 and Chao MP et al. *Current Opin Immunol*. 2012;24:225-232
Figure at right adapted from Majeti R et al. *Cell*. 2009;138:286-299.

Magrolimab Synergizes with Azacitidine to Induce Remissions in AML Xenograft Models

- Azacitidine (AZA) induces pro-phagocytic "eat me" signals like calreticulin on cancer cells
- Increased eat me signals induced by azacitidine synergizes with CD47 blockade of the "don't eat me" signal leading to enhanced phagocytosis





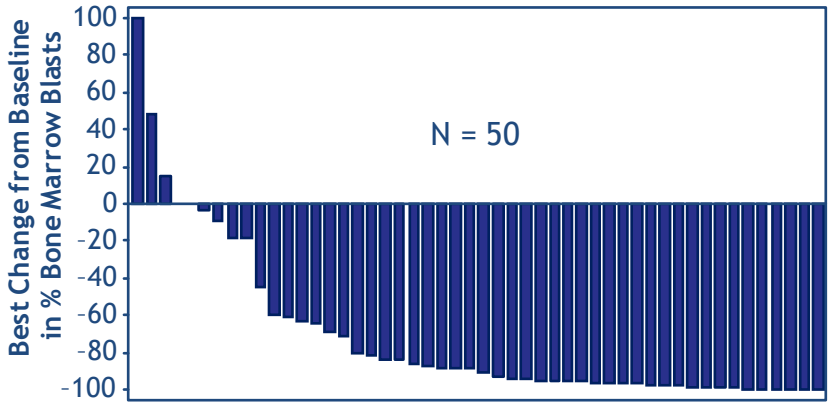
Feng D et al., ASH 2018

Magrolimab in Combination with AZA Demonstrated Encouraging Response Rates in *TP53*-mut AML

Efficacy Endpoints (Intent-to-Treat Analysis)

Outcome	N = 72
ORR, % (95% CI)	**48.6 (36.7, 60.7)**
CR, % (95% CI)	**33.3 (22.7, 45.4)** (n = 24/72)
MRD— CR*, % (95% CI)	50.0 (29.1, 70.9) (n = 12/24)
CRi/CRh, n (%)	6 (8.3)
PR, n (%)	4 (5.6)
MLFS, n (%)	1 (1.4)
DOR, median (95% CI), mo	**8.7 (6.5, 10.4)**
DCR, median (95% CI), mo	7.7 (4.7, 10.9)
TOR/TCR, median (range), mo	2.0 (1.0, 5.7) / 3.0 (1.8, 9.6)
CCyR, n/N[†] (%)	10/31 (32.3)
PFS, median (95% CI), mo	7.3 (3.7, 9.7)

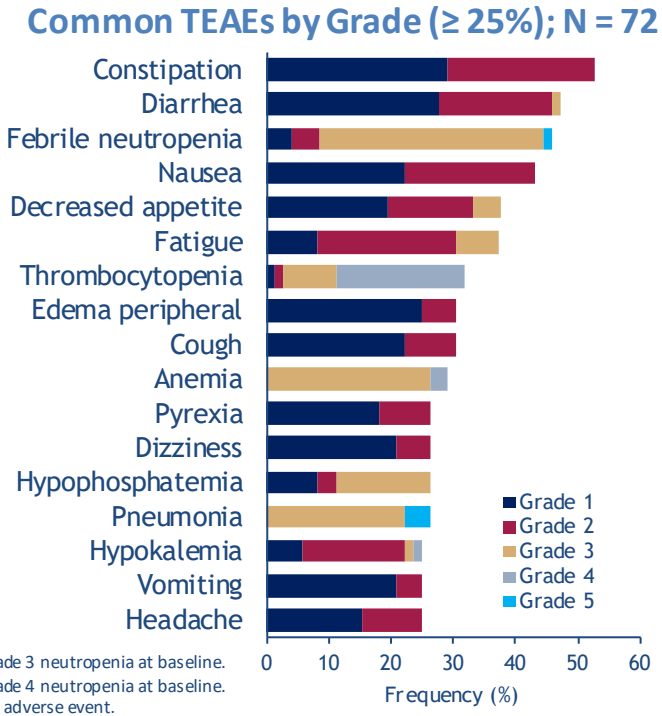
Best Change from Baseline in % Bone Marrow Blasts



- CR was achieved by 33.3% of patients with half of CR patients being MRD–.
- 30 (41.7%) patients achieved CR/CRi.
- 29.7% and 45.8% of baseline transfusion-dependent patients converted to RBC and platelet transfusion independence,[‡] respectively.

*MRD was assessed in bone marrow samples by a central laboratory using multiparameter flow cytometry with a lower limit of detection of 0.02%. [†]N = number with abnormal cytogenetics at baseline who achieved objective response. [‡]RBC and platelet transfusion independence were defined as ≥8 consecutive weeks without transfusion. CCyR = complete cytogenetic response; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete blood count recovery; DCR = duration of CR; DOR = duration of response; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; ORR = objective response rate; PFS = progression-free survival; PR = partial remission; TCR = time to CR; TOR = time to objective response.

Magrolimab in Combination with AZA Is Well Tolerated in *TP53*-mut AML Patients



13 (18.1%) patients had Grade 3 neutropenia at baseline.
35 (48.6%) patients had Grade 4 neutropenia at baseline.
TEAE = treatment-emergent adverse event.

- No patient had magrolimab dose reduction; magrolimab dose delays occurred in 45.8% of patients.
- TEAEs led to discontinuation of magrolimab in 22 (30.6%) and of AZA in 21 (29.2%) patients.
- 13 (18.1%) patients died within 60 days of the first study drug dose.
- Infusion-related reaction (all grades) in 22.2%, Grade 3+ in 1.4%.
- 19 (26.4%) patients had Grade 3 anemia, and 2 (2.8%) had Grade 4 anemia, regardless of attribution.

AZA-VEN-Magro in frontline and R/R AMLResults: Response Rates per ITT (n=48)

Outcomes	Frontline Cohort (n=25)		R/R Cohort (n=23)	
	TP53 mutated (n=14)	*TP53* wild type (n=11)	VEN-naïve (n=8)	Prior VEN (n=15)
ORR	12 (86)	11 (100)	6 (75)	3 (20)
CR/CRi	9 (64)	10 (91)	5 (63)	3 (20)
CR	9 (64)	7 (64)	3 (38)	0
CRi	0	3 (27)	2 (25)	3 (20)
MLFS / PR[1]	3 (21)	1 (9)	1 (13)	0
MRD neg FCM	5/9* (55)	4/9 (45)	2/6 (33)	0
CCyR	4/9‡ (44)	5/6 (83)	3/5 (60)	1/2 (50)
No response	2 (14)	0	2 (25)	12 (80)
TT 1st response	0.7 [0.6-1.9]	0.7 [0.7-1.5]	0.7 [0.6-4.1]	2.2 [1.8-2.6]
TT Best response	1.5 [0.7-3.2]	1.1 [0.7-2.9]	1.5 [1.0-4.1]	2.0 [1.2-3.9]
Med TT ANC>500	28 (20 – 41) days			
Med TT Plt>50K	24 (18 – 41) days			
8-wk mortality	0	0	1 (13)	3 (20)

Results expressed as n (%), n/N (%) or median [range]. FCM = multiparametric FCM, sensitivity 0.1-0.01%, *Only among pts with evaluable longitudinal samples; ‡Only among patients with baseline cytogenetic aberrations and longitudinal cytogenetic samples; [1]Two with PR per ELN2017

Daver N et al, ASH 2021

5. Immune Strategies to Kill AML
Potentially Mutation-Agnostic Approaches

ADAPTIVE:

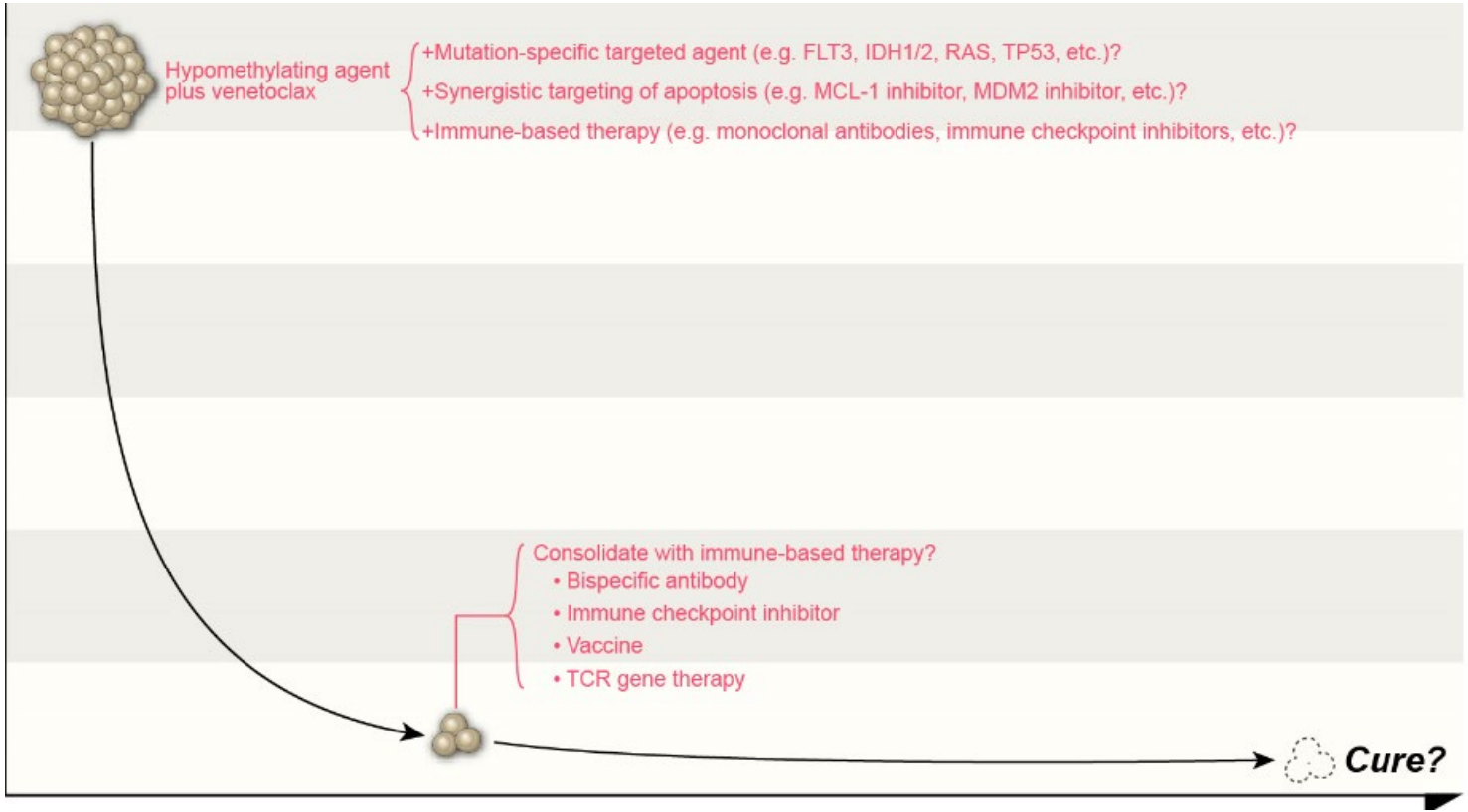
- Recruiting anti-**CD3** T cells: **BiTEs** linking to CD3 and targeting CD33/123
- **CAR Ts** with modified CD3 killer cells (success in ALL, lymphoma, MM)
- Targets beyond CD33/123 (eg, **CLL1,** IL1RAP, TIM3, CD70)

INNATE (appears to be more resilient and preserved in AML):

- Recruiting **macrophages**: targeting CD47 on AML (magrolimab, lemzoparlimab) or SIRP-alpha on macrophages (Trillium, CC95251, ALX148)
- Recruiting **NK** cells: allogeneic NK CAR Ts; NK engineered cells (human, CD38 knockout, IL15); repeated infusions

ALL, acute lympocytic leukemia; BiTE, bispecific T-cell engager; MM, multiple myeloma.
Short N, et al. N. Cancer Discov. 2020;10:506-525.

Sequential approach to debulk AML/MDS followed by IO approaches (innate and/or adaptive) to eradicate residual disease may be a potential future strategy



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Global Leukemia Academy

Genetic Characterization and Risk Stratification in AML

Agnieszka Wierzbowska

APTITUDE HEALTH

UNIWERSYTET MEDYCZNY W ŁODZI

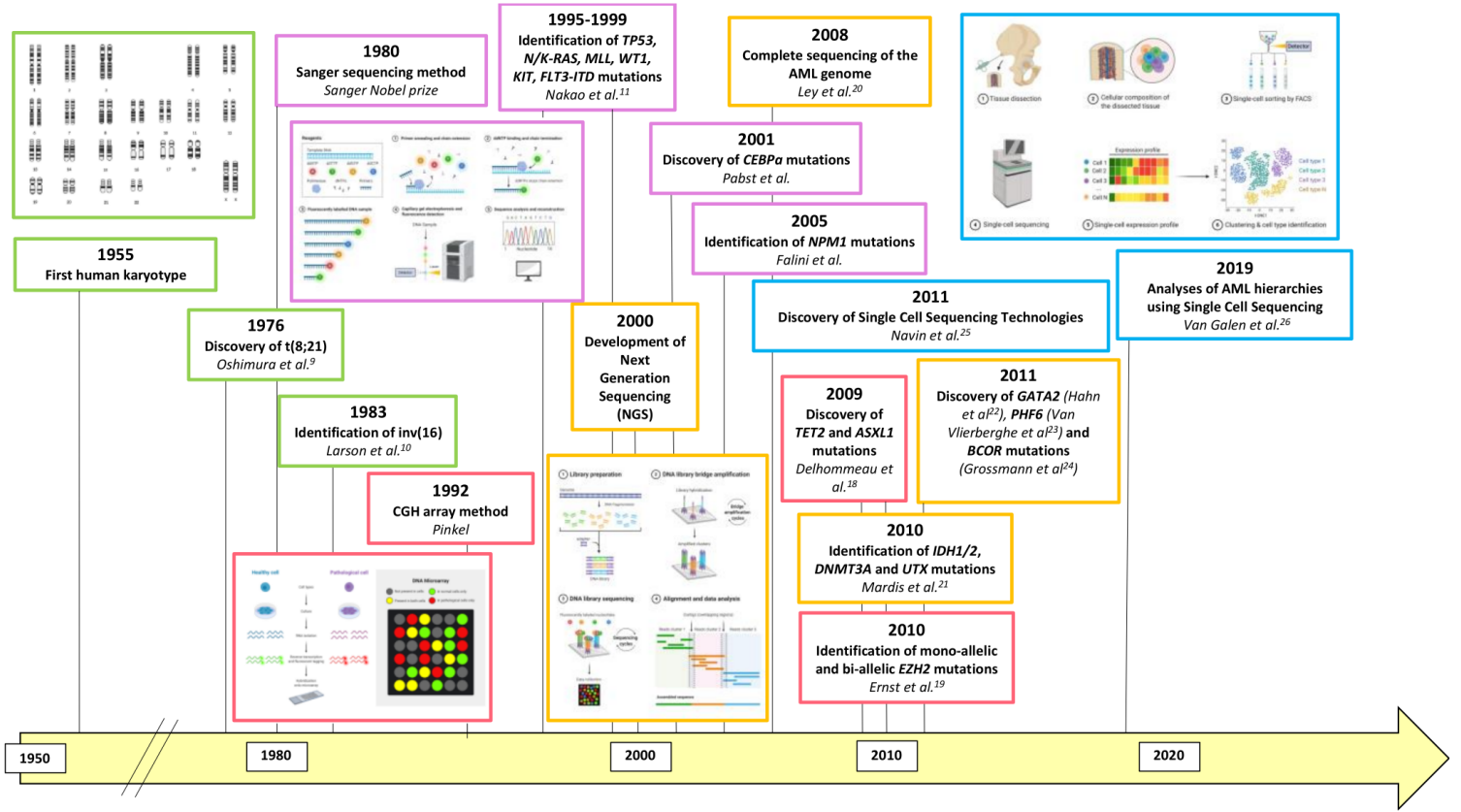
KOPERNIK

Genetic Characterization and Risk Stratification in AML

Molecular alterations, risk stratification, and relevant therapeutic decision-making in AML

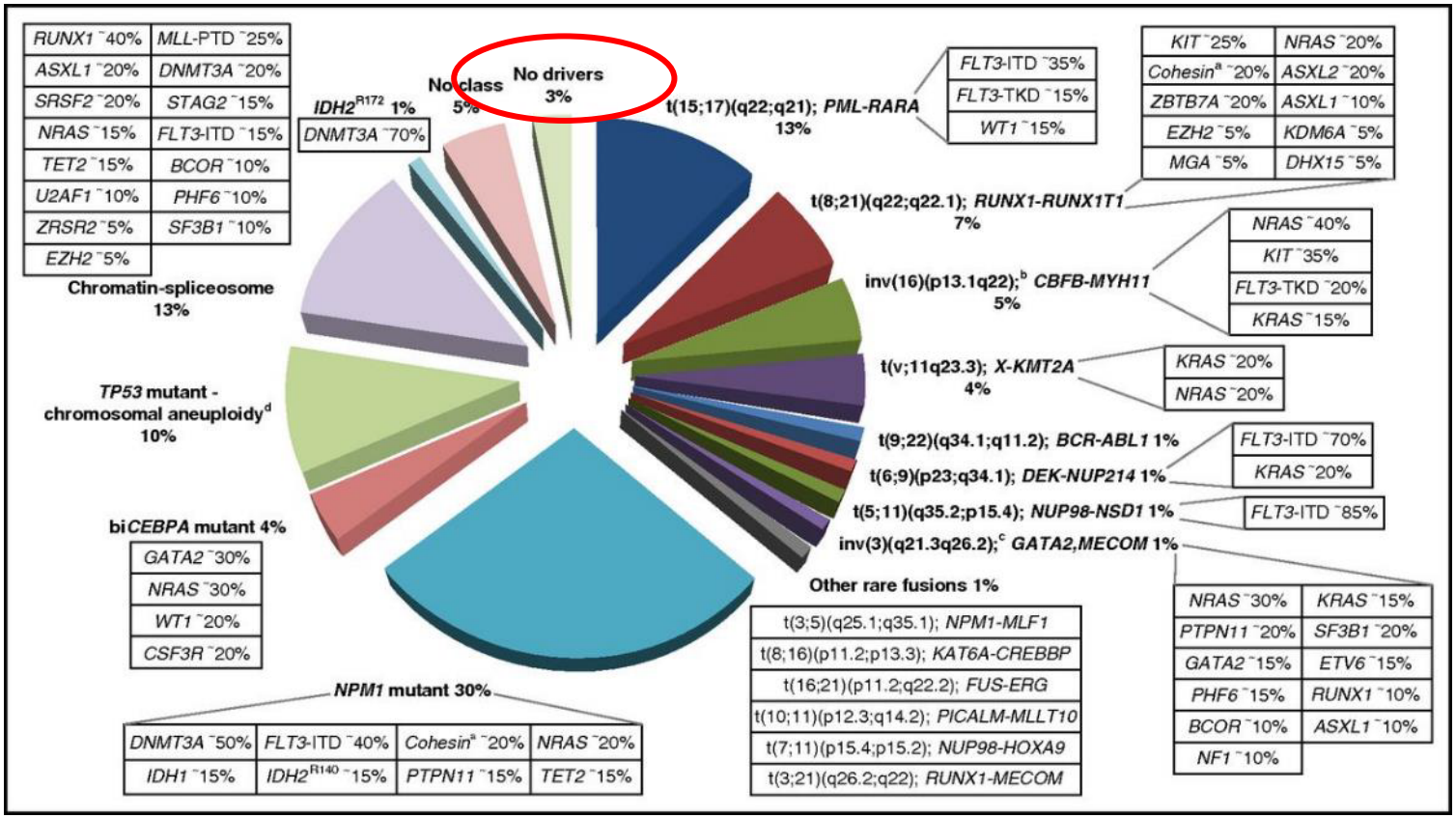
Agnieszka Wierzbowska

Molecular diagnosis of AML



Pasquer H, et al. *Cancers.* 2021;13:748-770.

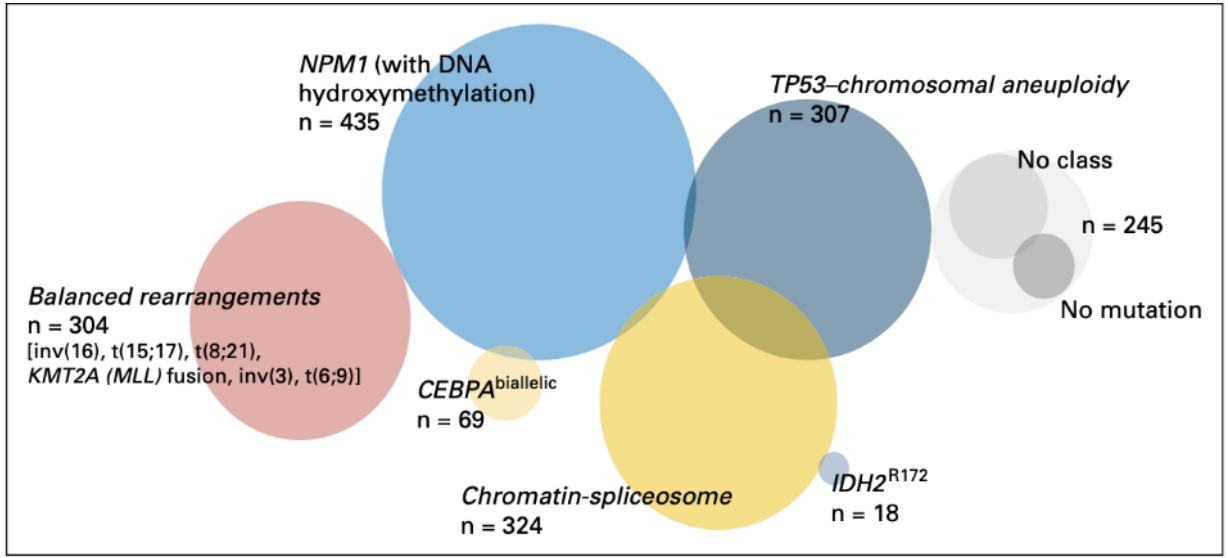
Genetic heterogeneity of AML



Döhner H et al. *Blood.* 2017;129:424-447.

Genetic heterogeneity of AML

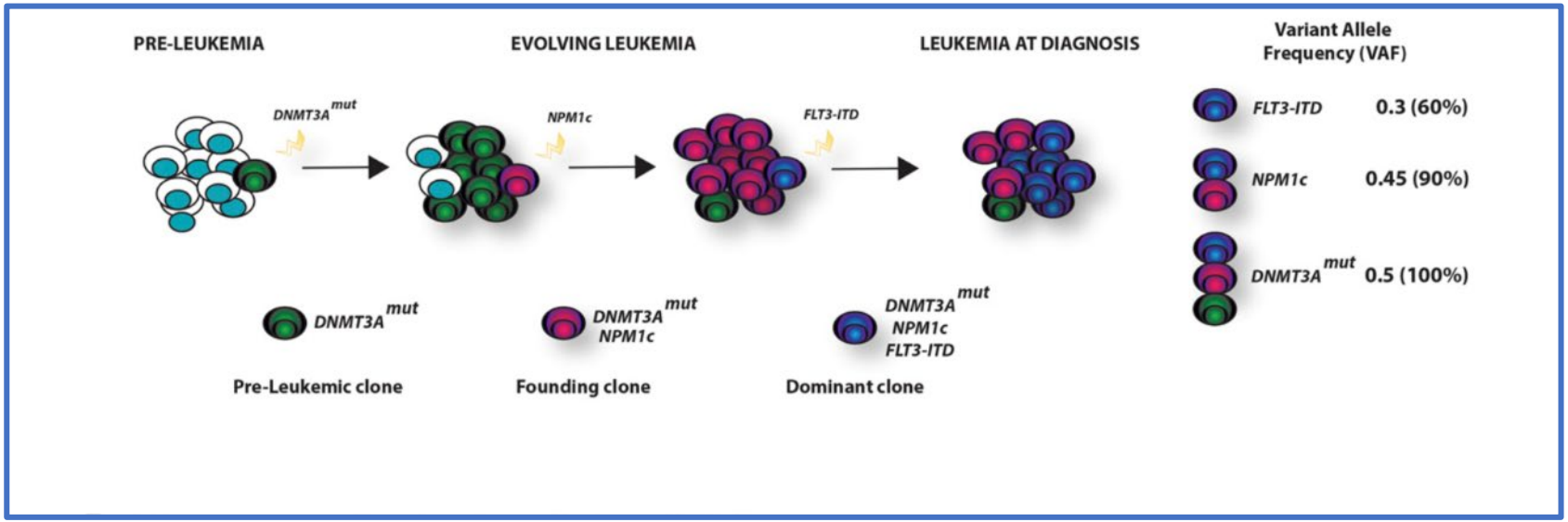
Genomic classes according to Papaemmanuil and Gerstung et al.



The 6 genomic groups characterized by gene rearrangements (translocations and/or inversions) are displayed as 1 group

Adapted from Bullinger L, et al. *J Clin Oncol*. 2017;35(9):934-946; Papaemmanuil E, et al. *N Engl J Med.* 2016;374:2209-2221.

Clonal architecture of AML



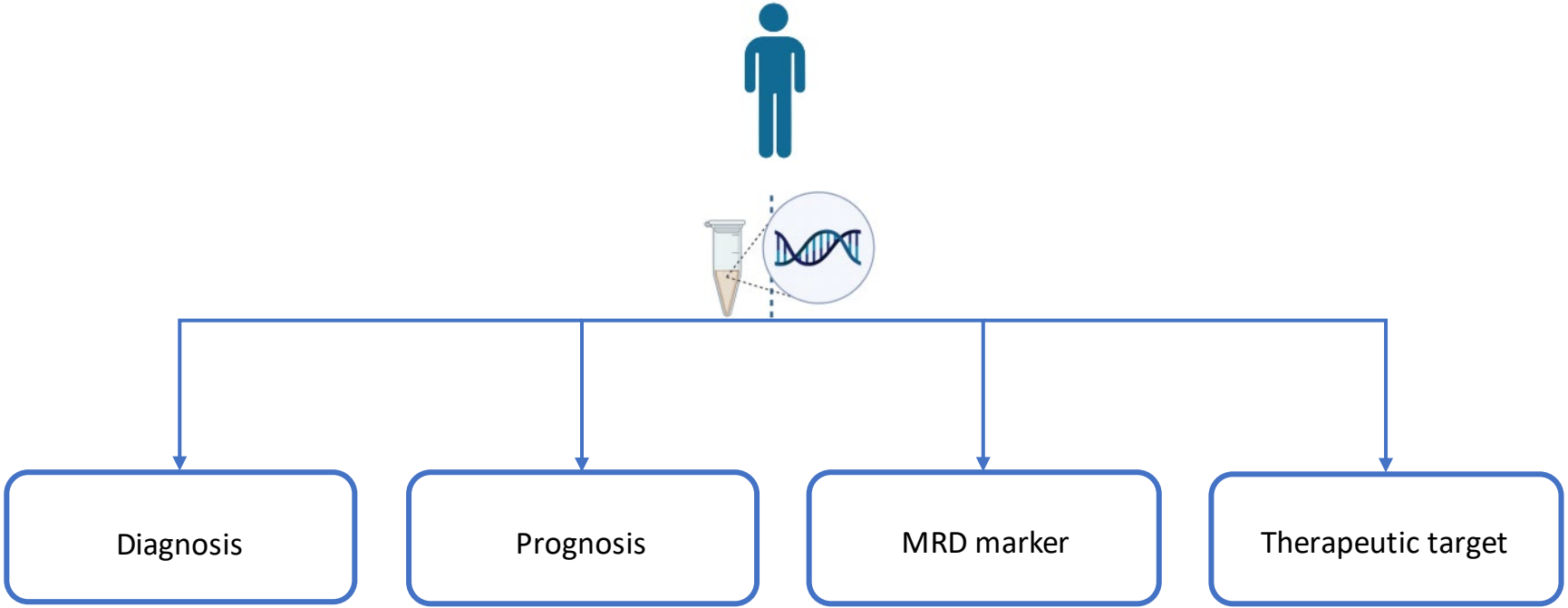
The stepwise acquisition of mutations and the emergence of new clones carrying novel mutations at different times during the evolution of the leukemia

Adapted from Grimwade D, et al *Blood.* 2016;127;29-41.

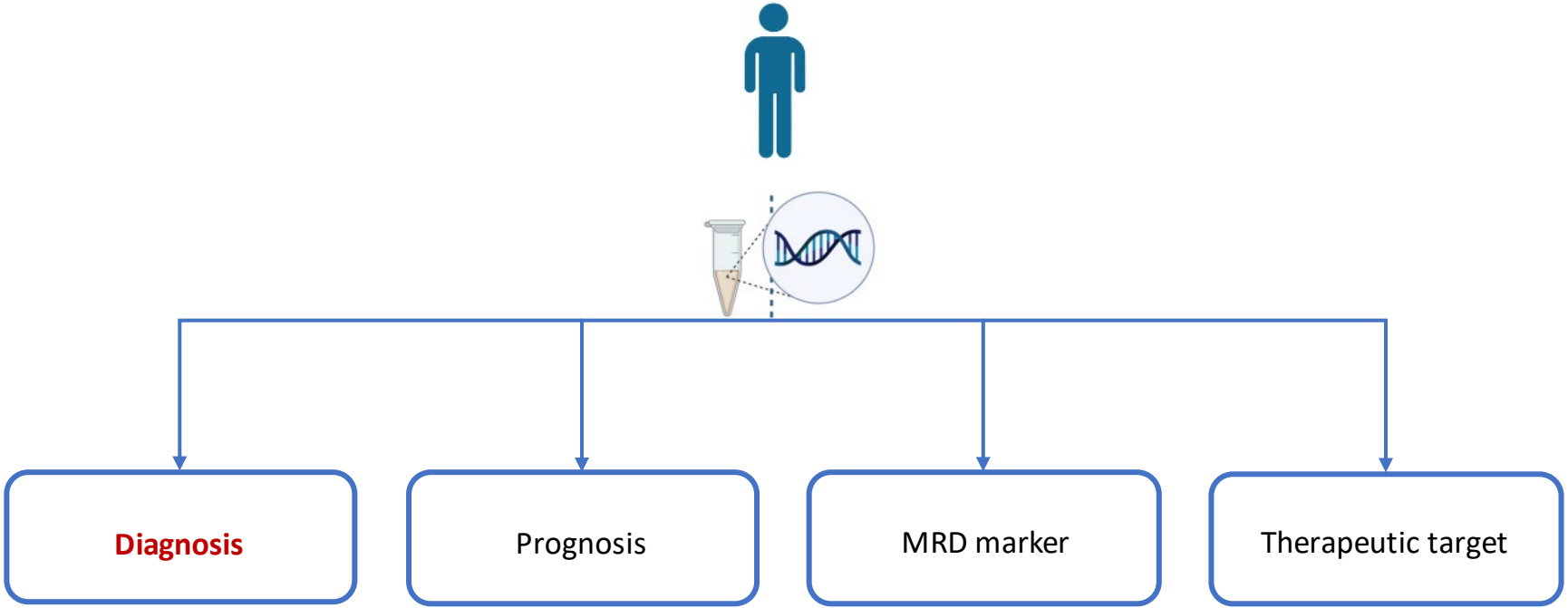
Molecular alterations in AML

Clinical implications

Molecular alterations in AML



Molecular alterations in AML



Molecular abnormalities in AML – diagnostic role

Diagnosis of AML according to WHO 2016 – ≥20% blasts in bone marrow (BM) or peripheral blood (PB)

Genetic rearrangements	Chromosomal abnormalities
PML::*RARA*	t(15;17)(q22,q21)
CBFB::*MYH11*	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)
RUNX1::*RUNX1T1*	t(8;21)(q22;q22.1)

Criterion of 20% blasts – not required

Foucar K, et al. *Am J Clin Pathol*. 2015;144(1):6-18.

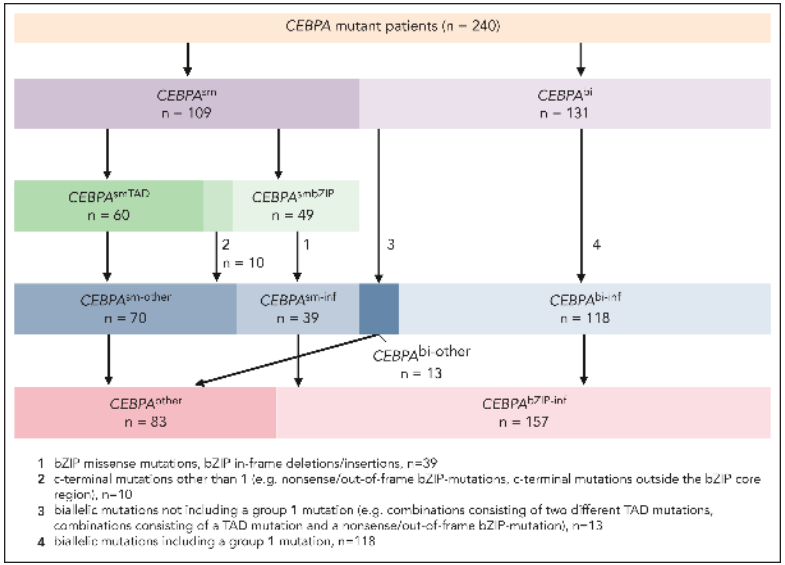
AML with recurrent genetic abnormalities – new entities according to the International Consensus Classification 2022

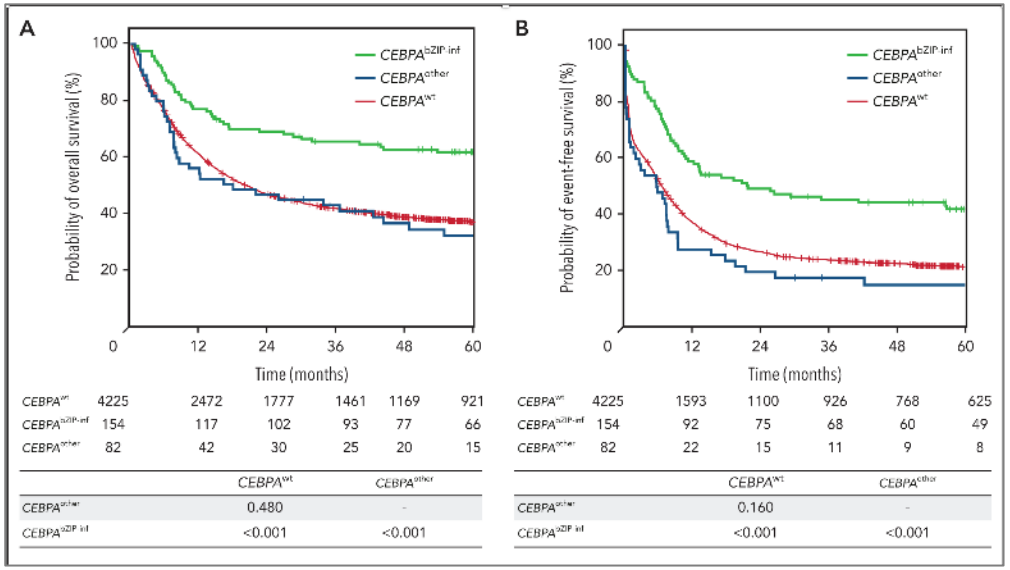
AML with recurrent genetic abnormalities
Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/PML::RARA ≥10%
APL with other *RARA* rearrangements ≥10%
AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 ≥10%
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 ≥10%
AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A ≥10%
AML with other *KMT2A* rearrangements ≥10%
AML with t(6;9)(p22.3;q34.1)/DEK::NUP214 ≥10%
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2; MECOM(EVI1) ≥10%
AML with other MECOM rearrangements ≥10%
AML with other rare recurring translocations ≥10%
AML with t(9;22)(q34.1;q11.2)/BCR::ABL1‡ ≥20%
AML with mutated *NPM1* ≥10%
AML with in-frame *bZIP CEBPA* mutations ≥10%

In the presence of recurrent genetic abnormalities ≥10% blasts is required for AML diagnosis (excluding AML with BCR::ABL1 due to its overlap with progression of chronic myeloid leukemia, BCR::ABL1-positive)

Arber DA, et al. *Blood.* 2022;140(11):1200-1228; Döhner H, et al. *Blood*. 2022;2022016867.

CEBPA mutations in 4708 patients with AML: differential impact of *bZIP* and *TAD* mutations on outcome





Only in-frame mutations in *CEBPA-bZIP* are associated with favorable clinical response in monoallelic and biallelic constellations

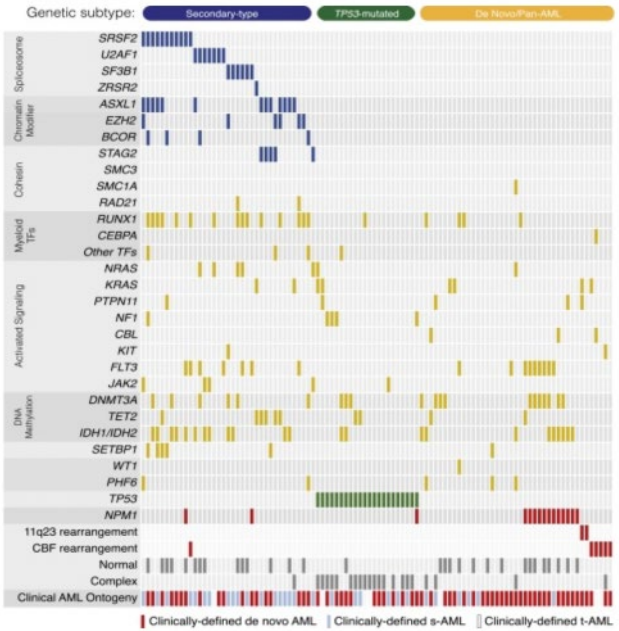
Taube F, et al. *Blood.* 2022;139(1):87-103.

Classification of AML according to the International Consensus Classification 2022

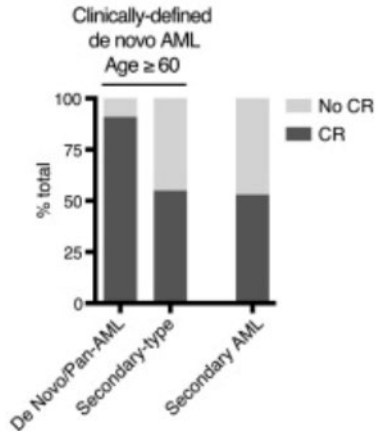
- AML with recurrent genetic abnormalities
- AML and MDS/AML **with mutated *TP53*** 10%–19% (MDS/AML) and ≥20% (AML)
- AML and MDS/AML **with myelodysplasia-related gene mutations** 10%–19% (MDS/AML) and ≥20% (AML)
  - Defined by mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2*
- AML with **myelodysplasia-related cytogenetic abnormalities** 10%–19% (MDS/AML) and ≥20% (AML)
  - Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
- AML not otherwise specified (NOS) 10%–19%(MDS/AML) and ≥20% (AML)
- Myeloid sarcoma

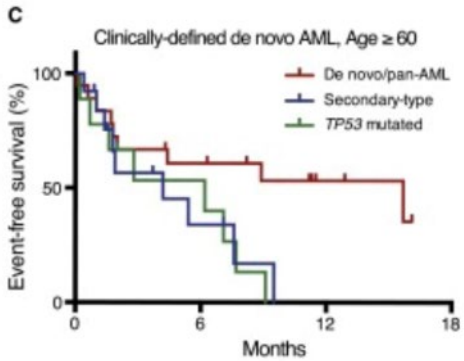
Arber DA, et al. *Blood.* 2022;140(11):1200-1228.

AML with myelodysplasia-related gene mutations



N = 194 (s-AML n=93, t-AML n = 101)
validation cohort (n = 105) unselected AML pts treated at DFCI

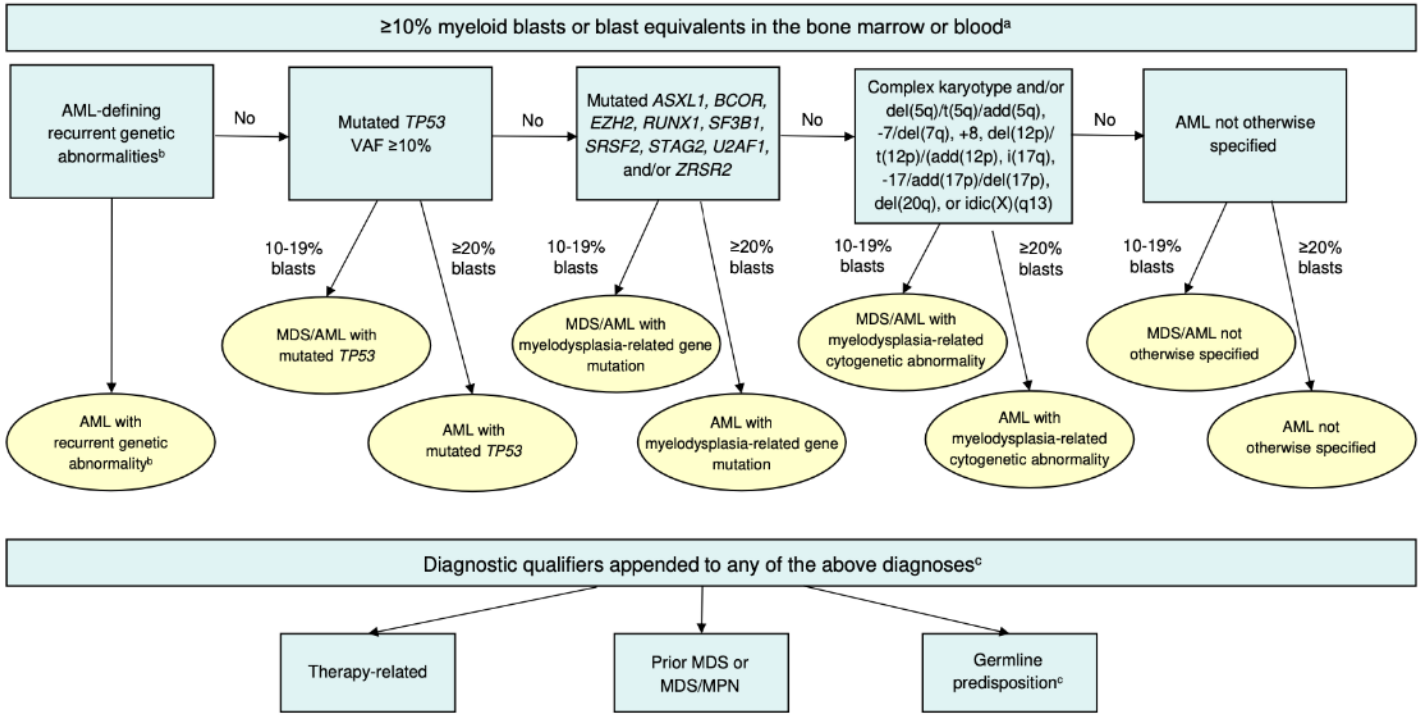




- The presence of a mutation in *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, or *STAG2* is highly specific for secondary AML
- Secondary-type mutations define an s-AML–like disease within t-AML and elderly de novo AML

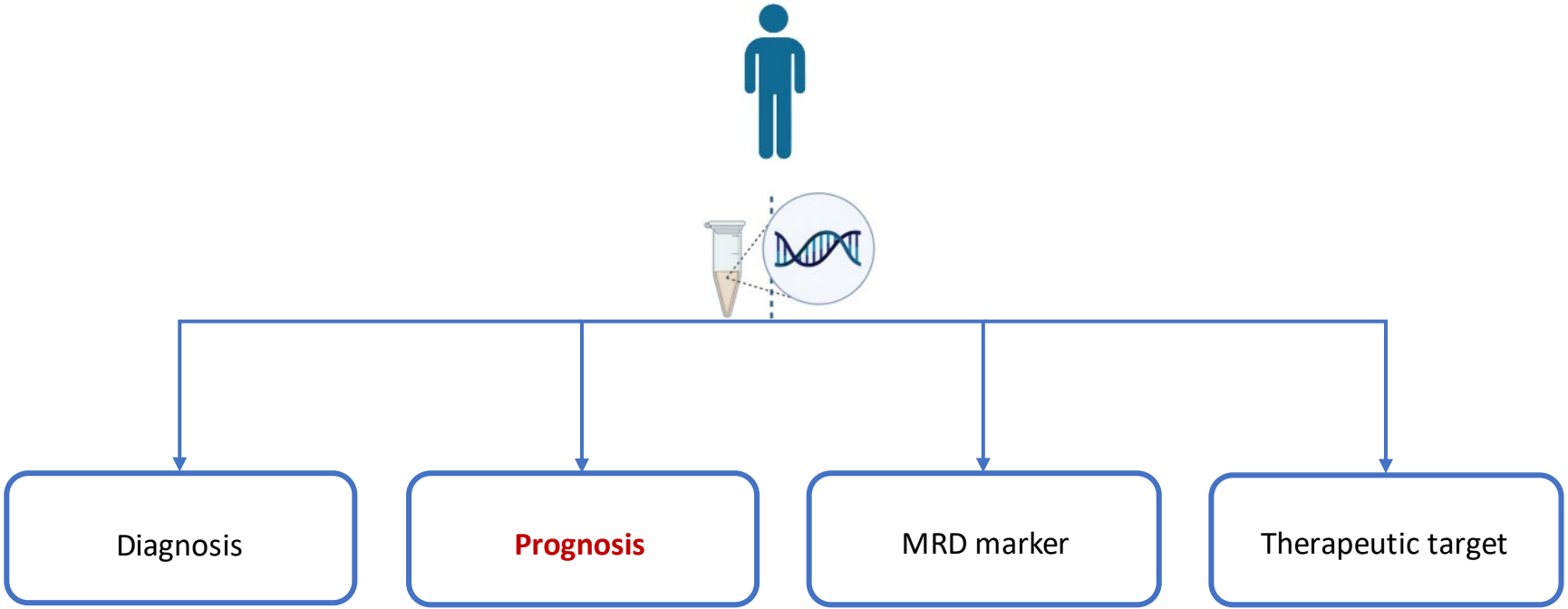
Lindsley RC, et al. *Blood.* 2015;125(9):1367-1376.

Hierarchical classification of AML according to the International Consensus Classification 2022



Arber DA, et al. *Blood.* 2022;140(11):1200-1228; Döhner H, et al. *Blood*. 2022;2022016867.

Molecular alterations in AML



ELN 2022 genetic risk classification

Risk Group	ELN 2017	ELN 2022
Good	• t(8;21)(q22;q22) AML/ETO • inv (16)(p13.1;q22) or t(16;16) (p13.1;q22) CBF-MYH11 • NK+ *NPM1*mut and *FLT3*-ITD (–) lub *FLT3*-ITD (+) AR <0.5 • NK+ *CEBPA* mut (biallelic)	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[a] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[a] • *NPM1*mut without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[b]
Intermediate	• *NPM1*mut and *FLT3-ITD* (high) AR ≥0.5 • *NPM1*wt and *FLT3*-ITD (–) lub *FLT3*-ITD (AR <0.5) [without adverse genetic aberrations] • t(9;11)(p22;q23) *MLLT3-KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse	• *NPM1*mut with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

[a]Concurrent of *KIT* and/or *FLT3* gene mutation does not alter risk categorization

[b]Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, irrespective whether they occur as monoallelic or biallelic mutations

Döhner H, et al. *Blood*. 2017;129(4):424-447; Döhner H, et al. *Blood*. 2022;2022016867.

ELN 2022 genetic risk classification

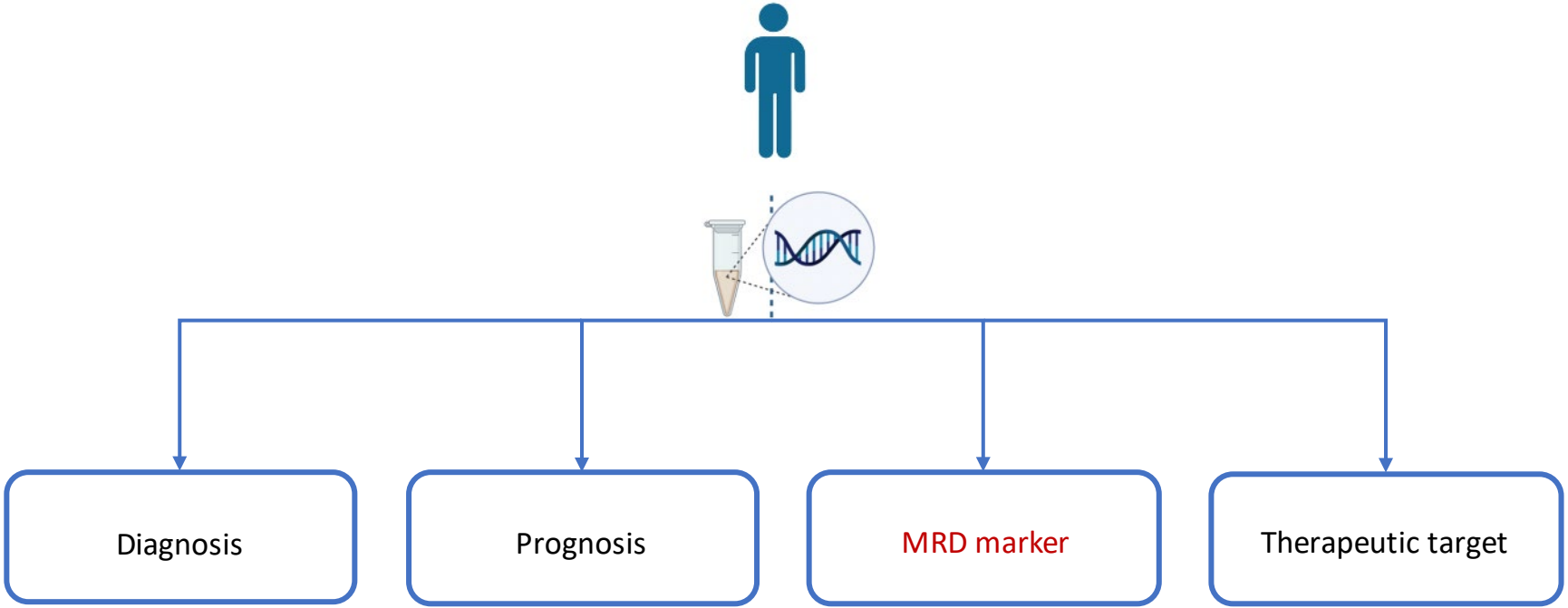
Risk Group	ELN 2017	ELN 2022
Poor	• t(6;9)(p23;q34); DEK-NUP214 • t(v;11)(v;q23), rearrangement *KMT2A* • t(9;22) *BCR/ABL1* • inv3(q21;q26) lub t(3;3)(q21;q26.2) • Complex karyotype (>2 aber) • Monosomal karyotype • -5 lub del5; -7, -17, abn(17p) • *NPM1*wt and *FLT3-ITD* (high) AR ≥0.5 • *RUNX1*mut • *AXLS1*mut • *p53*mut	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, lub ZRSR2*[a] • Mutated *TP53*[b]

[a]These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes

[b]*TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation)

Döhner H, et al. *Blood.* 2017;129(4):424-447; Döhner H, et al. *Blood*. 2022;2022016867.

Molecular alterations in AML

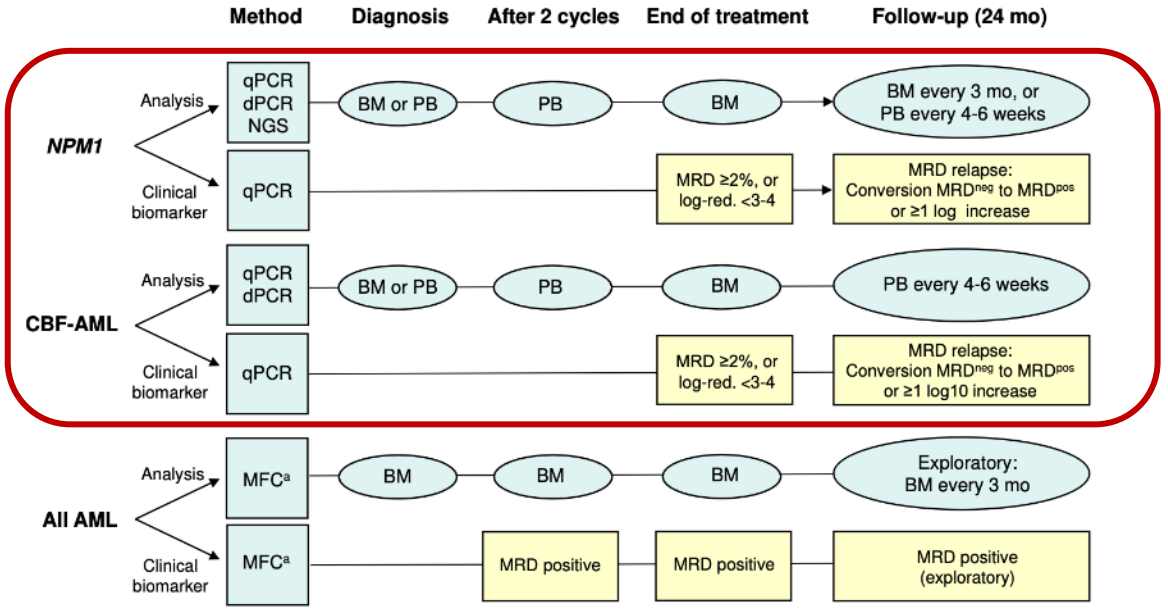


Molecular abnormalities as a marker of MRD

Genetic abnormality	Marker of MRD	Marking Technique
PML-RARa	**Yes**	**qPCR**/dPCR
RUNX1-RUNX1T1	**Yes**	**qPCR**/dPCR
CBFb-MYH11	**Yes**	**qPCR**/dPCR
***NPM1*^{mut}**	**Yes**	**qPCR**/dPCR
BCR-ABL	Yes	**qPCR**/dPCR
KMT2A-MLLT3	Yes	**qPCR**/dPCR
DEK-NUP214	Yes	**qPCR**/dPCR
WT1	Yes	**qPCR**/dPCR
***FLT3*^{mut} (ITD or TKD)**	No	-
***IDH1/IDH2*^{mut}**	No	-
***TP53*^{mut}**	No	-

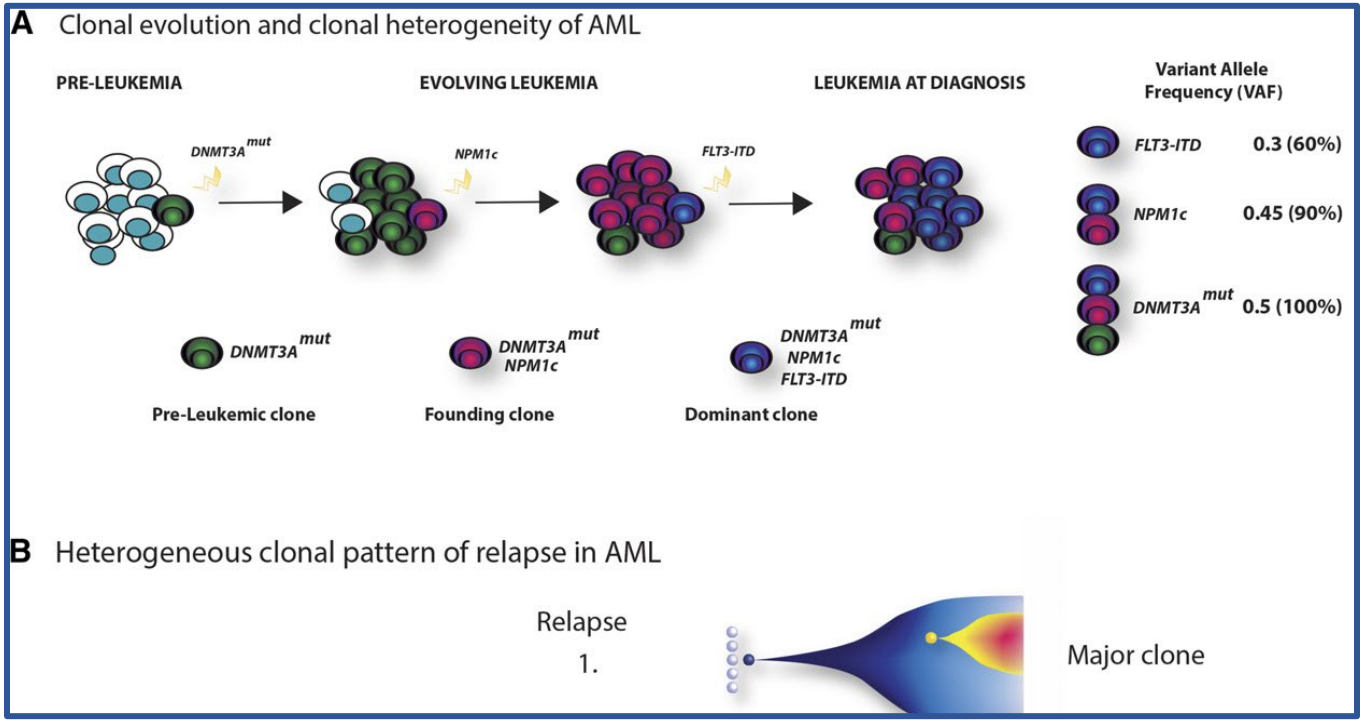
Heuser M, et al. *Blood.* 2021;138:2753-2767.

Algorithm of MRD assessment and time-points at which MRD is considered a clinically relevant biomarker



Heuser M, et al. *Blood.* 2021;138:2753-2767; Döhner H, et al. *Blood*. 2022;2022016867.

Clonal evolution and MRD monitoring



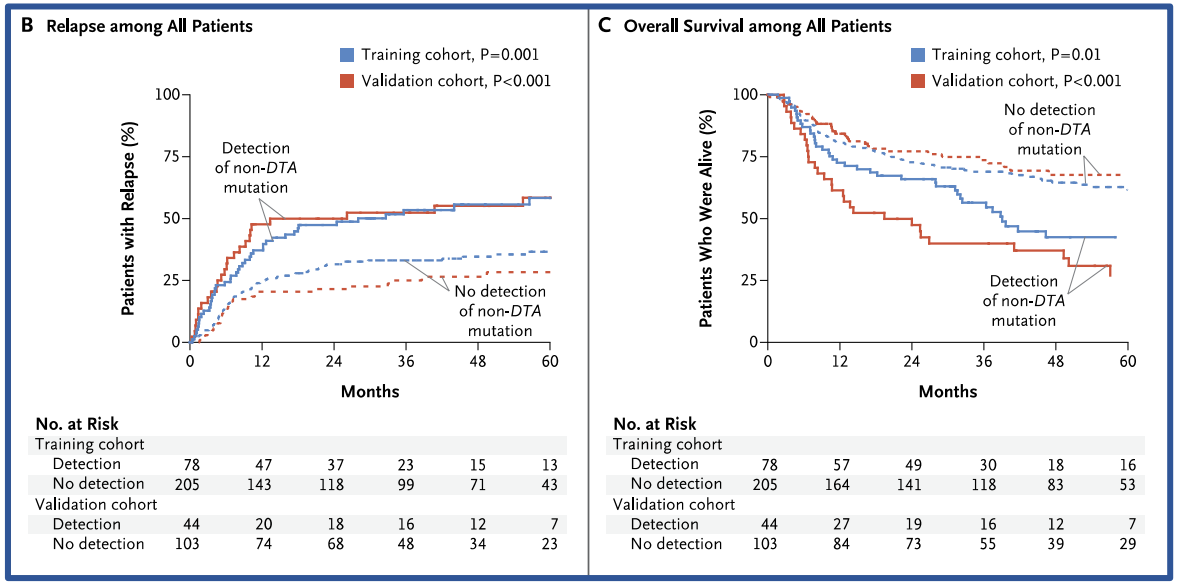
The genetic diversity of leukemia cells, both within a single patient and between different patients, significantly complicate the development of MRD tests for AML other than APL

Grimwade D, et al. *Blood.* 2016;127:29-41.

Next-generation sequencing in MRD monitoring

- Persisting **DTA** (*DNMT3A, TET2* i *ASXL1*) mutations may reflect a precursor CH
- Persisting non-DTA mutations
  - Correlation with relapse (CIR [5-lat] **58.3%** vs **33.9%** [*P* <.001])
  - Correlation with shorter OS (HR: 1.64 [95% CI: 1.18–2.27]; *P* = .003)

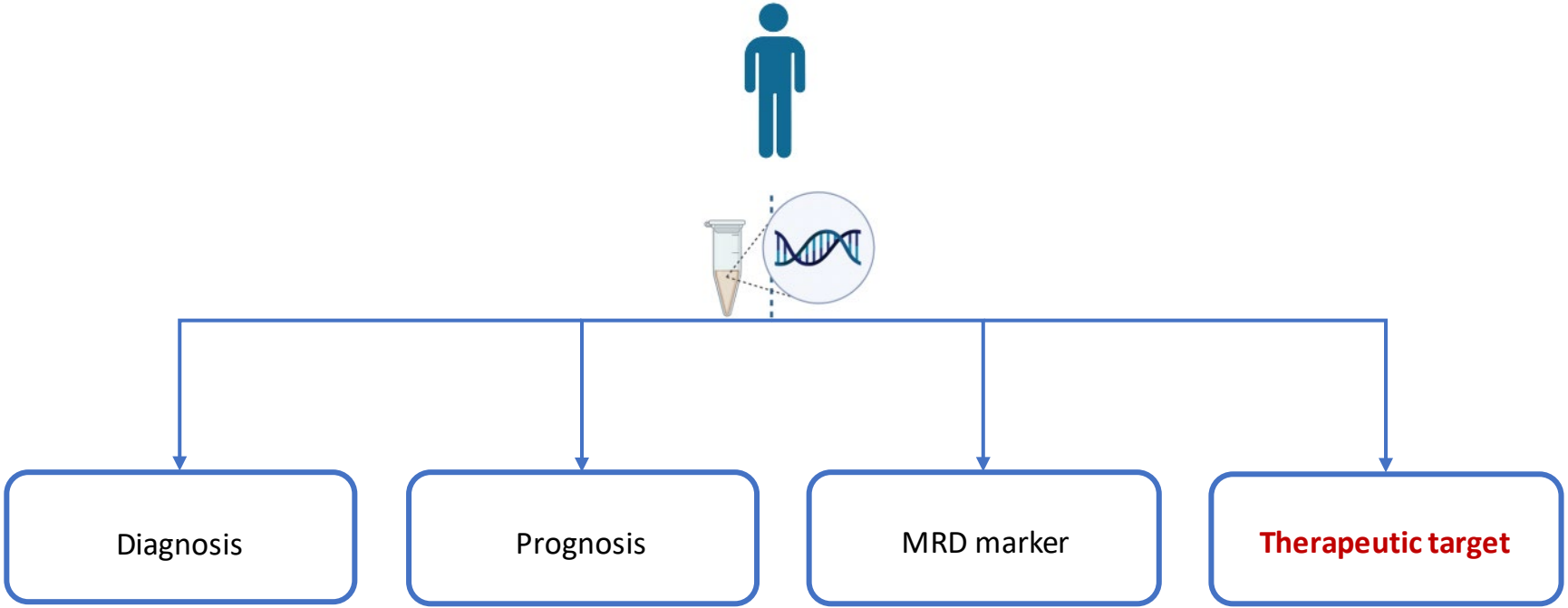
AML (<65 years) n = 482



Mutations in several genes (such as *DDX41*, *CEBPA*, and *RUNX1*) can be either somatically acquired in the AML clone or occur as germline mutations

Jongen-Lavrencic M, et al. *N Engl J Med.* 2018;378(13):1189-1199.

Molecular alterations in AML

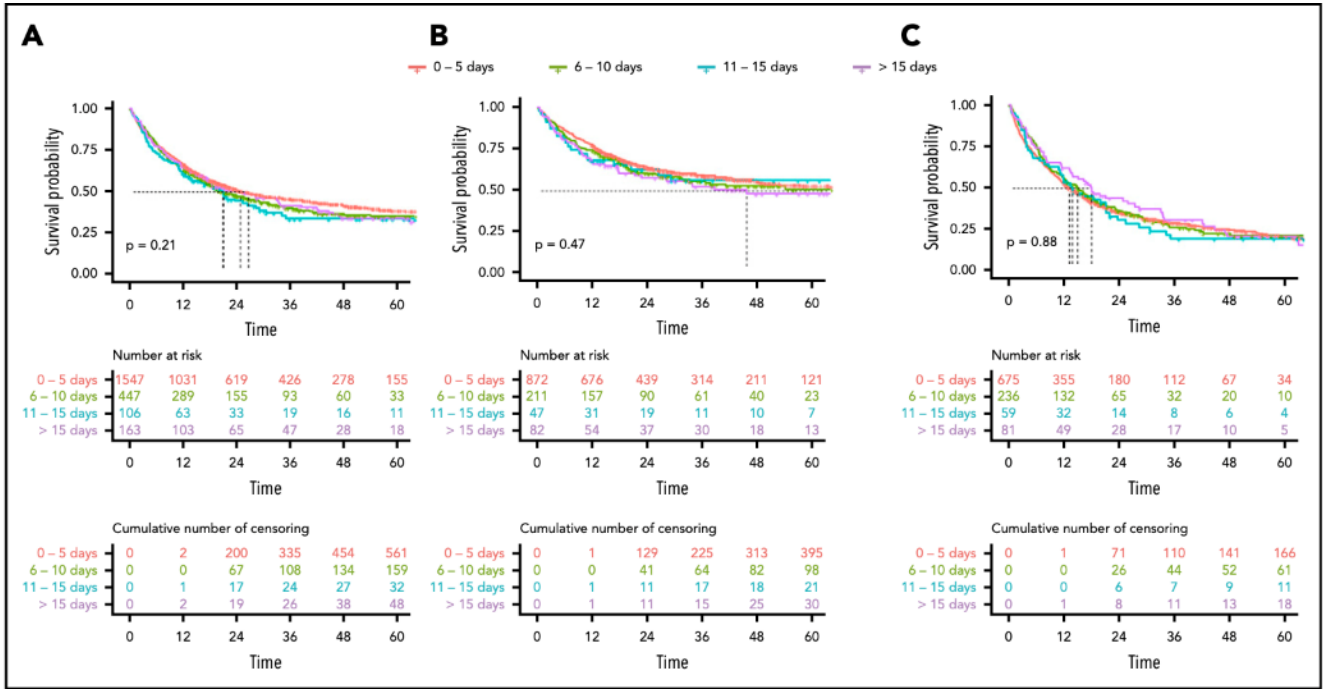


Genetic abnormalities and relevant therapeutic decision-making in AML

Molecular abnormality	Potential therapeutic target	Biomarker for selected therapy
PML-RARa	**ATRA** **ATO**	
RUNX1-RUNX1T1	No	Yes (**GO**)
CBFb-MYH11	No	Yes (**GO**)
***NPM1*^{mut}**	Yes* (menin inhibitors, ntospletinib)	Yes (**GO**)
***FLT3*^{mut} (ITD lub TKD)**	**Midostaurin** **Gilteritinib**	? (DA + Mido + **GO**)*
***IDH1/IDH2*^{mut}**	**Ivosidenib** **Enasidenib**	Yes (**AZA + VEN**)
Myelodysplasia-related cytogenetic abnormalities	No	Yes (**CPX-351**)
***TP53*^{mut}**	Yes* eprenetapopt	Yes* Magrolimab + AZA

*Clinical trials

Genetic abnormalities and relevant therapeutic decision-making in AML



Analyses of time from diagnosis of AML to start of intensive treatment indicate that a treatment delay has no negative prognostic impact

Röllig C, et al. *Blood.* 2020;136(7):823-830.

Summary

- With rapid advances in sequencing technologies, tremendous progress has been made in understanding the molecular pathogenesis of AML, thus revealing enormous genetic and clonal heterogeneity
- The understanding of molecular heterogeneity of AML
  - Provides background for genetic classification of AML and prognostic system
  - Is paving the way for precision therapeutic strategies according to the specific genetic characteristics of leukemia in individual patients
  - Provides tools to monitor measurable residual disease (MRD) by molecular assessments to inform the selection of postremission therapy

Global Leukemia Academy

Moving the Treatment of AML to the Outpatient Setting: Is It Feasible?

Gail J. Roboz

APTITUDE HEALTH

Weill Cornell Medicine

NewYork-Presbyterian

Moving the Treatment of AML to the Outpatient Setting: Is It Feasible?

Global Leukemia Academy

Sept 2022

Gail J. Roboz, MD

Professor of Medicine

Director, Clinical and Translational Leukemia Programs

Disclosures of Commercial Support

- Consultancy: AbbVie, Actinium, Agios, Amgen, Astellas, AstraZeneca, bluebird bio, Blueprint Medicines, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Jasper Therapeutics, Jazz, MEI Pharma (IDMC Chair), Mesoblast, Novartis, Pfizer, Syndax, Takeda (IRC Chair)
- Research Support: Janssen

Oral AML Drug Approvals 2017–2020 (USA)

Midostaurin – target: *FLT3*

Enasidenib – target: *IDH2*

Ivosidenib – target: *IDH1*

Gilteritinib – target: *FLT3*

Venetoclax – target: BCL2

CC-486 (oral azacitidine) – hypermethylation

But the Idea of Outpatient AML Treatment Isn't New . . .

Low intensity: azacitidine, decitabine, low-dose cytarabine

Patients treated with a low-intensity regimen spent median 26% of survival as inpatients and 5.9% of survival attending outpatient appointments

Patients treated with standard-intensity therapy spent median 30% of total survival time as inpatients and 1.6% as outpatients

Total time as outpatients was significantly longer for low-intensity regimen (P <.0001)

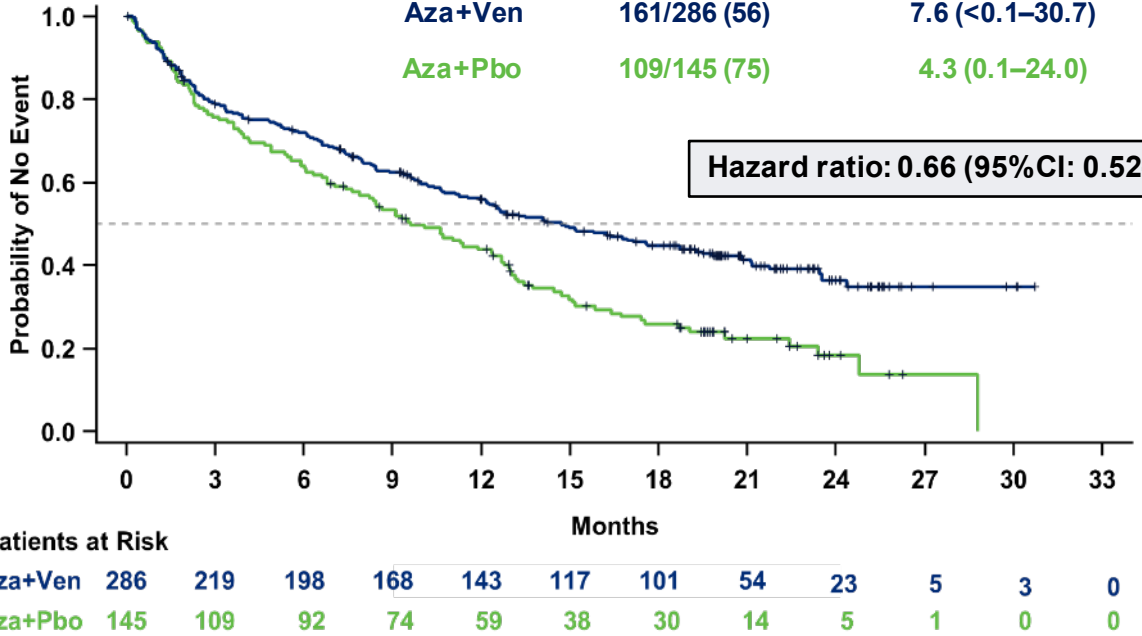
No significant difference in total time spent in a medical setting (inpatient + outpatient) between the 2 treatment groups: 34% for low intensity vs 38% for standard intensity (P = 0.10)

Weill Cornell Medicine NewYork-Presbyterian

Roboz GJ, et al. *Leuk Res*. 2012;36:407-412.

VIALE-A: Overall Survival

	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1–30.7)	14.7 (11.9–18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1–24.0)	9.6 (7.4–12.7)

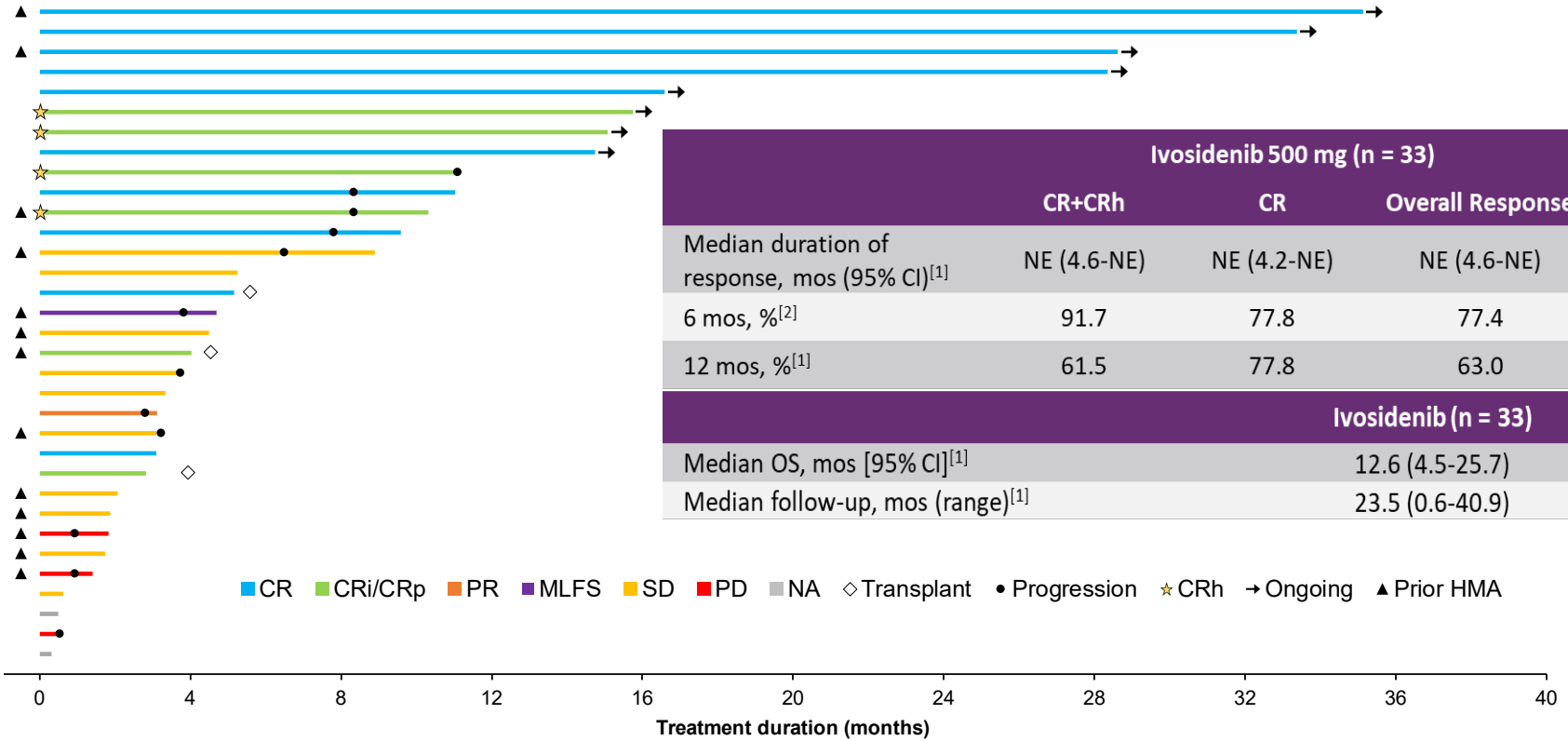


Hazard ratio: 0.66 (95%CI: 0.52–0.85), *P* <.001

Median follow-up time: 20.5 months (range: <0.1–30.7)

DiNardo CD, et al. *N Engl J Med*. 2020;383:617-629.

Ivosidenib in Untreated *IDH1*-Mutated AML: Duration of Treatment and Best Overall Response



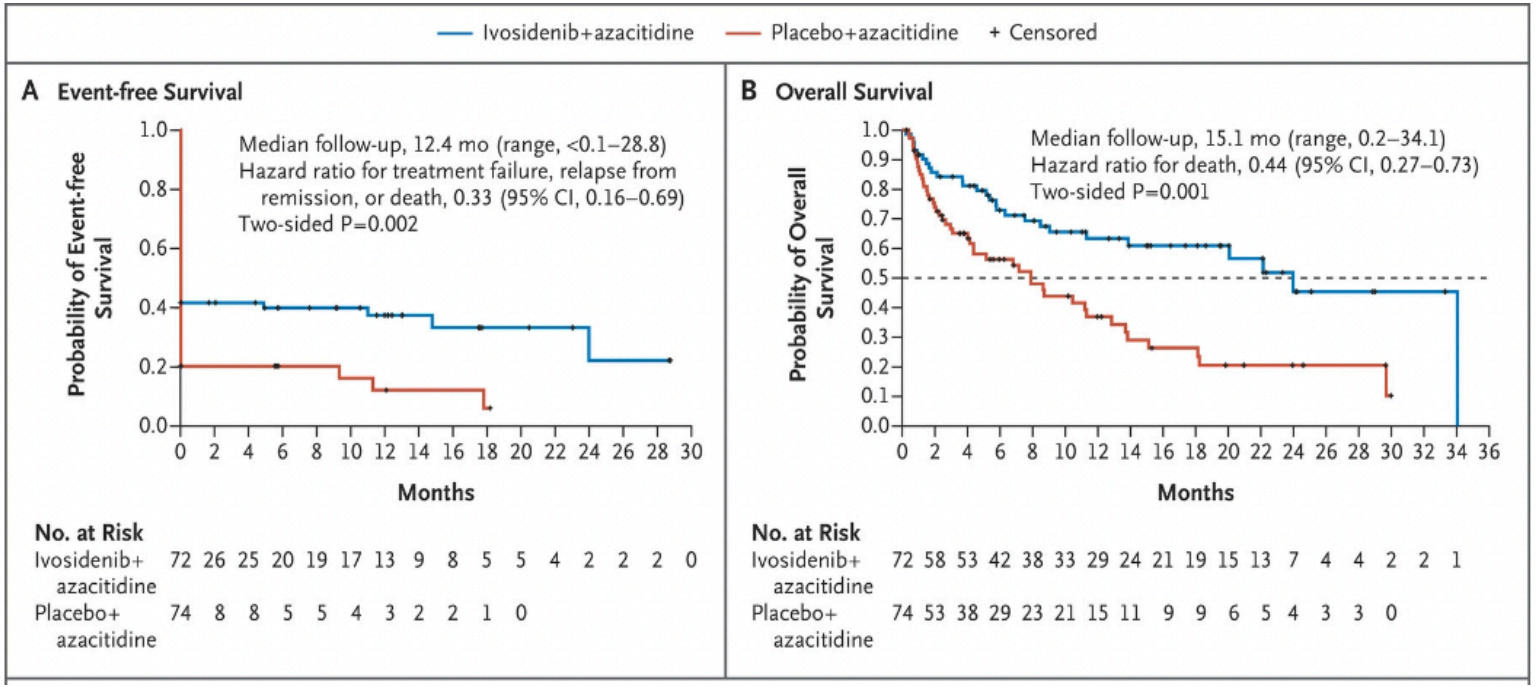
	Ivosidenib 500 mg (n = 33)		
	CR+CRh	CR	Overall Response
Median duration of response, mos (95% CI)[1]	NE (4.6-NE)	NE (4.2-NE)	NE (4.6-NE)
6 mos, %[2]	91.7	77.8	77.4
12 mos, %[1]	61.5	77.8	63.0

	Ivosidenib (n = 33)
Median OS, mos [95% CI][1]	12.6 (4.5-25.7)
Median follow-up, mos (range)[1]	23.5 (0.6-40.9)

Slide credit: clinicaloptions.com

1. Roboz GJ, et al. *Blood*. 2020;135:463-471; 2. Roboz GJ, et al. ASH 2018. Abstract 561.

Ivosidenib and Azacitidine in *IDH1*-Mutated AML



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Montesinos P, et al. *N Engl J Med*.2022;386:1519-1531.

Enasidenib in Untreated *IDH2*-Mutated AML: Duration of Treatment and Best Overall Response

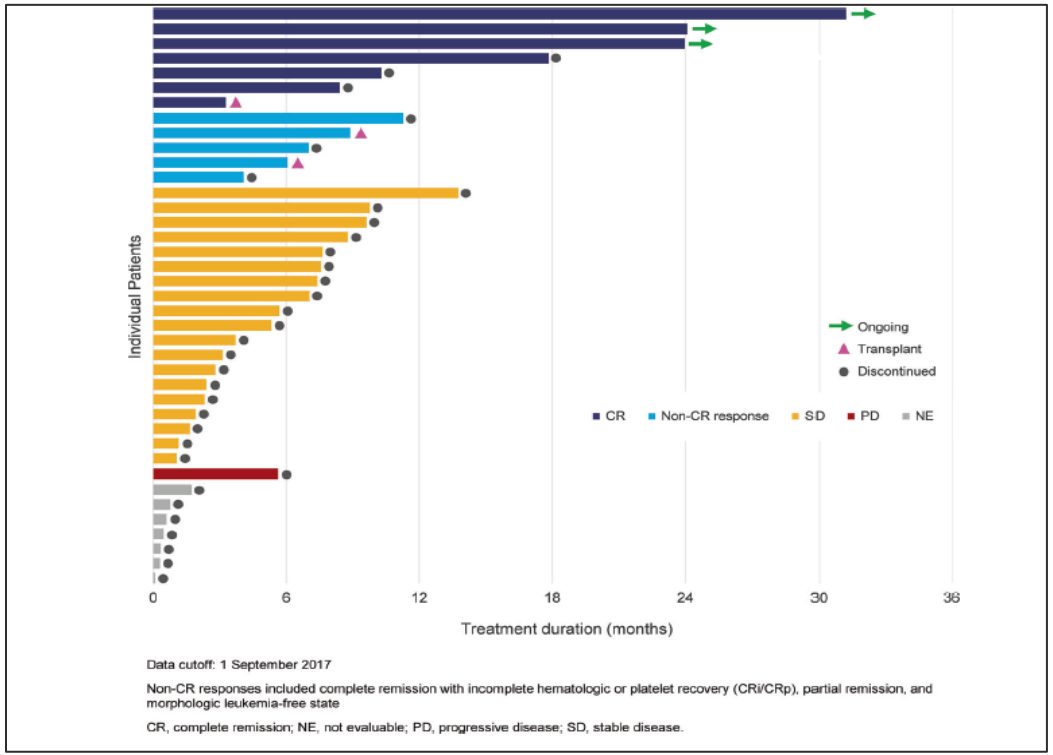


Table 3 Hematologic responses, times to response, and durations of response

	Patients with newly diagnosed AML $N = 39$
Overall response rate (ORR),[a] *n*(%)	**30.8 % (12/39)**
95% CI	17.0, 47.6
Best response, *n*(%)	
Complete remission (CR)	7 (18)
CR with incomplete count recovery (CRi/CRp)	1 (3)
Partial remission	2 (5)
Morphologic leukemia-free state	2 (5)
Stable disease,[b] *n*(%)	19 (49)
Disease progression, *n*(%)	1 (3)
Not evaluable,[c] *n*(%)	7 (18)
Time to first response, months, median (range)	1.9 (1.0–3.8)
Time to best response, months, median (range)	3.7 (1.0–12.9)
Duration of any response, months, median [95% CI]	NR [7.4, NR]
Time to CR, months, median (range)	5.6 (3.4–12.9)
Duration of CR, months, median [95% CI]	NR [3.7, NR]

Pollyea DA, et al. *Leukemia*. 2019;33:2575-2584.

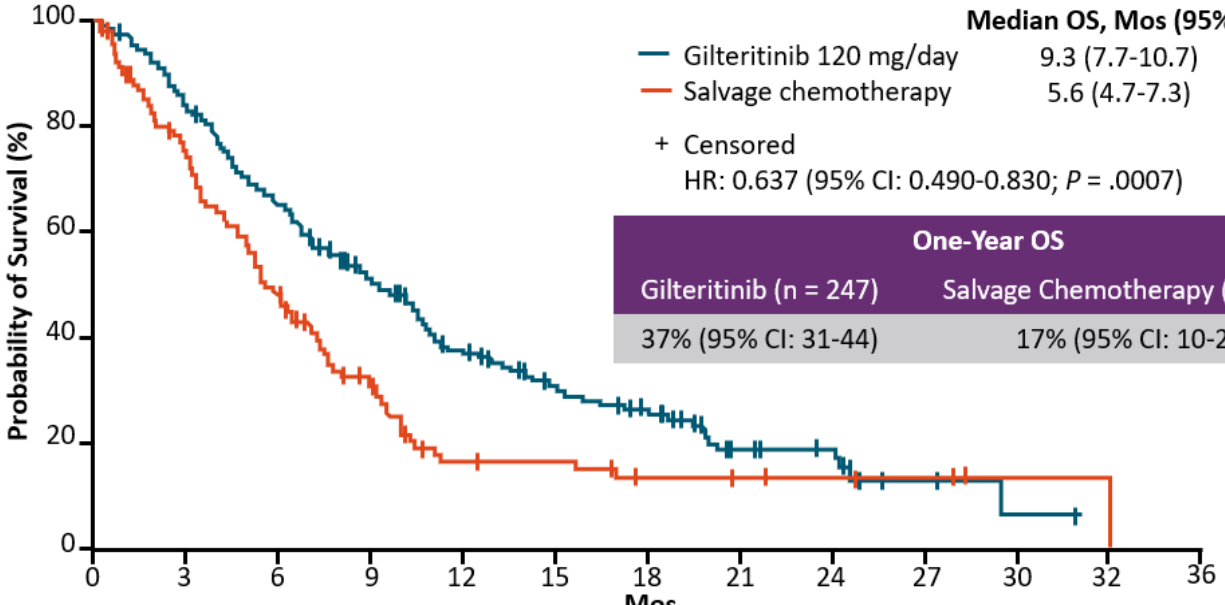
Enasidenib + AZA vs AZA in Newly Diagnosed AML: Response Summary

ORR and CR Substantially Higher With Combination Therapy

	ENA + AZA (n = 68)		AZA Only (n = 33)
Overall response [CR, CRi/CRp, PR, MLFS], n (%)	48 (71)	***P* = .0064**	14 (42)
ORR (95% CI)	(58–81)	***P* = .0001**	(26–61)
CR, n (%)	36 (53)		4 (12)
CR rate (95% CI)	(41–65)		(3–28)
CRi/CRp, n (%)	7 (10)		4 (12)

DiNardo CD, et al. ASCO 2020. Abstract 7501.

Gilteritinib Prolongs OS in *FLT3*-Mutant R/R AML



One-Year OS	
Gilteritinib (n = 247)	Salvage Chemotherapy (n = 124)
37% (95% CI: 31-44)	17% (95% CI: 10-25)

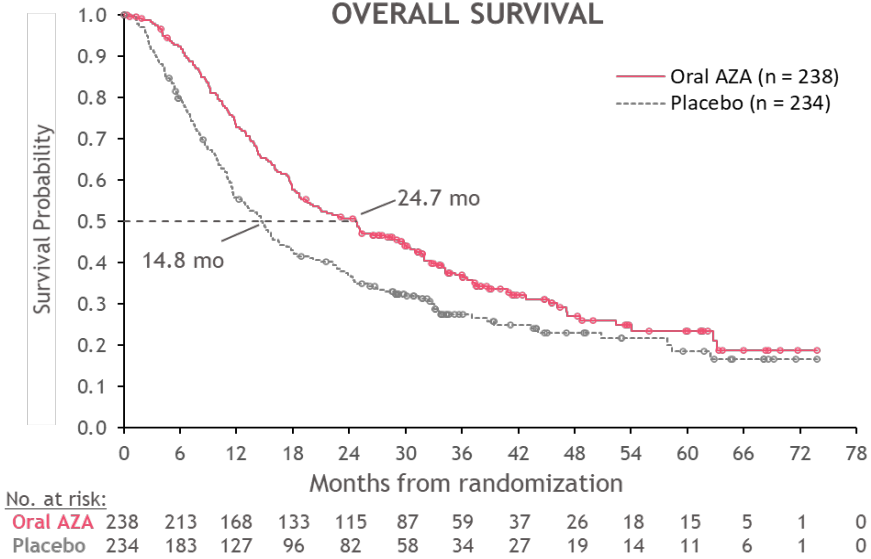
Patients at Risk, n													
Gilteritinib 120 mg/day	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

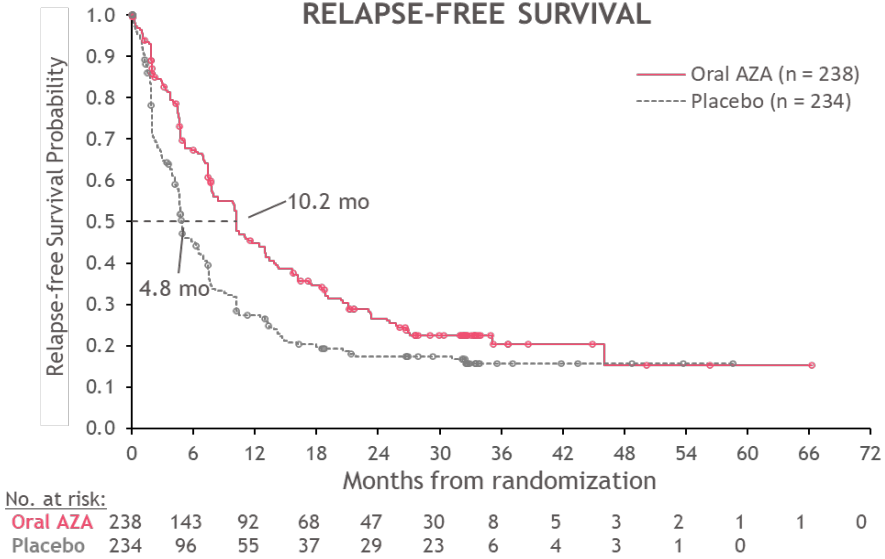
Slide credit: clinicaloptions.com

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740.

QUAZAR: Oral Azacitidine in Post-remission Maintenance

- Oral AZA 300 mg QD was associated with significantly improved overall survival (OS; *P* = .0009) and relapse-free survival (RFS; *P* = .0001) vs PBO





OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for oral AZA vs placebo by stratified log-rank test. HRs and 95% CIs were generated using a stratified Cox proportional hazards model.

AZA, azacitidine; No., number; PBO, placebo.

Wei AH, et al. *Blood.* 2019;134(suppl 2): abstract LBA-3.

AND THEN CAME COVID

Immediate Advantages of Telemedicine: Early March 2020 at Weill Cornell/NYP

- Allowed patients to stay home, avoid travel, public transportation, potential exposures in MD offices and emergency rooms
- Allowed healthcare workers to protect themselves and office personnel, conserve PPE (personal protective equipment), open clinic space for more hospital beds
- Allowed triage and assessment of patients to prevent non-essential office and ER visits

- Reduced on-site clinical volume
- Consolidation of practices
- Pre-visit and on-site COVID screening
- Separation of COVID-positive outpatient areas

Activity	February	March	Change in Volume	Percent Change
Video visits	4	702	+698	+17450%
On-site clinical visits	11,057	9561	-1496	-13.5%
Total volume	11,061	10,263	-798	-7.2%
Infusion center volume	2747	2398	-348	-12.7%

Weill Cornell Medicine NewYork-Presbyterian

Shah MA, et al. *CA Cancer J Clin*. 2020;70:349-354. https://doi.org/10.3322/caac.21627.

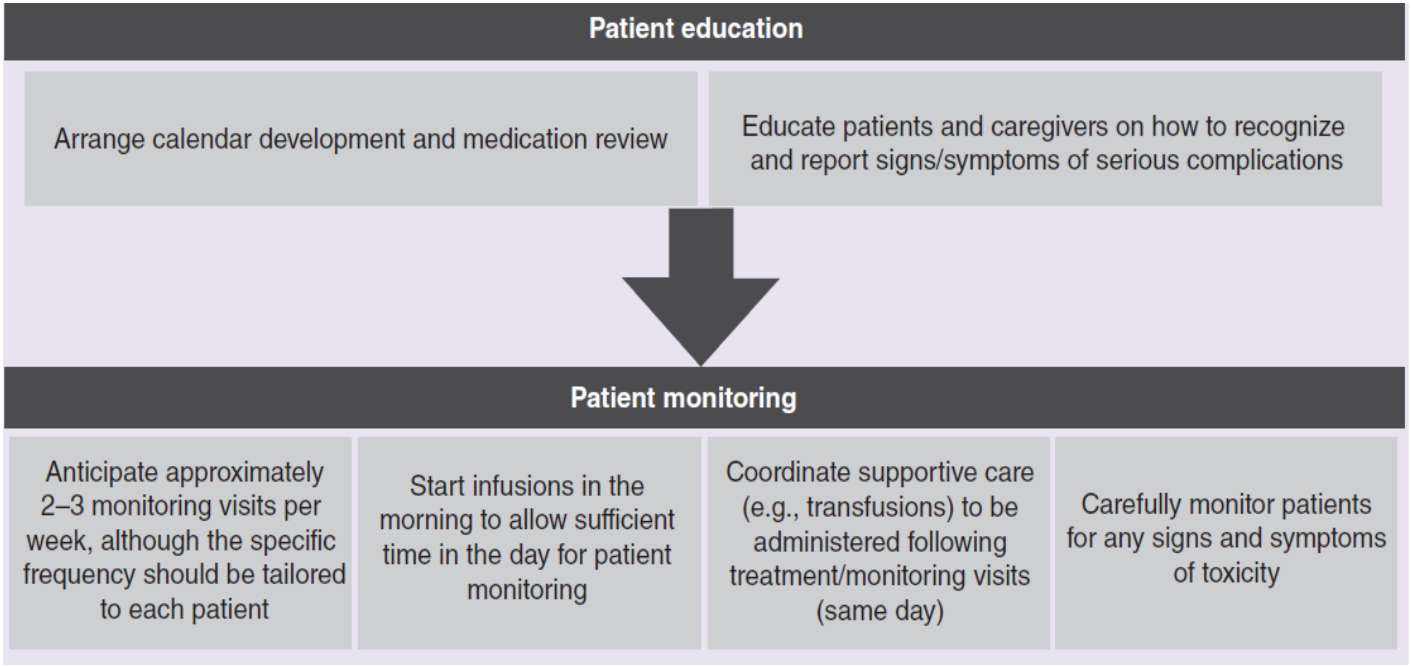
Selecting Patients for Outpatient Care

Patient selection	
Determine whether patients are candidates for regimens that can be administered in the outpatient setting on a case-by-case basis	Assess patient suitability for outpatient care: • Ensure patients are compliant and/or have a suitable caregiver • Limit commute between patient's lodging and treatment center to no more than 30–60 min • Evaluate patient's overall health/fitness (e.g., ECOG performance status, risk for complications, comorbidities, etc.) • Consider each patient's treatment goals and preferences

Weill Cornell Medicine NewYork-Presbyterian

Talati C, et al. *Future Oncol*. 2020;16:281-291.

Patient Education and Monitoring Are Essential



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Talati C, et al. *Future Oncol*. 2020;16:281-291.

Required Supportive Infrastructure for Outpatients

Inpatient management	Nursing education on treatment roadmap, expected complications CVC education and training Clear written discharge instructions with contact information for nonurgent and emergent situations Clear communication with outpatient team
Outpatient management	SOP for CVC care, antimicrobial prophylaxis, transfusion thresholds, management of neutropenic fever 24-h phone access to experienced provider in AML for emergencies Regular care team available for 3 times per week visits and nonscheduled evaluation of symptoms Infusion center with extended daily and weekend/holiday hours for frequent monitoring and transfusion Blood bank with large transfusion capability and rapid delivery of blood products to clinic setting Ability to rapidly evaluate and initiate treatment of neutropenic fever in clinic (eg, antimicrobial cocktail available for rapid administration before hospital transfer) Multidisciplinary expertise (infectious disease, pulmonary) in management of AML and therapy complications Ancillary support staff with expertise in AML management: nursing, social worker, pharmacists, physical therapists, nutritionists

CVC, central venous catheter; SOP, standard operating policy.

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Halpern AB, et al. *Hematol Am Soc Hematol Educ Program*. 2020;2020:129-134.

Problems With Shifting to Outpatient AML Therapy

AML IS STILL AML – location doesn't change the disease

Oral and "low intensity" don't mean easy and low-risk

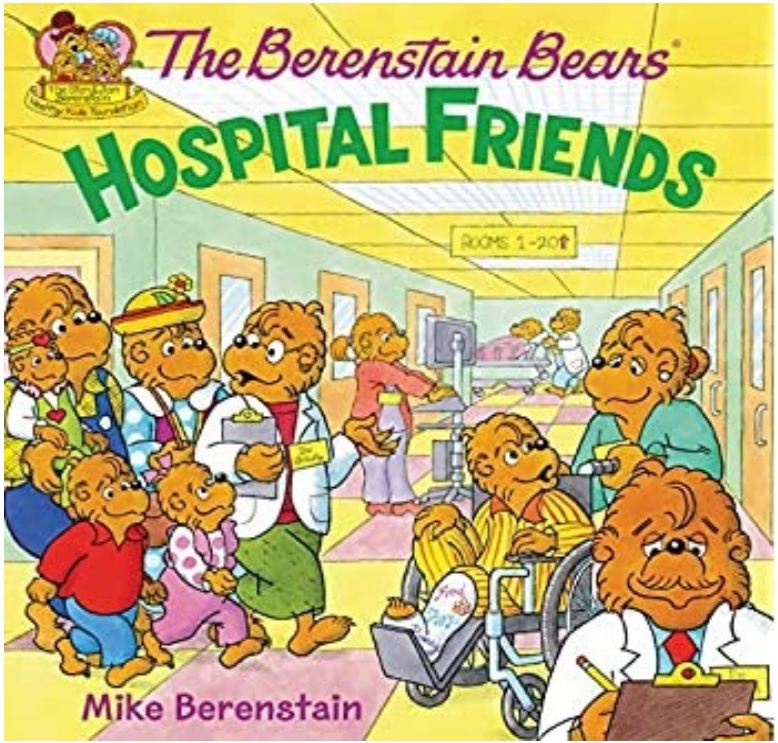
Many meds to manage

- Eg, aza + ven + gilt + abx + antifungal + antiemetic + HTN

Patient compliance with pancytopenia and fever precautions

Outpatient resources for clinic visits, transfusions

Potentially worse financial toxicity from copays, travel, parking, meals



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https://www.123rf.com/photo_115944666_home-sweet-home-typography-lettering-decorative-text.html?vti=nlppxeg59llgnl07rr-1-3

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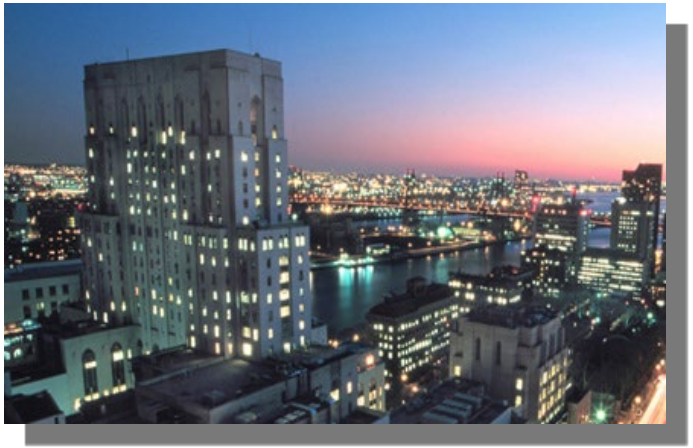
- Natalie Tafel, PA
- Adomah Sakibia Opong, NP
- Victoria Mendez, RN
- Rookmimi Singh, RN
- Maureen Thyne, PA
- Jill M. Kleczko, MPA, CCRP
- Abeer Elshewehy, BDS, CCRC
- Niamh Savage, BS



WCM Laboratory Collaborators

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- Olivier Elemento, PhD
- Christopher Mason, PhD
- Ari Melnick, MD

Leukemia Fighters

AA&MDSIF • MDS CLINICAL RESEARCH CONSORTIUM
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Global Leukemia Academy

Hot Topics and Regional Challenges of AML Management

All faculty

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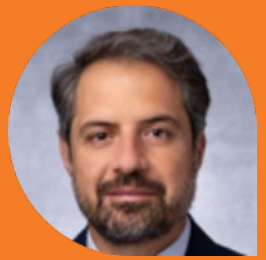
Session Close

Elias Jabbour



APTITUDE HEALTH

Question 3

Which of the following is NOT true?

A. Inotuzumab and blinatumomab + chemotherapy is active in both frontline and salvage for ALL

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

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

D. CAR T approaches are active beyond 2L in Ph-negative ALL

Question 4

In AML, the MRD assessment by RT-qPCR is especially useful for

A. *DNMT3A* mutation
B. *SF3B1* mutation
C. *NPM1* mutation
D. *ASXL1* mutation

Virtual Breakout – Pediatric ALL Sessions (Day 2)

24 September 2022, 10.00 – 12.45 CEST

Chair: Dr Franco Locatelli

Time (CEST)	Title	Speaker
10.00 – 10.10	**Session Open**	Franco Locatelli
10.10 – 10.30	**How to Use MRD and Genetics for Stratification and Therapy Guidance in First-Line Therapy of Childhood ALL**	Rob Pieters
10.30 – 10.55	**Optimizing First-Line Therapy in Pediatric ALL: How to Balance Cure and Long-Term Risks?**	Rob Pieters
10.55 – 11.15	**ALL Case-Based Panel Discussion** • Balancing Cure and Toxicity Risks	Moderator: Franco Locatelli Janine Stutterheim All faculty
11.15 – 11.25	***Break***	
11.25 – 11.55	**Current Treatment Options for High-Risk ALL in Children**	Christina Peters
11.55 – 12.35	**ALL Case-Based Panel Discussion** • Relapsed/Refractory ALL (Part 1) • Toxicity Management (Part 2)	Moderator: Franco Locatelli Hannah von Mersi Anna Cvrtak All faculty
12.35 – 12.45	**Session Close**	Franco Locatelli

Virtual Breakout – Adult ALL Sessions (Day 2)

24 September 2022, 11.00 – 13.45 CEST

Chair: Dr Elias Jabbour

Time (CEST)	Title	Speaker
11.00 – 11.10	**Session Open**	Elias Jabbour
11.10 – 11.35	**Optimizing First-Line Therapy in Adult and Older ALL: Integration of Immunotherapy Into Frontline Regimens**	Nicolas Boissel
11.35 – 12.00	**Current Treatment Options for Relapsed ALL in Adult and Older Patients**	Nicola Gökbuget
12.00 – 12.40	**ALL Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderator: Elias Jabbour Anjali Cremer Loic Vasseur All faculty
12.40 – 12.50	***Break***	
12.50 – 13.10	**Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL Patients**	Nicola Gökbuget
13.10 – 13.35	**Interactive Discussion: Treatment Landscape Evolution**	Moderator: Elias Jabbour All faculty
13.35 – 13.45	**Session Close**	Elias Jabbour

Virtual Breakout – AML Sessions (Day 2)

24 September 2022, 14.30 – 17.15 CEST

Chairs: Dr Gail J. Roboz/Dr Naval Daver

Time (CEST)	Title	Speaker
14.30 – 14.40	**Session Open**	Gail J. Roboz and Naval Daver
14.40 – 15.00	**Personalized Induction and Maintenance Approaches for AML**	Gail J. Roboz
15.00 – 15.25	**Fit and Unfit AML Patients: How Do We Distinguish? How Do We Treat Differently?**	Agnieszka Wierzbowska
15.25 – 16.05	**AML Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderators: Gail J. Roboz and Naval Daver Agnieszka Pluta Anna Torrent All faculty
16.05 – 16.15	***Break***	
16.15 – 16.40	**Optimizing Management of Relapsed/Refractory AML**	Naval Daver
16.40 – 17.05	**Interactive Discussion: Treatment Landscape Evolution**	Moderators: Gail J. Roboz and Naval Daver All faculty
17.05 – 17.15	**Session Close**	Gail J. Roboz and Naval Daver

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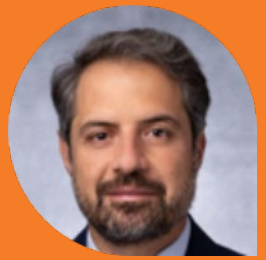
Closing Remarks

Elias Jabbour



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Thank you!

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

THANK YOU!

Day 2 – 24 September

Pediatric ALL Session 10.00 – 12.45 CEST
Adult ALL Session 11.00 – 13.45 CEST
Adult AML Session 14.30 – 17.15 CEST

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SEE YOU TOMORROW!

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