Global Leukemia Academy

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

October 16–17, 2024

Meeting sponsors AMGEN rigel

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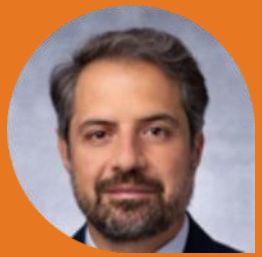
Welcome and meeting overview

Elias Jabbour



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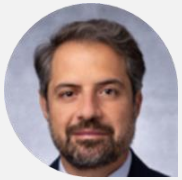
Meet the Faculty

CHAIR



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

CO-CHAIR

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

FACULTY

Nicola Gökbuget, MD
University Hospital Frankfurt
Frankfurt, Germany

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

Charles Craddock, CBE, FRCP (UK), FRCPath, DPhil
University of Birmingham
Queen Elizabeth Hospital
Birmingham, UK

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

Agenda: Day 1

Time UTC+2	Title	Speaker
18.00 – 18.10	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
18.10 – 18.25	Latest achievements and developments in ALL and AML	Elias Jabbour
18.25 – 18.40	Review of prognostic value of MRD in leukemias (focusing on ALL)	Josep-Maria Ribera
18.40 – 18.50	Best practices for first-line treatment in ALL	Elias Jabbour
18.50 – 19.05	AYA patients with ALL: What is the current treatment approach for this diverse patient population? Special considerations for adolescents and young adults and how we can use this experience in adult patients	Nicola Gökbuget
19.05 – 19.35	ALL case-based panel discussion • Case 1 ALL: Anjali Cremer (Germany) • Case 2 ALL: Fabian Lang (Germany)	Elias Jabbour Patient case presenters Panelists: All faculty
19.35 – 19.45	Break	
19.45 – 20.10	Genetic characterization and risk stratification of AML; role of *FLT3* and *IDH* in AML and special considerations for young and fit patients	Naval Daver
20.10 – 20.25	Therapeutic approaches in high-risk and frail patients with AML	Charles Craddock
20.25 – 20.50	Panel discussion: Open questions in ALL and AML – regional challenges (transplant, CAR T, studies, and other)	Elias Jabbour and all faculty
20.50 – 21.00	Session close	Elias Jabbour

Agenda: Day 2

Time UTC+2	Title	Speaker
18.30 – 18.40	Welcome to Day 2	Naval Daver
18.40 – 19.00	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
19.00 – 19.20	Long-term safety considerations for leukemias (focus on ALL)	Nicola Gökbuget
19.20 – 19.40	Current and future role of transplantation in acute leukemias in Europe	Josep-Maria Ribera
19.40 – 19.50	Break	
19.50 – 20.10	Current treatment options for relapsed AML in adult and elderly patients	Charles Craddock
20.10 – 20.40	AML case-based panel discussion • Case 1 AML: Vitor Botafogo (Spain) • Case 2 AML: Samantha Drummond (UK)	Naval Daver Patient case presenters Panelists: All faculty
20.40 – 21.20	Panel discussion: How treatment in first line influences further therapy approaches in ALL and AML • Will CAR T and bispecifics change the treatment landscape? • Role of HSCT – is it still necessary? • What does the future look like? Adoption of therapies and evolving standards of care in Europe	Naval Daver and all faculty
21.20 – 21.30	Session close	Naval Daver

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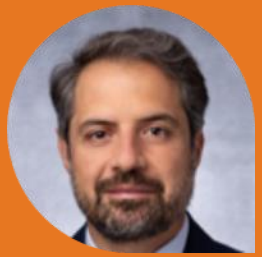
Introduction to the voting system

Elias Jabbour



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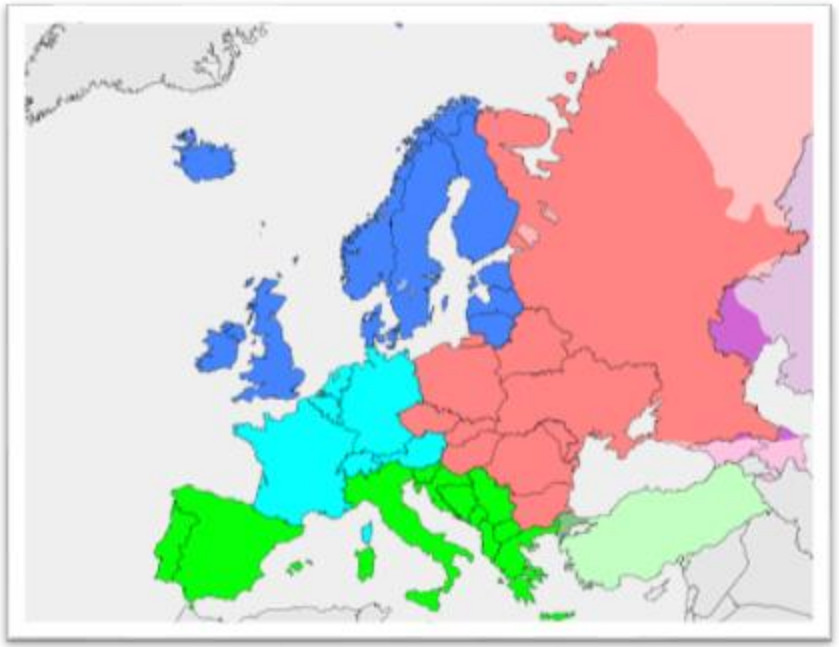
Question 1

In which region of Europe do you currently practice?

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



https://en.wikipedia.org/wiki/Regions_of_Europe#/media/File:Europe_subregion_map_UN_geoscheme.svg

Question 2

Which leukemias do you primarily treat?

A. AML

B. ALL

C. Both

Question 3

At what time points is MRD quantification prognostic for survival in ALL?

A. After induction/consolidation

B. Prior to allogeneic hematopoietic cell transplant

C. After transplant

D. All of the above

Question 4

Which of the following is NOT true for treating ALL?

A. Inotuzumab and blinatumomab plus chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients

B. Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL

C. MRD– CR does not correlate strongly with outcome

D. Since 1999, median survival for patients with ALL older than 60 has been increasing with each successive decade

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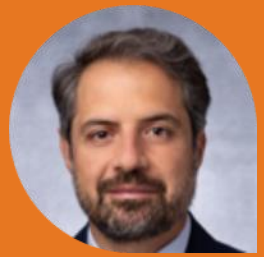
Latest achievements and developments in ALL and AML

Elias Jabbour



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What Is New in Acute Leukemia

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

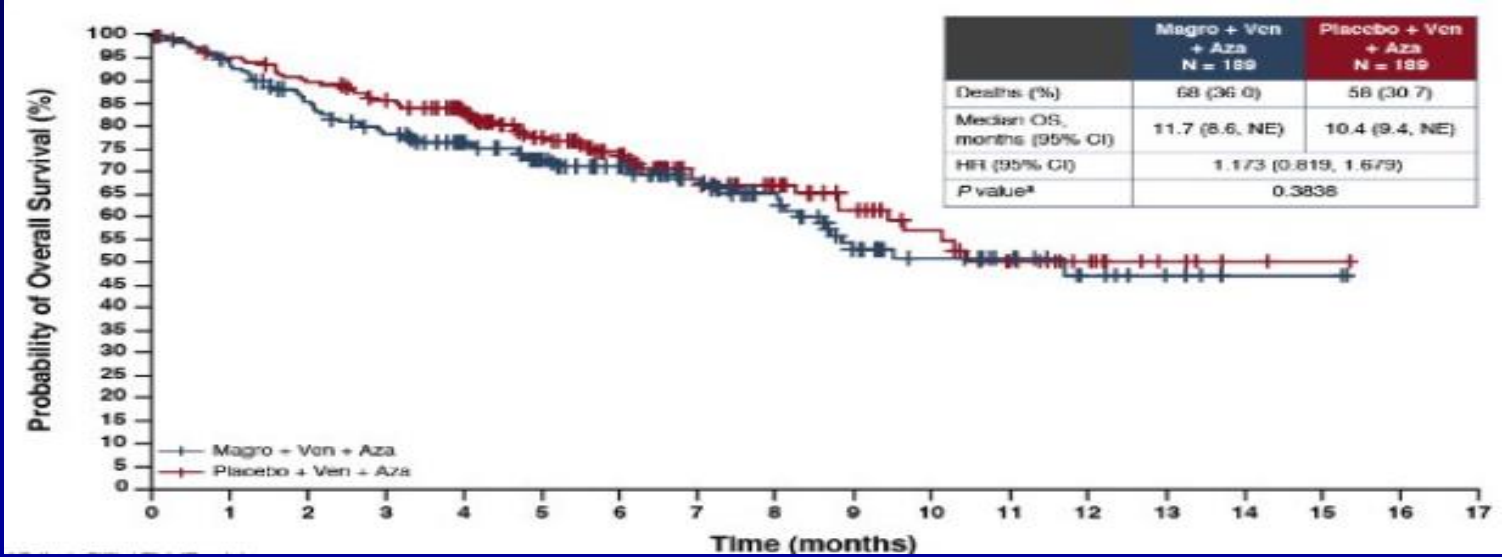
2024

What Is New in AML

Azacitidine, Venetoclax ± Magrolimab in Older AML

- 378 pts randomized to AZA-VEN-MAGRO (n=189) or AZA-VEN-PBO (n=198)

Parameter	MAGRO	PBO
Median OS (mos)	11.7	10.4
% CR	40	43

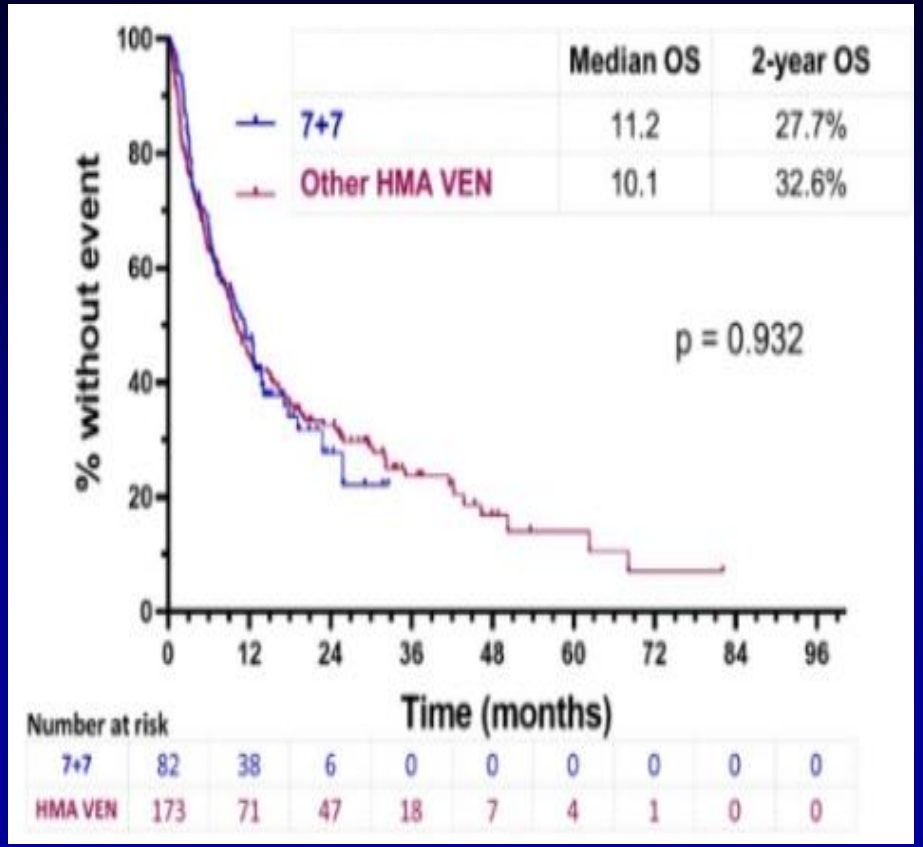


Daver. *HemaSphere.* 2024;8:S138.

Venetoclax 7D/Mo vs Daily in AML

- Comparison of 82 pts (France, 7 centers) Rx with AZA-VEN 7-7 to 173 pts Rx at MDACC with DAC10-VEN 21-28

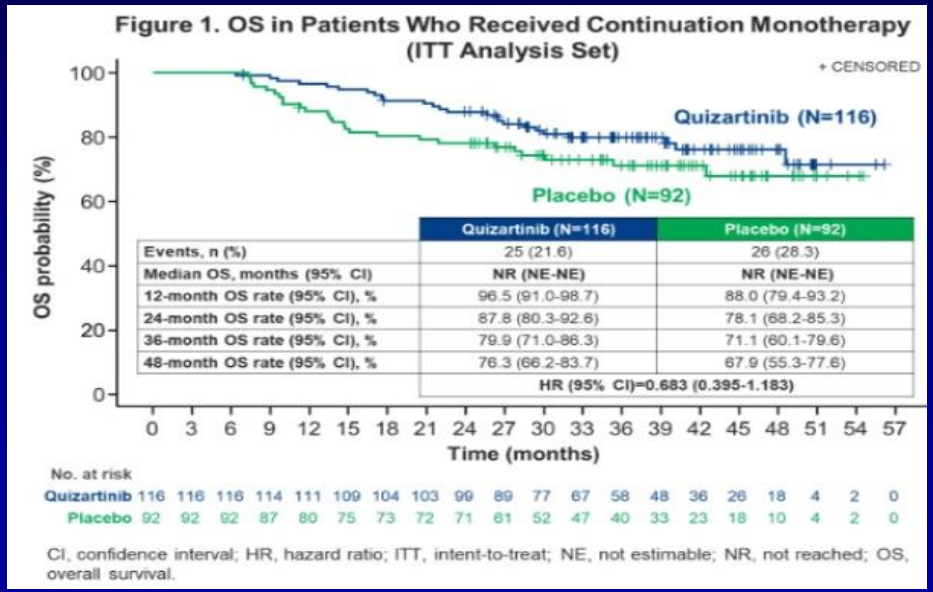
Parameter	7+7	DAC10-VEN 21-28	*P* Value
% CRc	71	72	-
% CR	57	55	-
Median courses to best response	2	1	.02
% 4/8 wk mortality	2/6	7/17	.02
% allo SCT	1	14	.002
% 2-yr OS	28	32	-

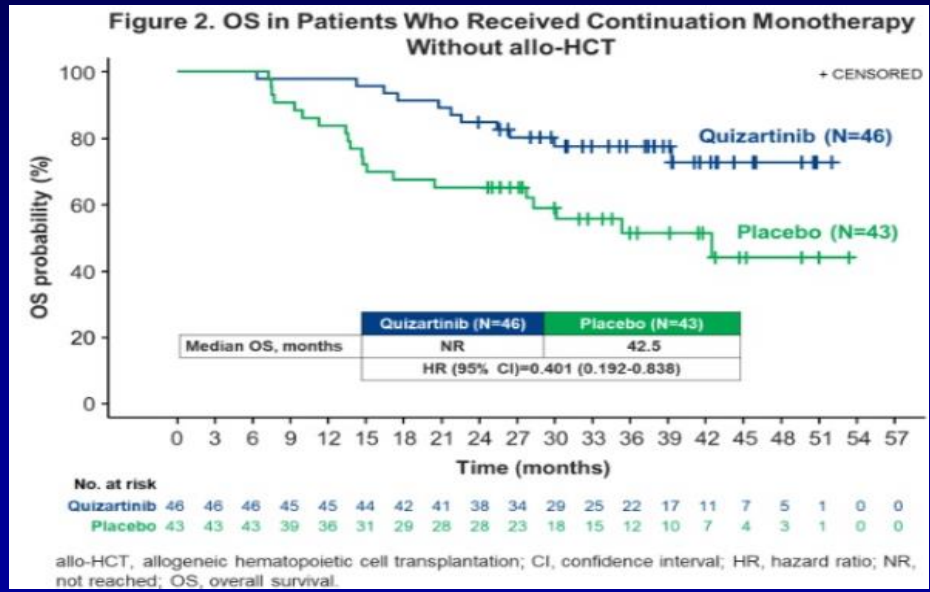


Willekens. *HemaSphere.* 2024;8:P590.

Continuation of Quizartinib Improves Survival in Newly Dx FLT3-ITD AML

- 539 pt randomized; 208 (39%) received CONT with QUIZ (n=116) or placebo (n=92)
- OS favors QUIZ (HR 0.68) – 3-yr OS 80% vs 71%
- If CONT/no SCT (n=89) = marked ↑ OS with QUIZ





Sekeres. *HemaSphere.* 2024;8:S142.

FLAG-GO Better Than FLAG-IDA in CBF AML

- 179 pts with newly Dx CBF-AML Rx with FLAG-GO (n=85) or FLAG-IDA (n=94)

Parameter	FLAG-GO	FLAG-IDA	*P* Value
% 6-yr OS	80	70	.07
% 6-yr RFS	76	58	.02
% Optimal molecular response			
--end of induction	61	41	-
--post consolidation	83	56	-

Borthakur. *HemaSphere.* 2024;8:P565.

FLAG-IDA + Venetoclax in Newly Dx and R-R AML

- 134 pts: 68 ND; 59 R/R. Median age 64 yrs (18-73)
- F 30 mg/m^2/D ×5; araC 1.5 g/m^2/D ×5; IDA 6-8 mg/m^2/D ×3; VEN 14-7 days

Parameter	ND	R-R
% ORR	99	68
% CR-CRc	96	64
% CR	82	41
% MRD-neg	89	79
% allo SCT	57	58
Median OS (mos)	NR	12
SCT	NR	NR
No SCT	23	2
% 2-yr OS	75	40

Jen. *J Clin Oncol.* 2024;24:abstract 6519.

Revumenib MonoRx in R-R KMT2A AML/ALL (AUGMENT 101)

- 94 pts; median age 37 yrs (1.3-75); 78 AML, 16 ALL-MPAL
- Median prior Rxs 2 (1-11); prior SCT 50%
- Efficacy population (phase 2) 57 pts
- CR-CRh 13 (23%); median DOR 6.4 mos. ORR 63%
- Differentiation syndrome 16%; QTC prolongation 14%

-------. *HemaSphere.* 2024;8:S131.

Revumenib + AZA + VEN in Newly Dx Older NPM1/KMT2A AML

- Beat AML trial-- age 60+yrs
- AZA x 7, VEN daily, REV daily (113-163 mg BID)
- 13 Rx—CR 10, CRh-i 3; ORR 13/13 (100%)
- MRD-neg 12/13 (92%)
- 2 relapses; 2 deaths. 1-yr OS 90%

Zeidner. *HemaSphere.* 2024;8:S134.

DSP 5336 (Menin Inhibitor) in R/R AML-ALL

- 58 pts; DSP 40-300 mg BID; 27 pts no azoles, 31 pts with azoles
- AML 93%; median prior Rx 3 (1-9); KMT2A 45%, NPM1 24%
- Responses at >140 mg BID
- KMT2A-NPM1, no prior menin-inhibitors, dose >140 mg BID: ORR 10/22 (45%); CR-CRh 5/22 (23%)

Daver. *HemaSphere*. 2024;8:S132.

JNJ-617 + VEN-AZA in KMT2A-NPM1 R/R AML

- 60 pts; median age 60 yrs (20-82); NPM1 50%, KMT2A 50%. median prior Rx 2 (1-5)
- Rx AZA x 7, VEN x 28, JNJ 15+ mg BID (D4 +)
- JNJ 50+ mg BID (n=34): ORR 27/34 (79%); CR/CRh-i 14/34 (41%)

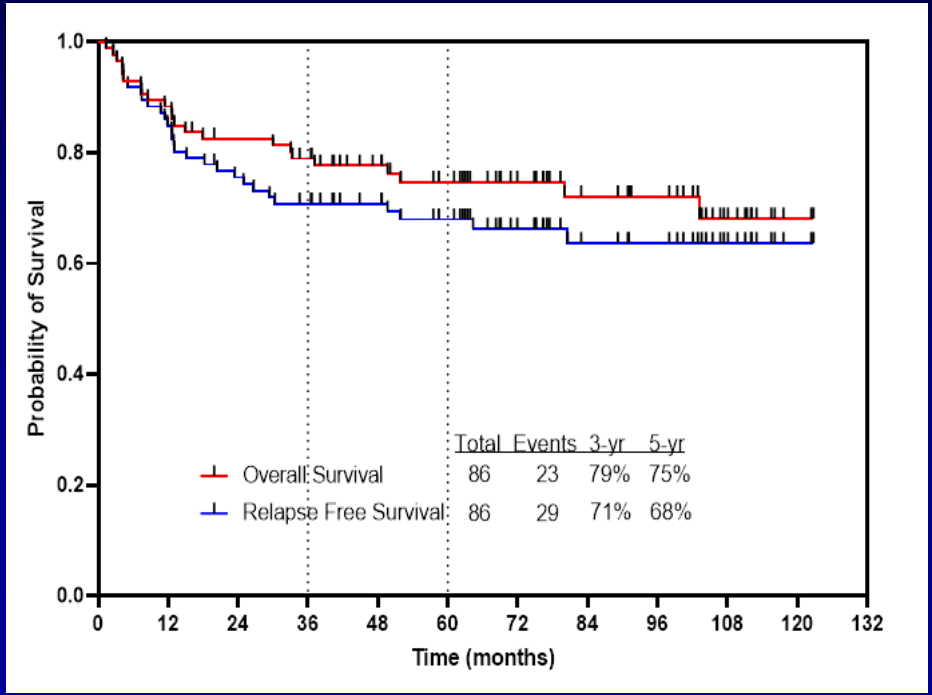
Wei. *HemaSphere*. 2024;8:S133.

What Is New in ALL

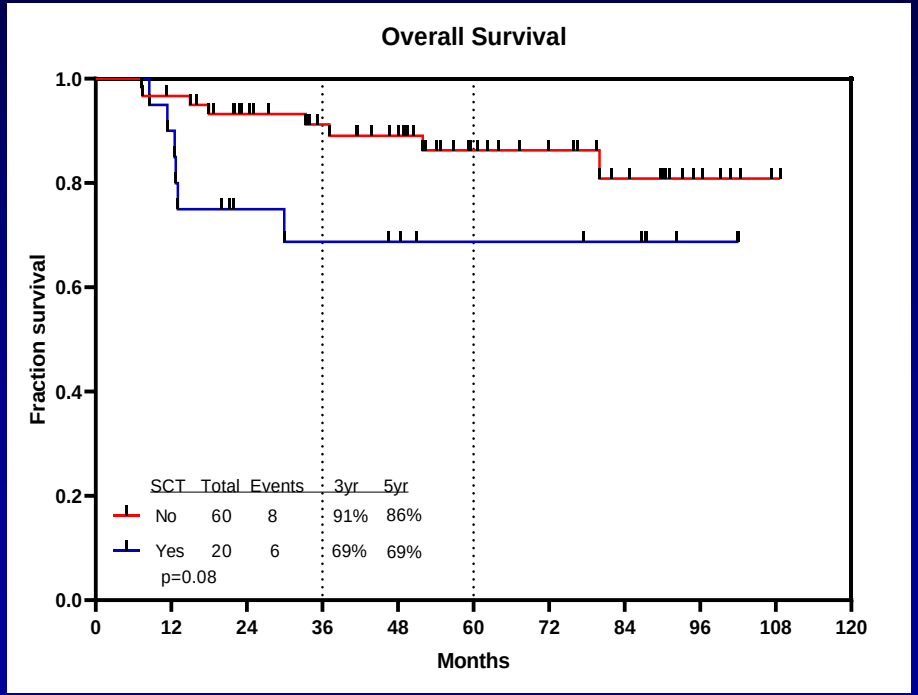
HyperCVAD + Ponatinib in Ph+ ALL

- 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%; 5-yr OS 75%, EFS 68%

RFS and survival



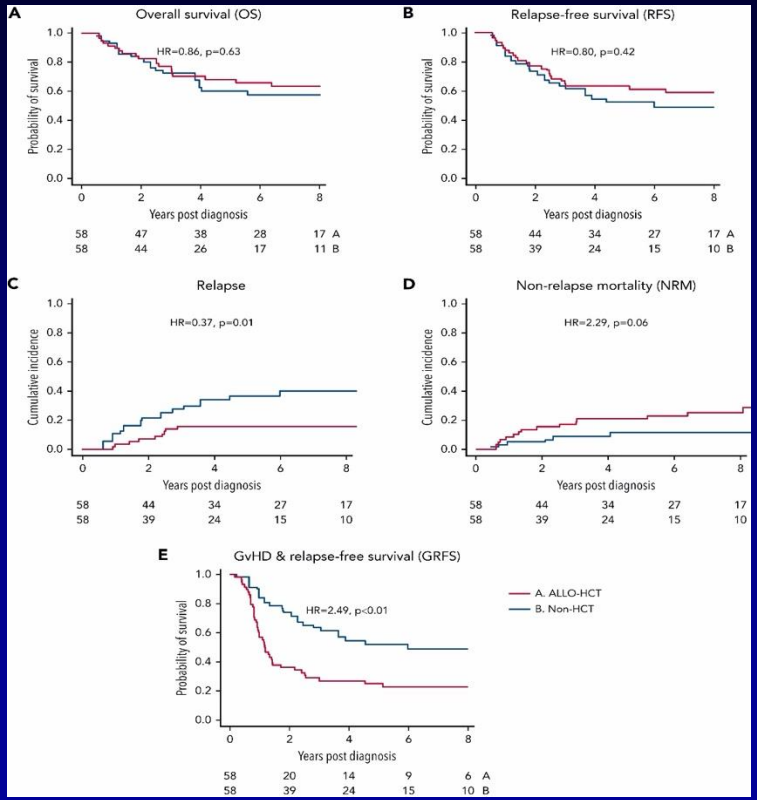
6-month Landmark



Kantarjian. *Am J Hematol.* 2023;98:493-501.

No Benefit of Allogeneic SCT in Patients With Ph+ ALL Who Achieve CMR

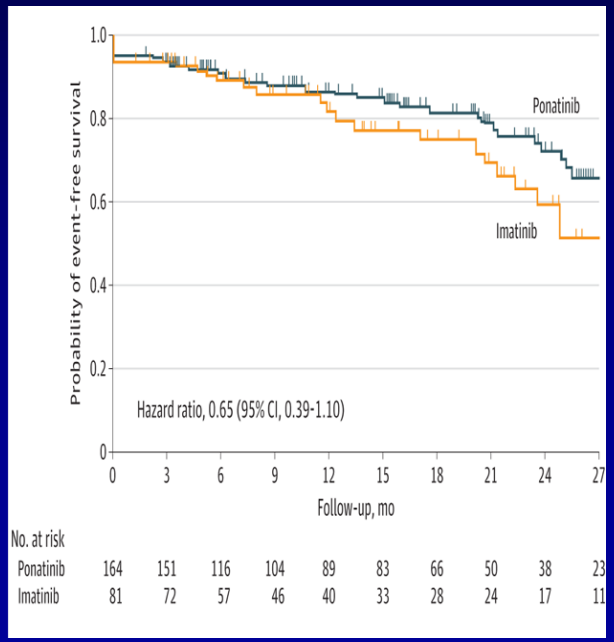
- Propensity score analysis of patients who achieved CMR within 3 months
- Allogeneic SCT → lower risk of relapse but higher NRM
- No impact of SCT on OS or RFS

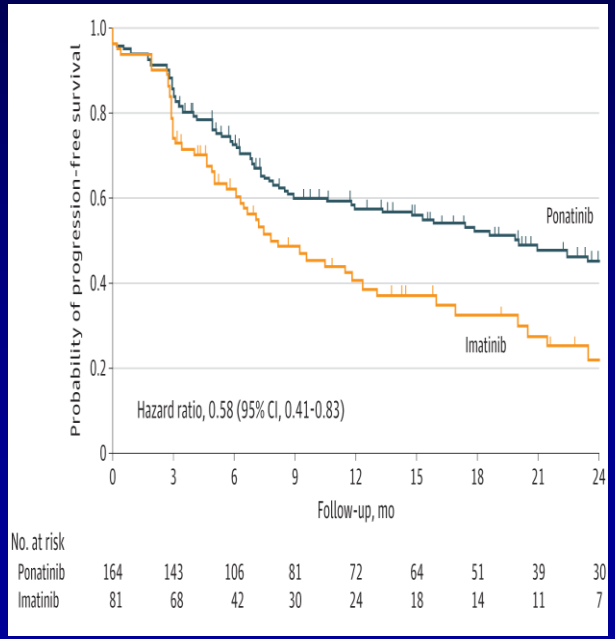


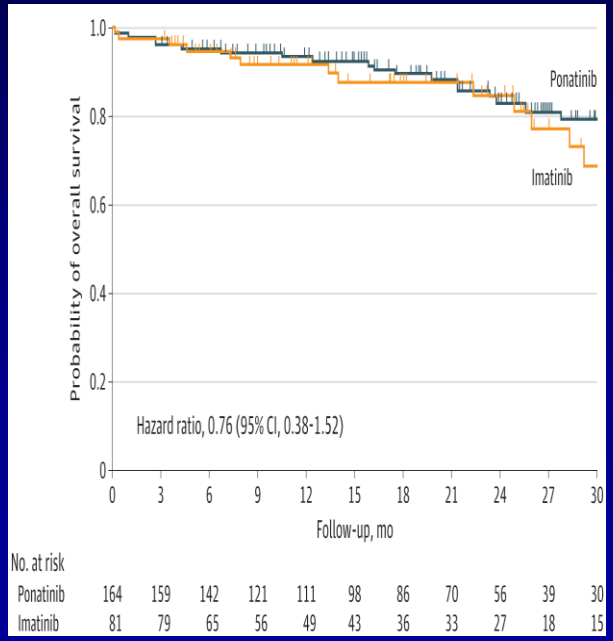
Ghobadi A, et al. *Blood.* 2022;140(20):2101-2112.

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

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



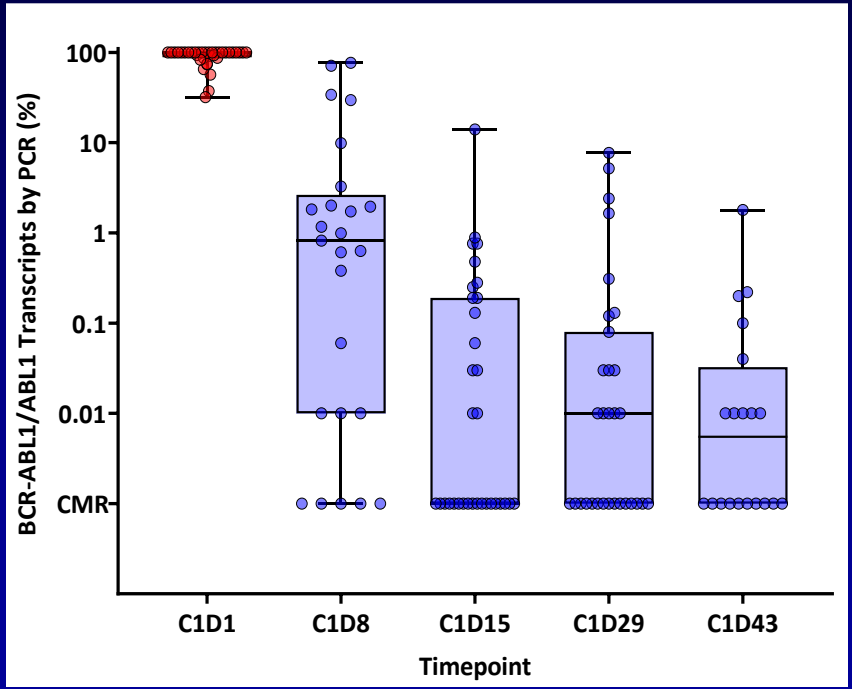


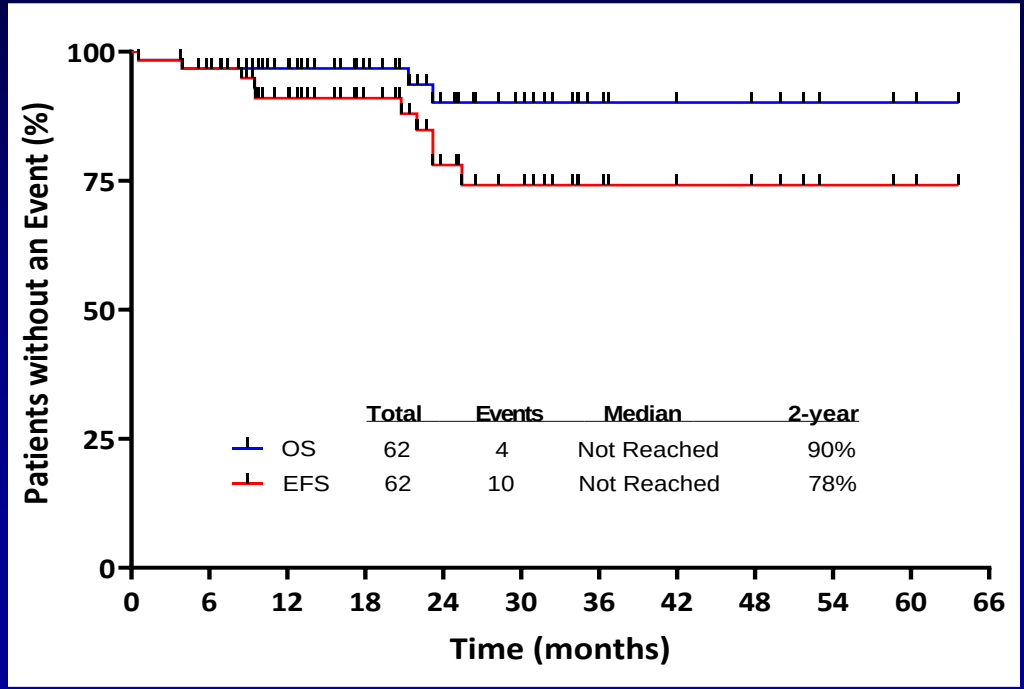


Jabbour E, et al. *JAMA*. 2024:e244783.

Ponatinib and Blinatumomab in Newly Dx Ph+ ALL

- 62 pts Rx with simultaneous ponatinib 30-15 mg/D and blinatumomab ×5 courses. 12-15 ITs
- Only 2 pt had SCT(3%); Median F/U 17 mos
- CR/CRi 98% (CR 95%); CMR 84% (67% after C1); NGS-MRD negativity 94%
- 2-yr EFS 78%, OS 90%. 7 relapses (all p190): 4 CNS, 1 CRLF2+ (Ph-), 2 systemic. 5/7 WBC >75k





Jabbour E, et al. *Lancet Haematol.* 2023;10(1):e24-e34.

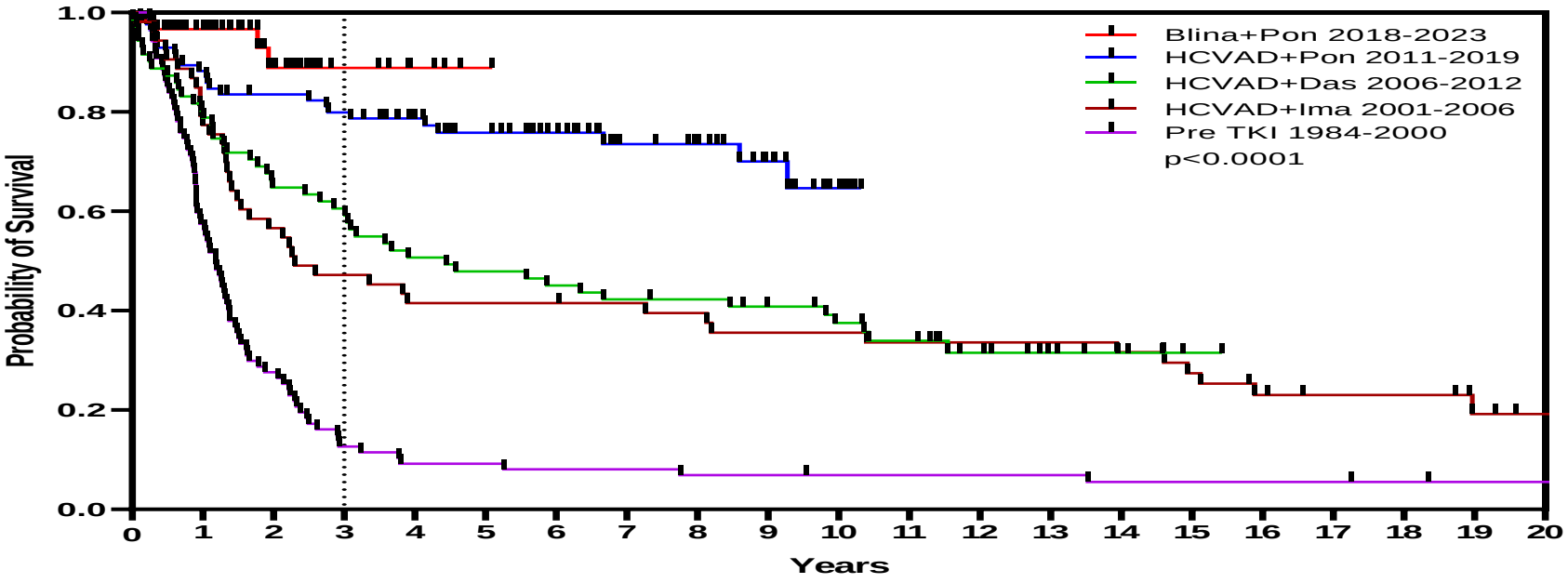
Haddad. *Blood.* 2023;142:abstract6 2827.

Ponatinib vs Dasatinib + Blinatumomab in Ph+ ALL

Parameter	Pona+Blina (n=62; 5 blina)	Dasa+Blina (n=63; 2+blina)	Dasa+ Blina (n=24; 3 blina)
Median age (yrs)	58	54	73
% PCR neg % NGS-clonoSEQ neg	84 94	93 (+PNQ)	63
% 4-yr OS	90	82	75
% allo SCT	3	48	5
Relapses (CNS)	7 (4)	9 (4)	8 [3 T315I]

Jabbour E, et al. *Lancet Haematol.* 2023;10(1):e24-e34. Foa. *J Clin Oncol.* online, December 23; 2023. Advani. *Blood.* 2023;142:abstract 1499.

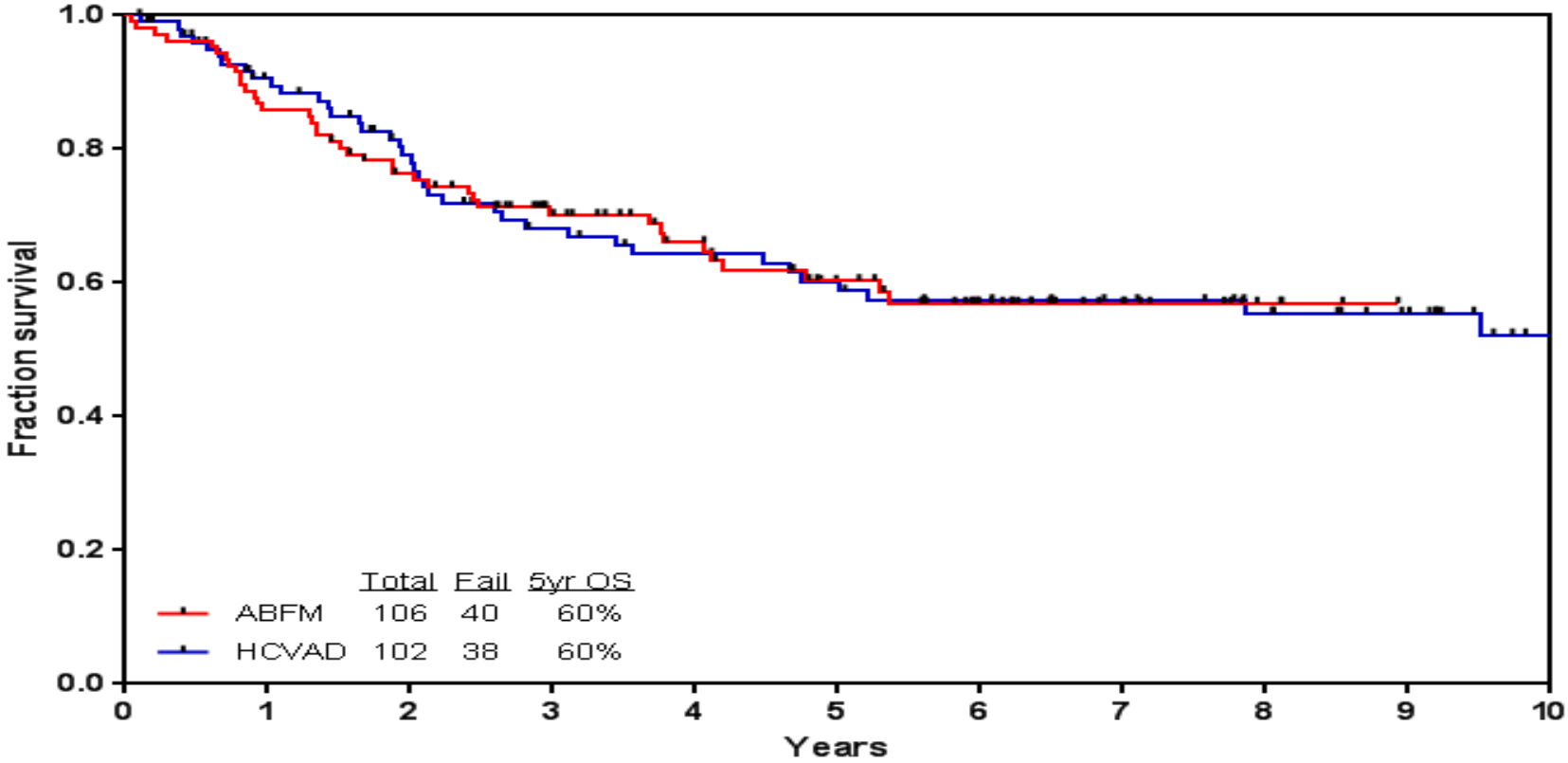
Ph+ ALL: Survival by Decade (MDACC 1984–2023)



	Total	Events	3yr OS	5yr OS	Median
Blina+Pon 2018-2022	62	4	89%	——	Not reached
HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
Pre TKI 1984-2000	87	83	13%	9%	14 mos

p<0.0001

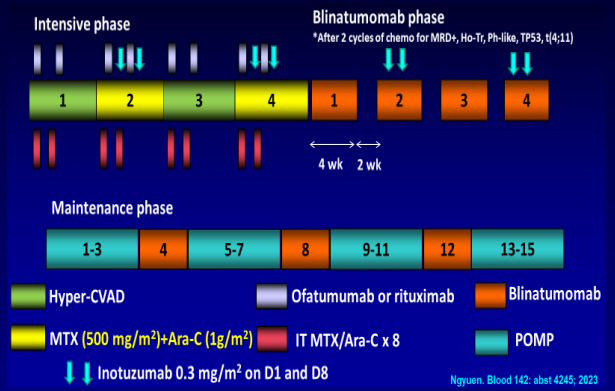
Hyper-CVAD vs ABFM: Overall Survival

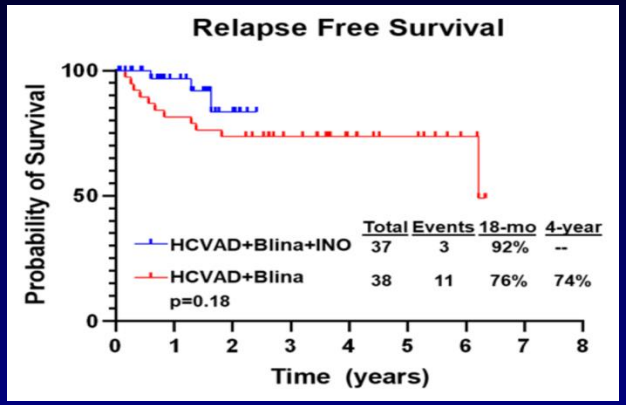


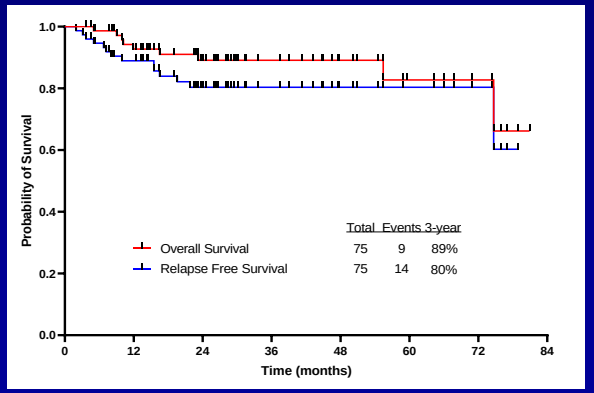
Rytting. *Cancer.* 2014;120:3660-3668; Rytting. *Am J Hematol.* 2016;91:819.

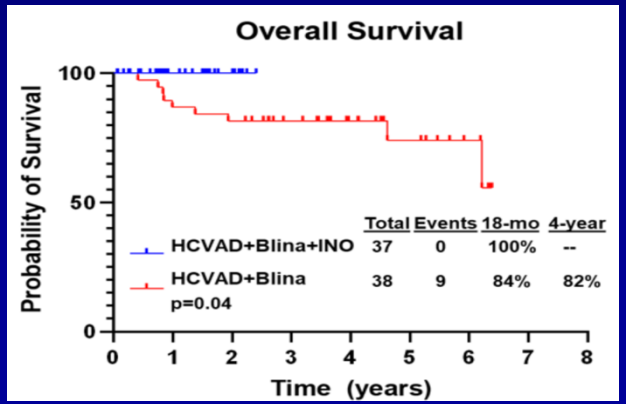
Hyper CVAD-Inotuzumab → Blina in Newly Dx Adult ALL

- 75 pts; median age 33 yrs (18-59); Median F/U 26 months (1-77)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 73%; 60-day mortality 0%; 24 (32%) allo-SCT

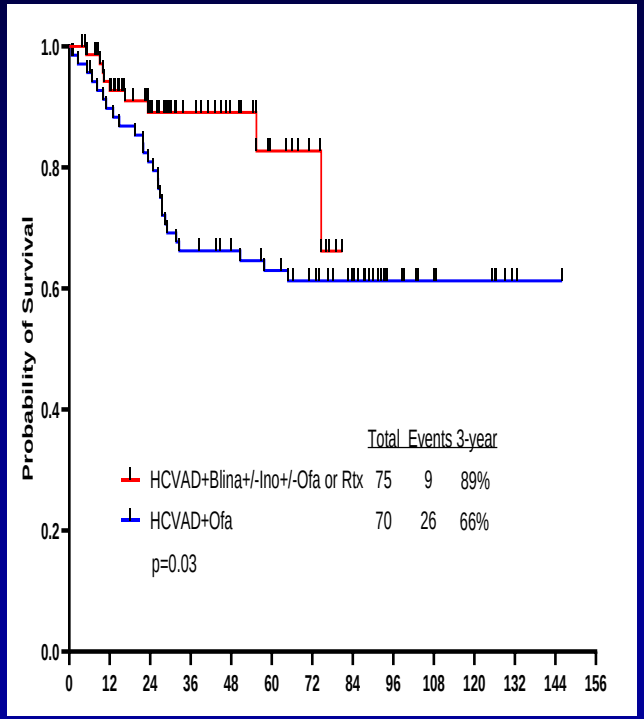






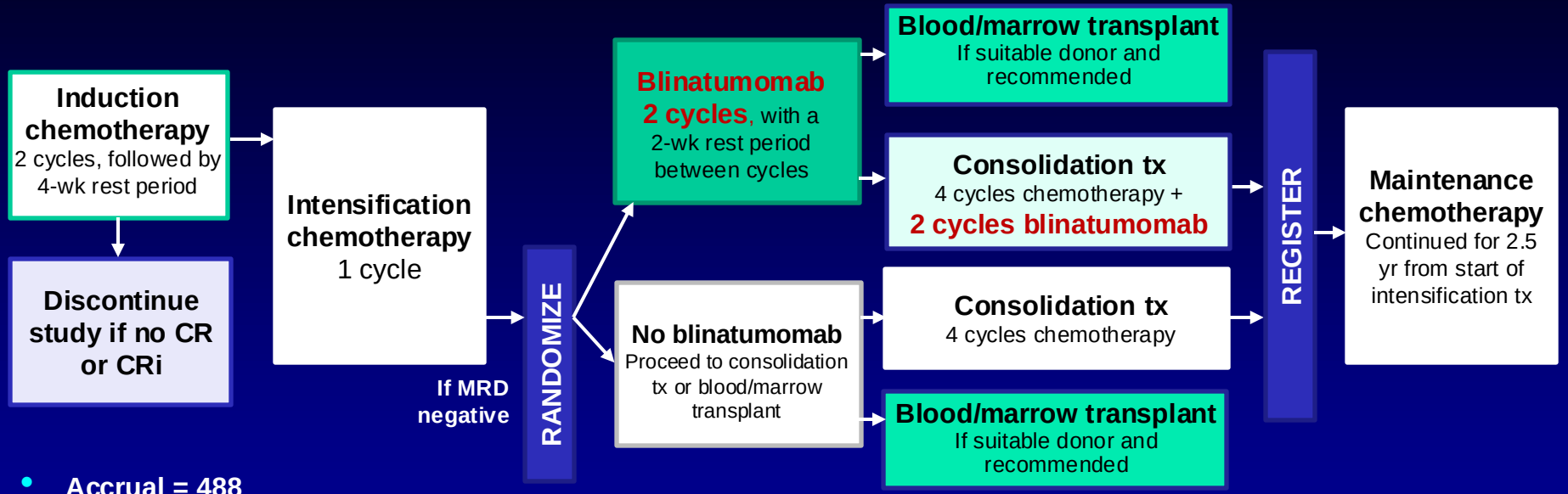


Overall Survival



Nguyen. *Blood.* 2023;142:abstract 4245.

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



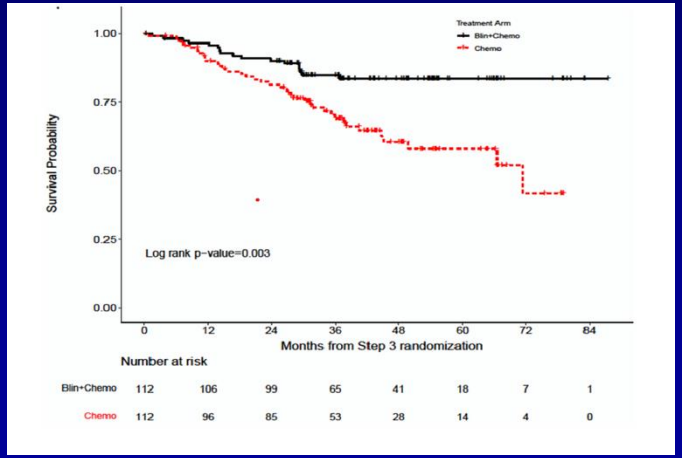
- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

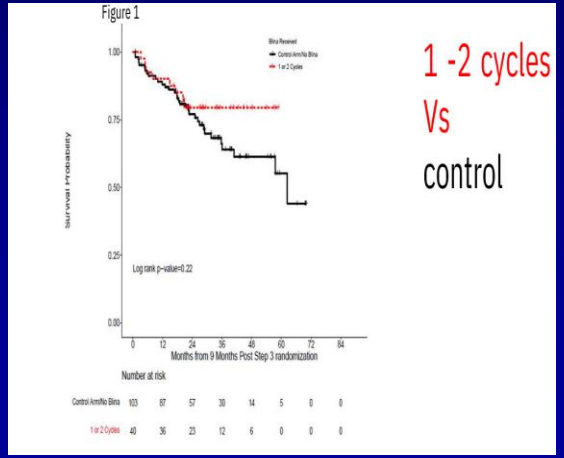
Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

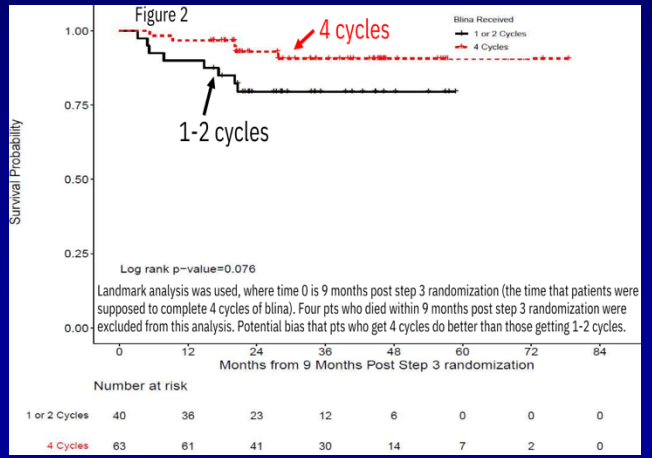
E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD–: Outcomes by Number of Cycles

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

# cycles	121
1	12
2	32
3	4
4	**63 (52%)**



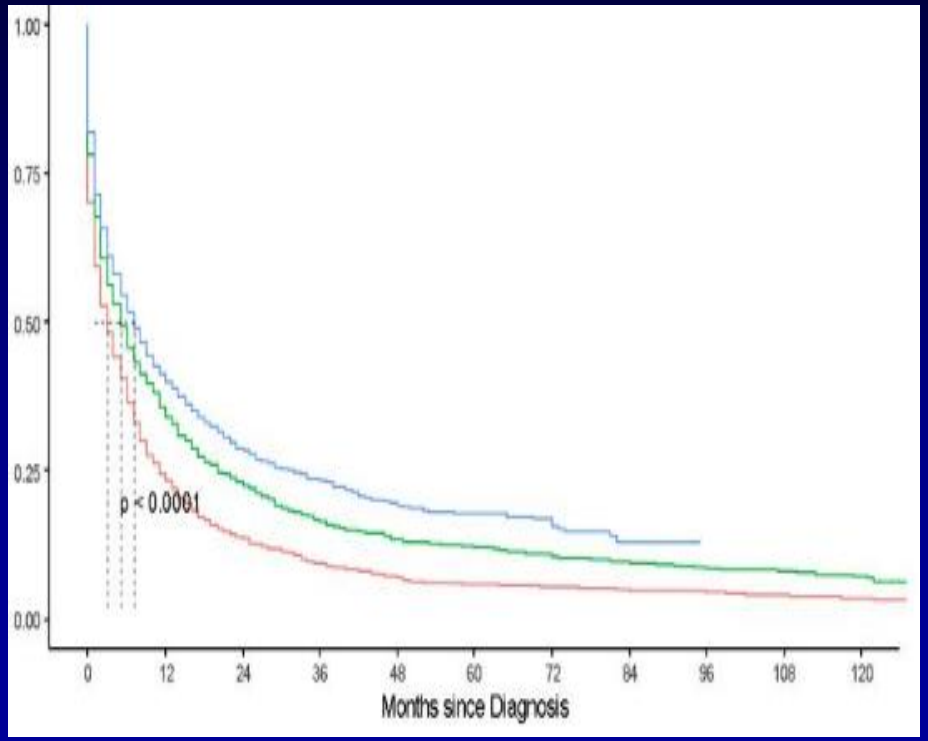


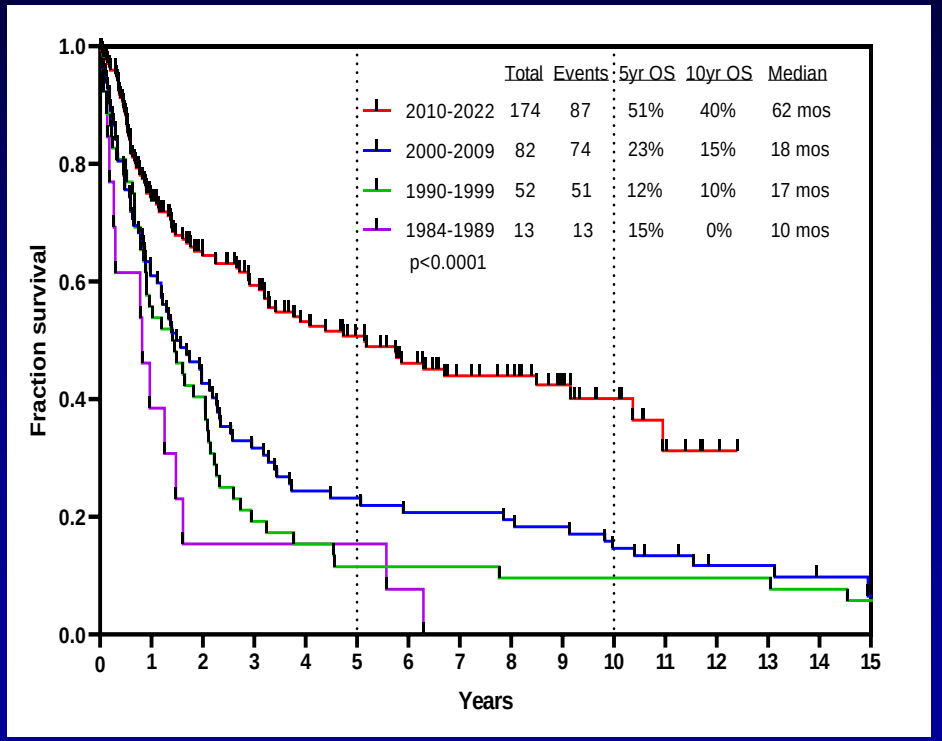


Luger. *Blood.* 2023;142:abstract 2877.

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

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

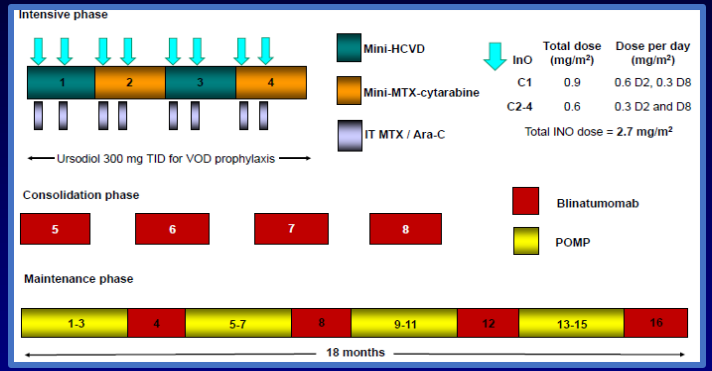




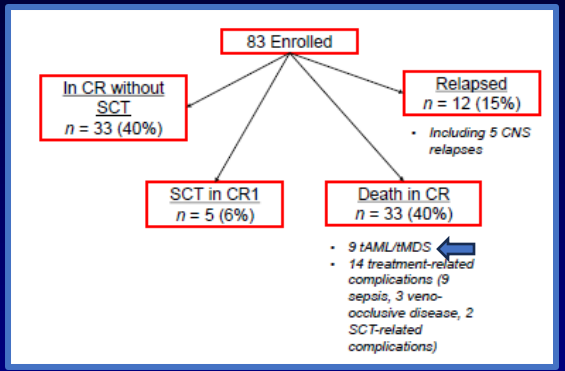
Gupta. *Blood.* 2022;140:abstract 1379.

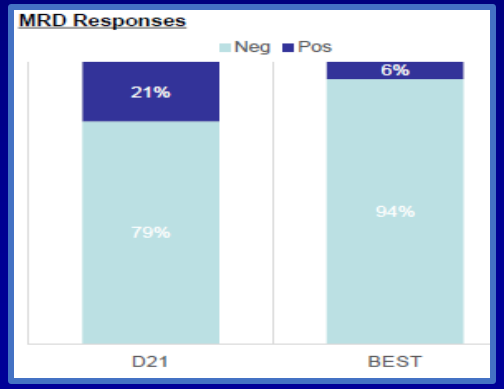
Mini-HCVD + INO ± Blina in Older ALL (N=83)

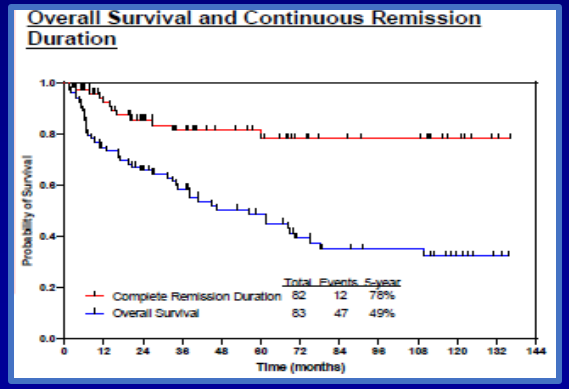
- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: *TP53* 39%; Ph-like 18%; poor cytogenetics 23%
- ORR 99% (CR 90%); MRD negativity 94% (79% at CR)



Characteristic	Category	N (%) / Median [range]
Age (years)	≥70	68 [60 - 87] 28 (34)
Cytogenetics	Diploid HeH Ho-Tr Tetraploidy Complex t(4;11) Misc IM/ND	27 (33) 5 (6) 12 (14) 3 (4) 3 (4) 1 (1) 16 (19) 16 (19)
CD19 (%)		99.6 [26-100]
CD22 (%)		96.9 [27-100]
CD20	≥20%	46/76 (61)
Ph-like ALL		9/50 (18)
TP53 mutation		25/64 (39)





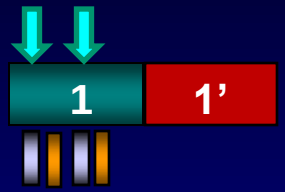


- Median F/U 88 months
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; 6%)
- Death due PD/NR: 12/83 (15%); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (11%); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: 33/83 (40%); 11/28 (39%) in pts ≥70 yrs
- 14/33 deaths (42%) Rx related (9 sepsis, 3 VOD, 2 ASCT)

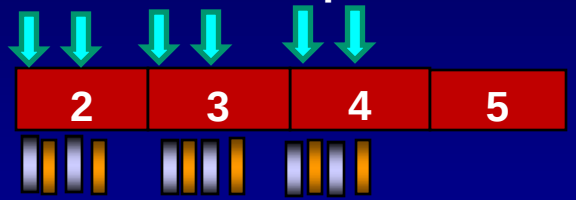
Jen. *Blood.* 2023;142:abstract 2878.

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

Induction (D1-14)



Consolidation phase



Maintenance phase

Dexa 20 mg D1-4 and VCR 1 mg D4

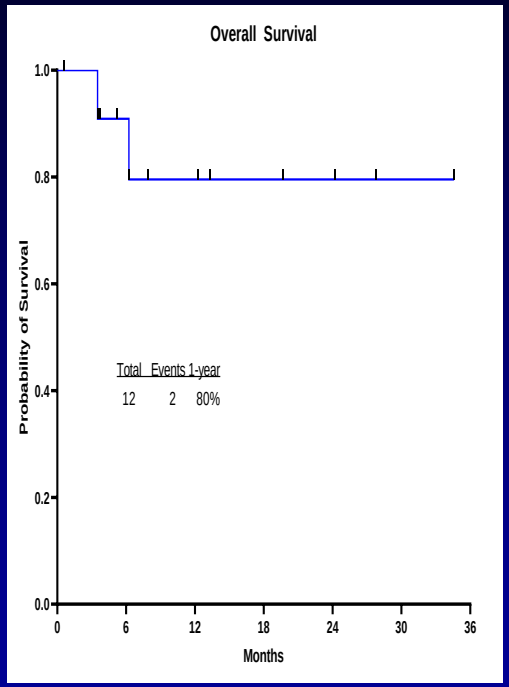
Blinatumomab

IT MTX, Ara-C Rituximab if CD20+

1' Blinatumomab for 2 weeks

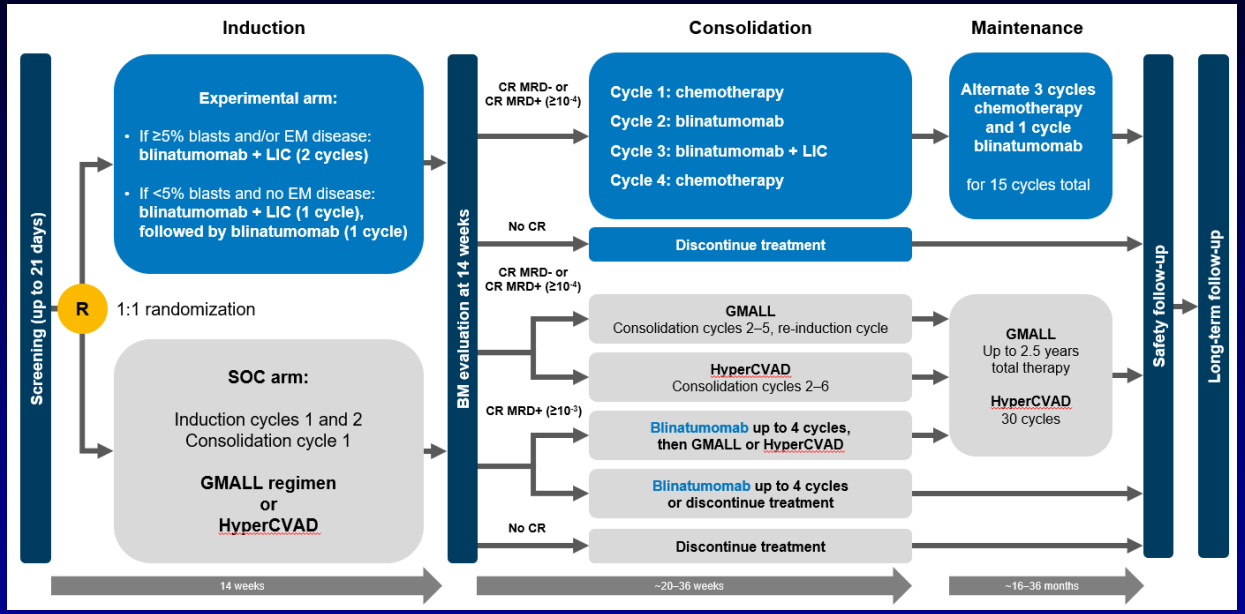
INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2-C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²



*Ursodiol 300 mg tid for VOD prophylaxis

Blina + Low-Intensity ChemoRx in Older Pre-B ALL: Golden Gate Safety Run-In Results of Phase III



Characteristic	N=10
Age, median (range), years	69 (57–77)
≥70, n (%)	4 (40)
≥55 to <70, n (%)	6 (60)
>40 to <55, n (%)	0

Response	After cycle 1 (N=10)	After cycle 2 (N=10)
Disease response available, n	10	9
Complete remission	10	8
MRD response	9	7
MRD complete response	7	5
MRD nonresponder	1	1
CRh	0	0
CRi	0	0
Blast-free hypoplastic or aplastic BM without CRh or CRi	0	0
Nonresponse	0	0
Relapse	0	1
PD	0	0
PR	0	0

- 10 pts; median age 69 yrs (57–77); 40% ≥70 yrs
- 9/10 had molecular response after C1; 7/10 MRD-negative CR
- No grade ≥3 CRS or ICAN

Jabbour E, et al. ASH 2022; Abstract 2732;
NCT04994717. Available at https://clinicaltrials.gov/ct2/show/NCT04994717. Accessed January 2024.

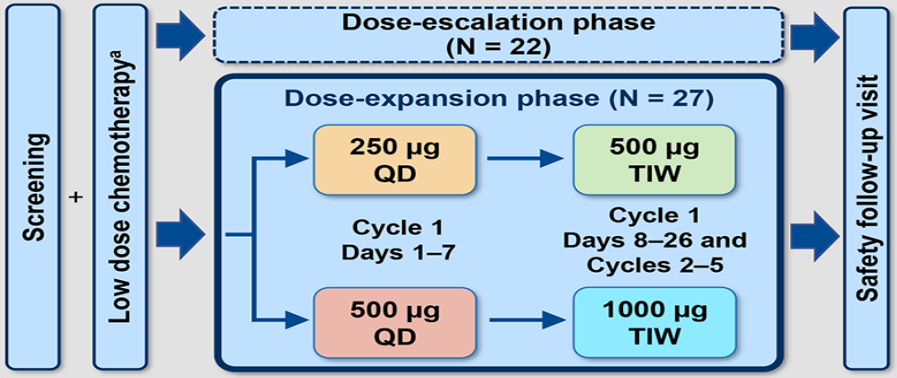
Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia

Results from the expansion phase of a phase 1b trial

Objective

To assess the efficacy and safety of subcutaneous blinatumomab in heavily pretreated adults with R/R B-ALL at two doses

Study Schema



Results

Efficacy

250 µg QD/500 µg TIW (N = 14)
- CR/CRh: 85.7%
- MRD-neg CR/CRh: 75%

500 µg QD/1000 µg TIW (N = 13)
- CR/CRh: 92.3%
- MRD-neg CR/CRh: 100%

Dosing regimen 500 µg QD/1000 µg TIW demonstrated higher MRD-negative CR/CRh within 2 cycles (100%) compared with dosing regimen 250 µg QD/500 µg TIW (75%)

Safety

250 µg QD/500 µg TIW (N = 14)
- Grade ≥3 CRS[b]: 21.4%
- Grade ≥3 NE[b]: 42.9%

500 µg QD/1000 µg TIW (N = 13)
- Grade ≥3 CRS[b]: 23.1%
- Grade ≥3 NE[b]: 23.1%

- SC injections were well tolerated
- No treatment-related grade 4 CRS or NE

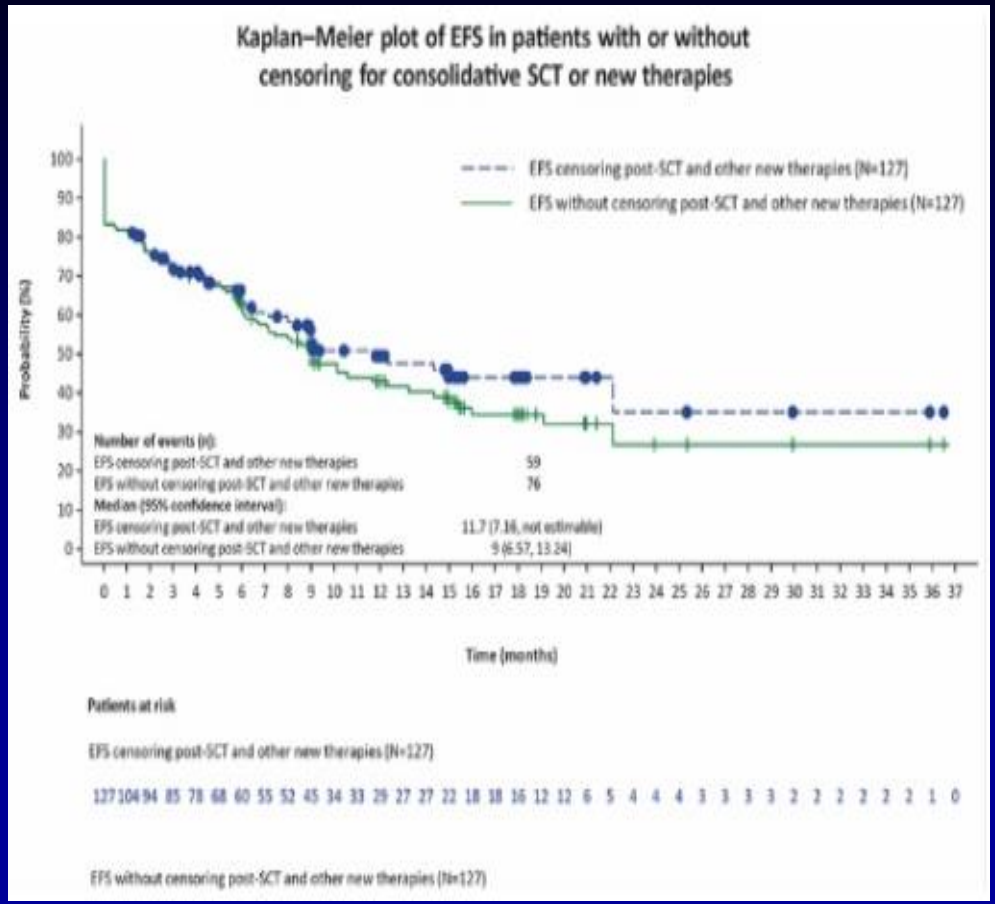
Conclusion

Treatment with single agent SC blinatumomab resulted in a high CR rate, high MRD-negativity rate, and an acceptable safety profile in heavily pretreated adults with R/R B-ALL

Jabbour E, et al. *Am J Hematol.* 2024, In press

Obecaptagene Autoleucel (OBE-CEL) in Adult R/R ALL (FELIX)

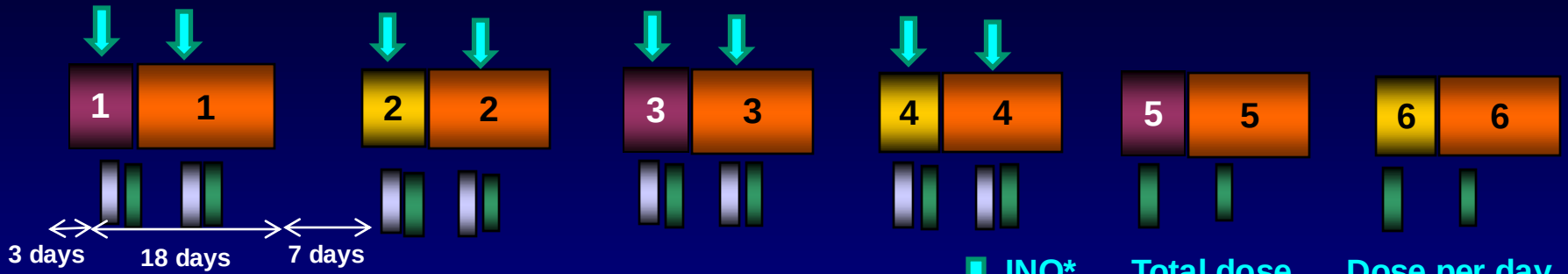
- AUTO 1 fast off-rate CD19 binder CAR T
- 153 enrolled, 127 (83%) infused. Median age 47 yrs
- Prior blina 42%, ino 31%, allo SCT 44%
- cCR-CRi 99/127 = 78% (99/153 = 65%). 19/77 allo SCT
- Loss of CAR T = HR 2.9
- 12-mos EFS 49%, 12-mos OS 61%



Jabbour E, et al. *J Clin Oncol.* 2024;24:S6504; Roddie et al. *HemaSphere.* 2024;8:S114.

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

Induction phase: C1–C6



INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Consolidation phase

CAR T Consolidation

Mini-HCVD

Mini-MTX, Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

Leukemia Questions?

- Email: ejabbour@mdanderson.org
- Cell: 713-498-2929
- Office: 713-792-4764

Global Leukemia Academy

Q&A

APTITUDE HEALTH®

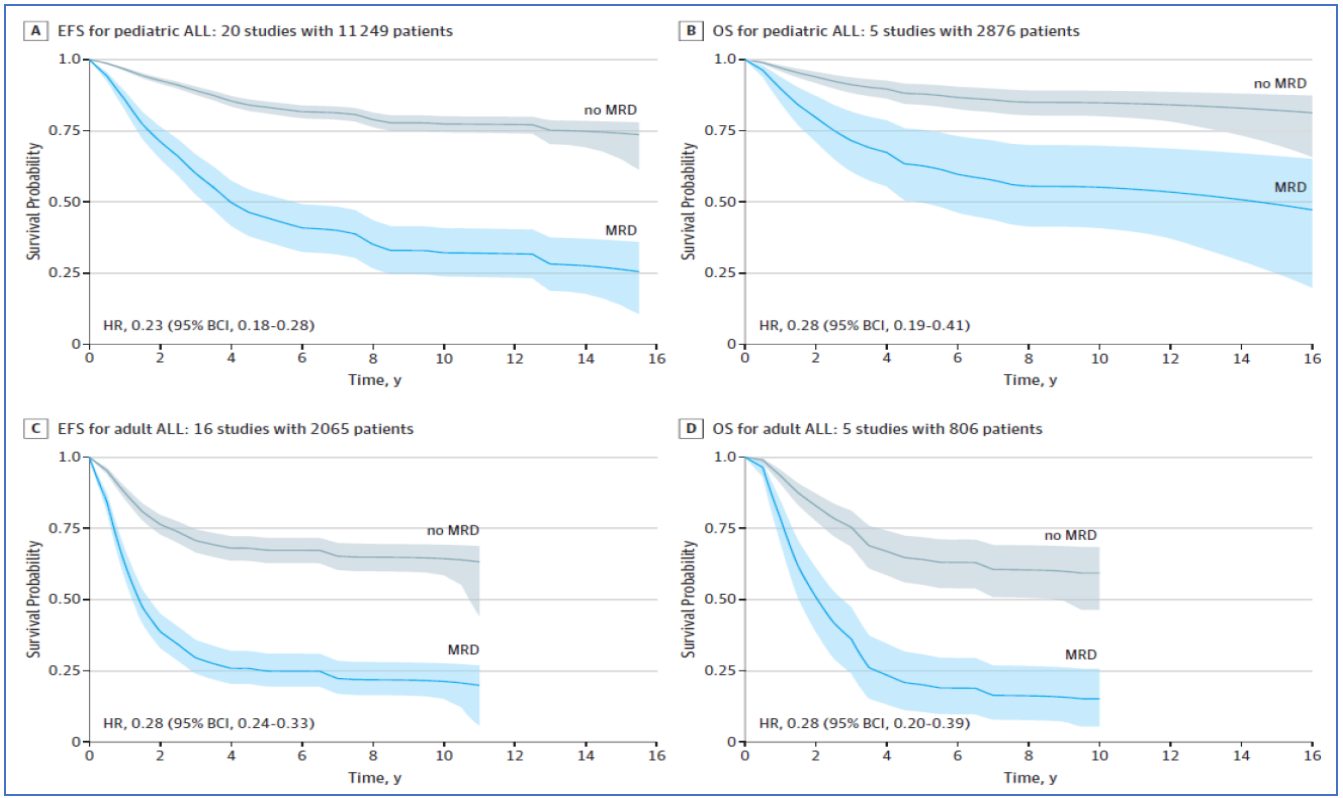
Global Leukemia Academy

Review of prognostic value of MRD in leukemias (focusing on ALL)

Josep-Maria Ribera

APTITUDE HEALTH®

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

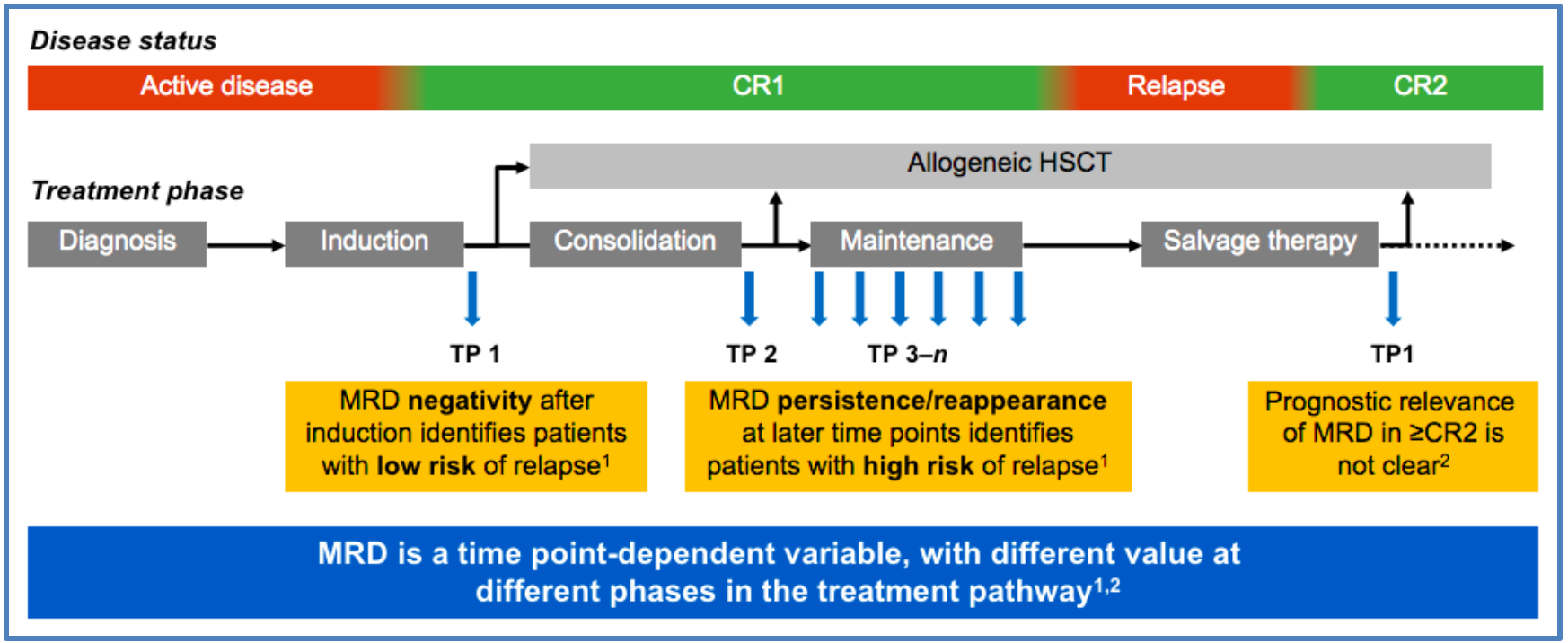


Meta-analysis of 20 pediatric ALL trials >11,000 patients

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

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

Time Points to MRD Detection

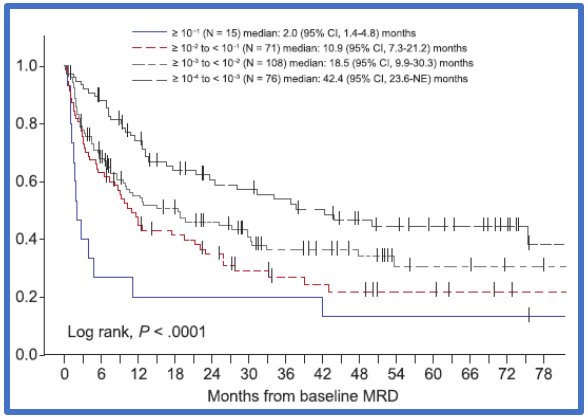


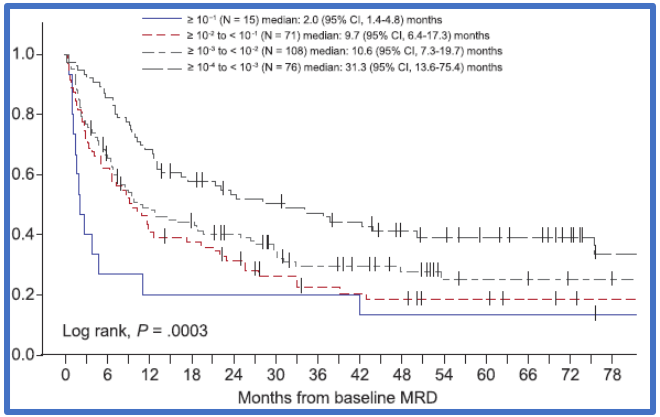
- **Negative** MRD at **TP1**: useful for recognizing patients with **low risk** of relapse
- **Positive** MRD at **TP2**: useful for recognizing patients with **high risk** of relapse

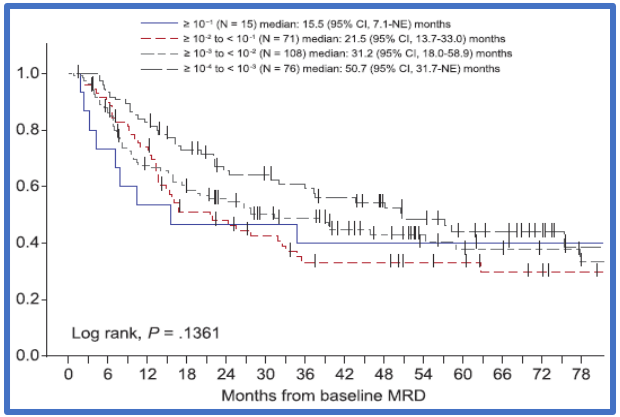
1. Brüggemann M, Kotrova M. *Blood Adv.* 2017;1:2456-2466; 2. Jabbour E, et al. *Cancer.* 2017;123:294-302.

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

RFS

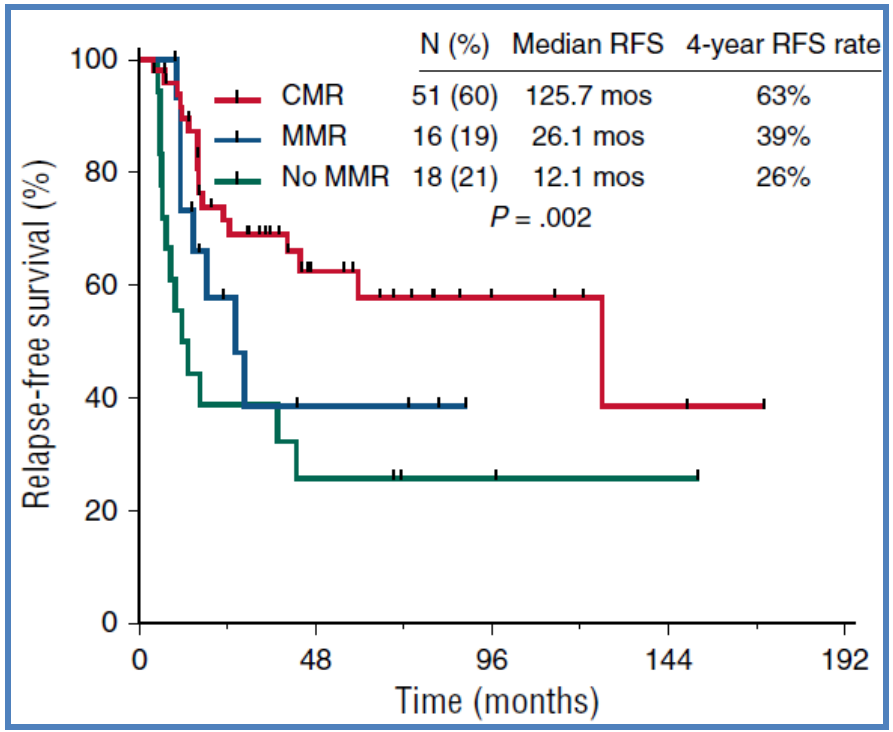
≥10^{-1} (N=15) median 2 months
≥10^{-1} to <10^{-2} (N=71) median 9.7 months
≥10^{-2} to <10^{-3} (N=108) median 10.6 months
≥10^{-3} to <10^{-4} (N=76) median 31.3 months

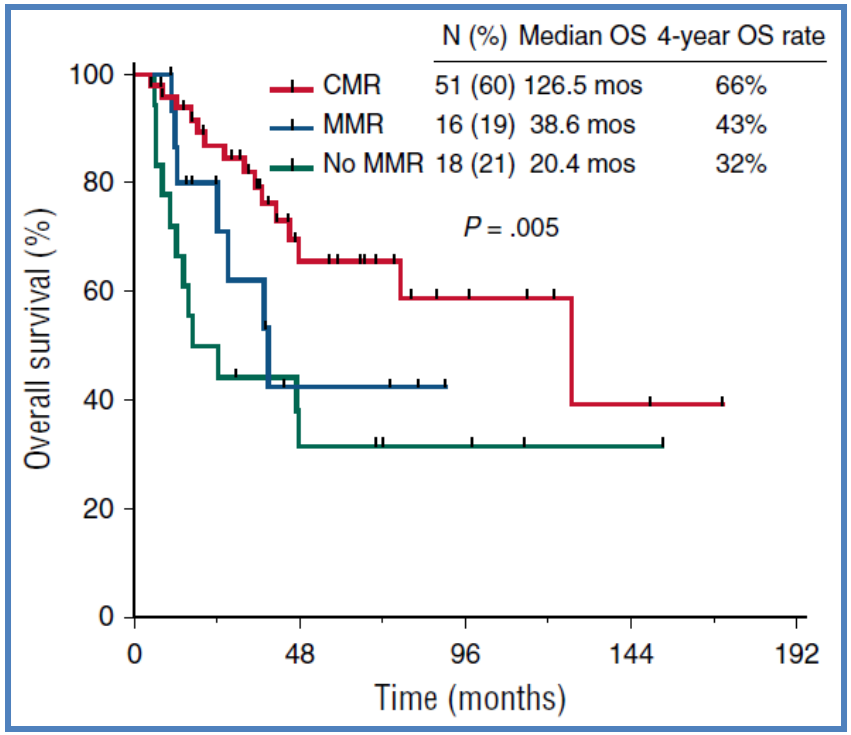
OS

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

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

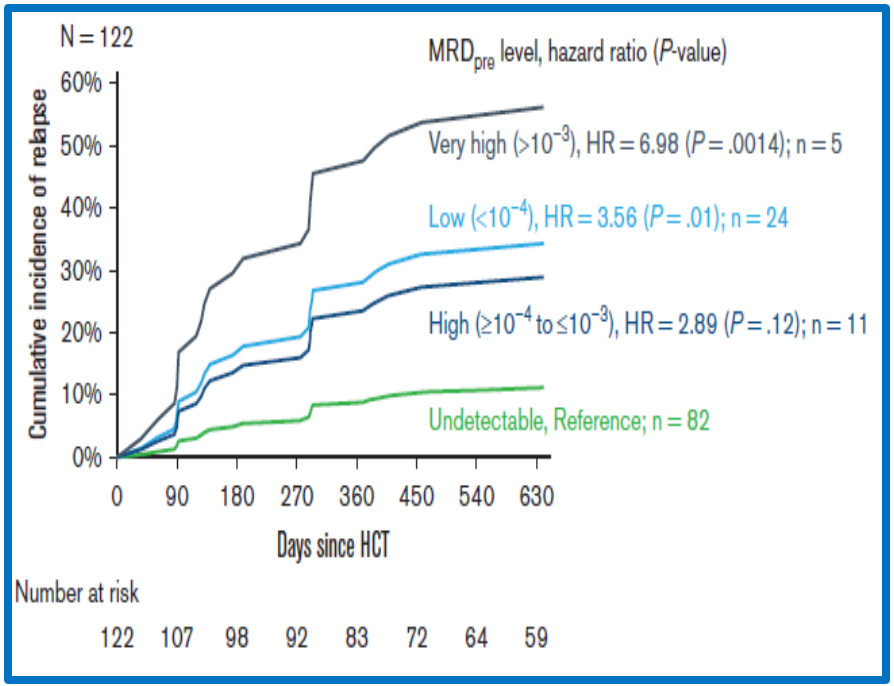
CMR at 3 Months: The Best Prognostic Factor in Ph+ ALL

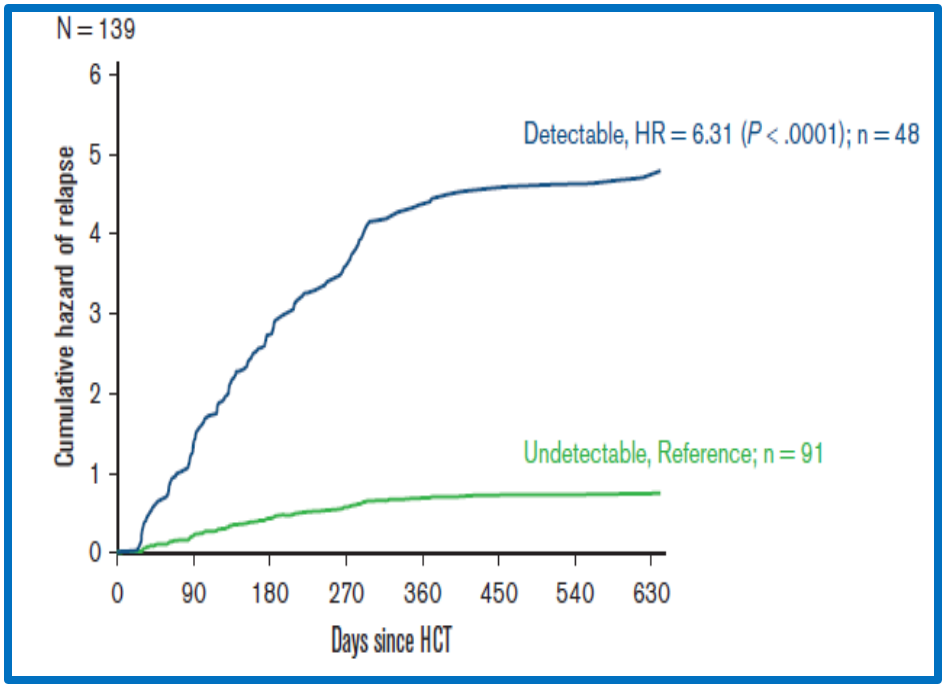




Short NJ, et al. *Blood*. 2016;128:504-507.

Detectable pre-HSCT MRD, Even at Level of <10^{-4}, and Any Detectable post-HSCT MRD Increase the Risk of post-HSCT Relapse





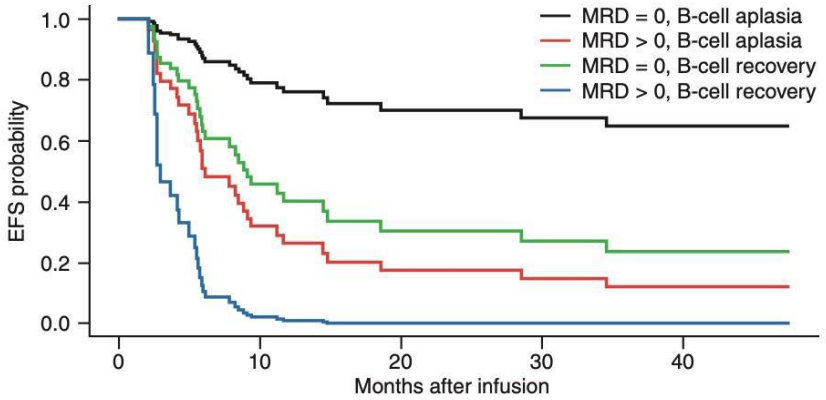
Liang EC, et al. *Blood Adv.* 2023;7(14):3395-3402.

NGS MRD on Day 28, Months 3 and 6 After Tisa-Cel Predicts Outcome

A

	HR (95% CI)	*P*
Day 28 NGS-MRD status		
MRD = 0	—	—
MRD > 0	4.87 (2.18–10.8)	<0.001
B-cell recovery	3.33 (1.44–7.69)	0.005

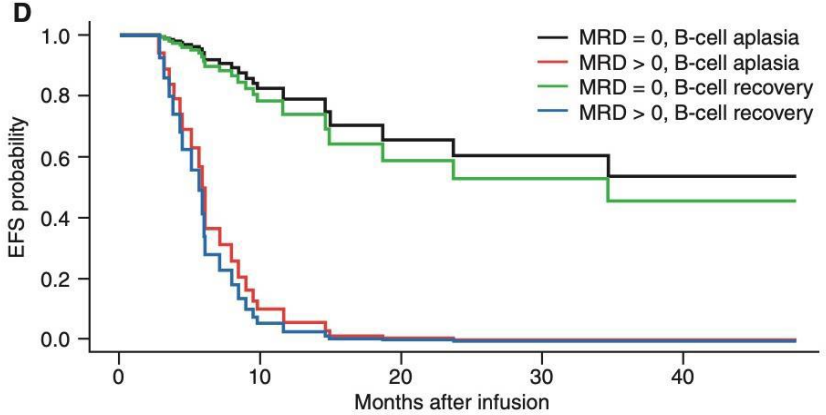
B



C

	HR (95% CI)	*P*
Month 3 NGS-MRD status		
MRD = 0	—	—
MRD > 0	12.0 (2.87–50.0)	<0.001
B-cell recovery	1.27 (0.33–4.79)	0.7

D



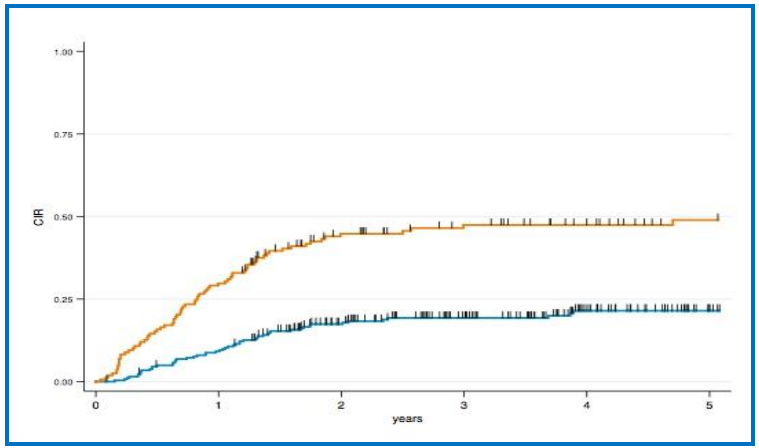
Pulsipher MA, et al. *Blood Cancer Discov*. 2022;3:66-81.

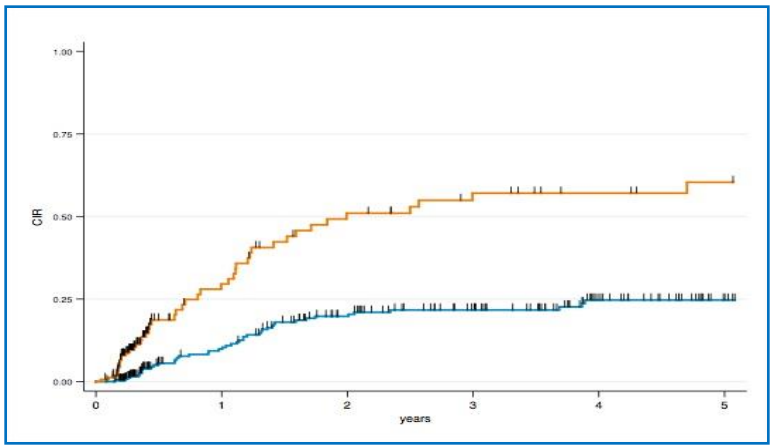
MRD Is Not a Perfect Predictive Factor in Adult Ph– ALL

Post-induction Ig-TCR MRD

$\geq 10^{-4}$

$< 10^{-4}$





	Without AlloHSCT Censoring	With AlloHSCT Censoring
5-yr CCR in MRD+ pts	51.2%	39.6%
5-yr CIR in MRD– pts	21.2%	24.7%
Harrel's C-index	0.63	0.64

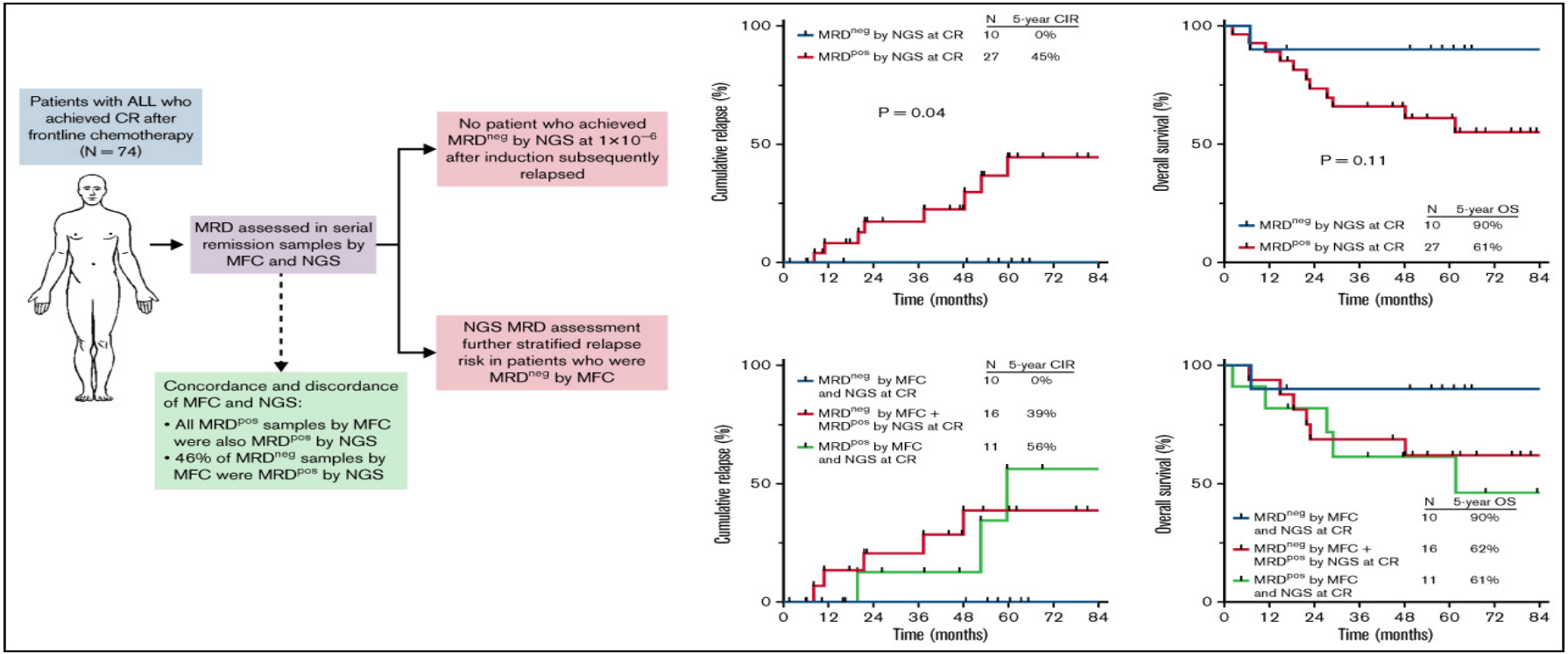
Courtesy of H. Dombret.

Beldjord K, et al. *Blood.* 2014;123:3739-3749; GRAALL data on file.

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

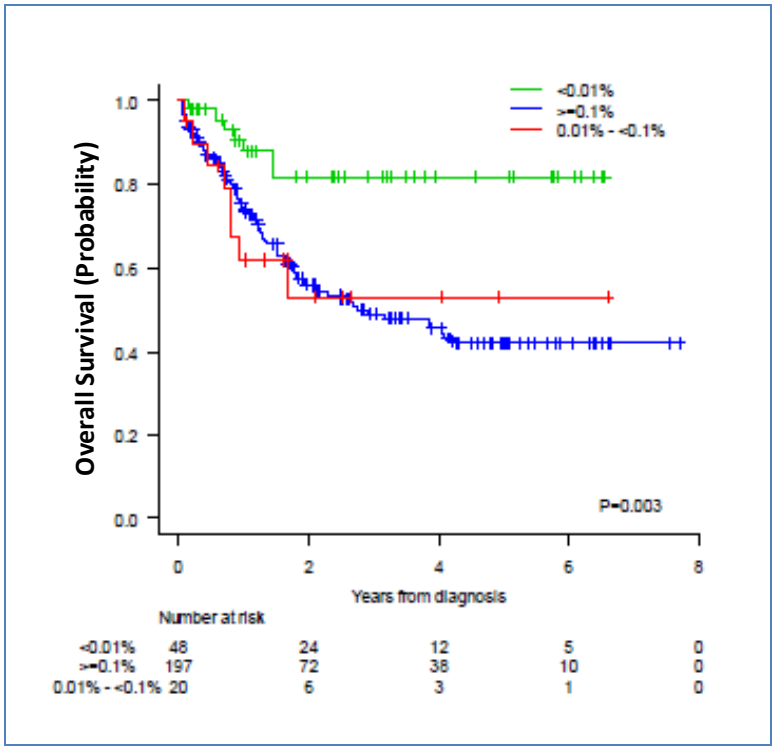


Predictive value of MRD increases with increasing sensitivity!

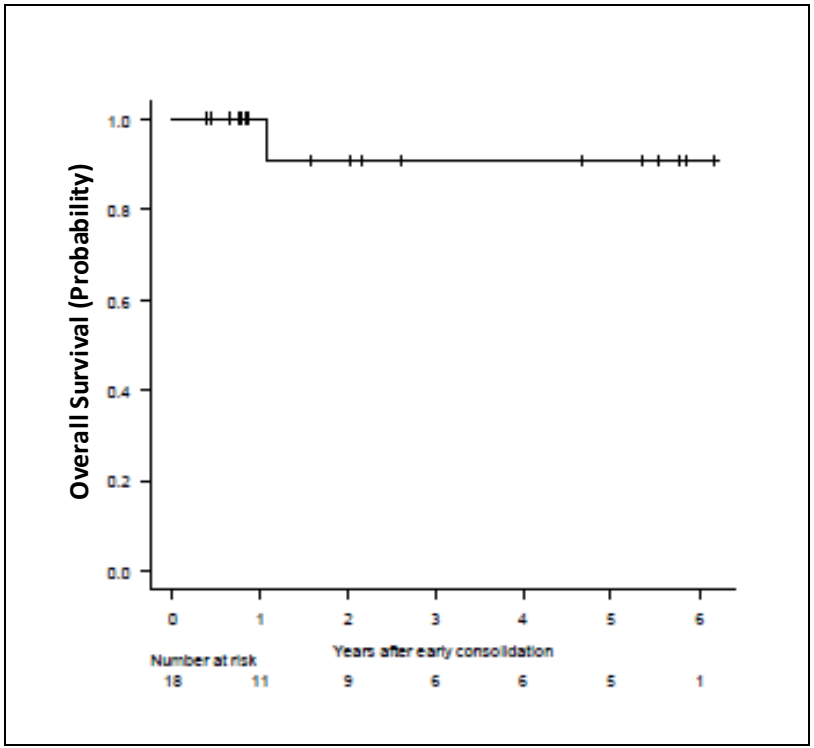
Short N, et al. *Blood Adv.* 2022;6(13):4006-4014.

Outcomes in Ph– ALL by MRD Centrally Assessed by Next-Generation FCM (sensitivity 2 × 10^{-6})

According to post-induction MRD level



Patients with MRD <0.01% from d14



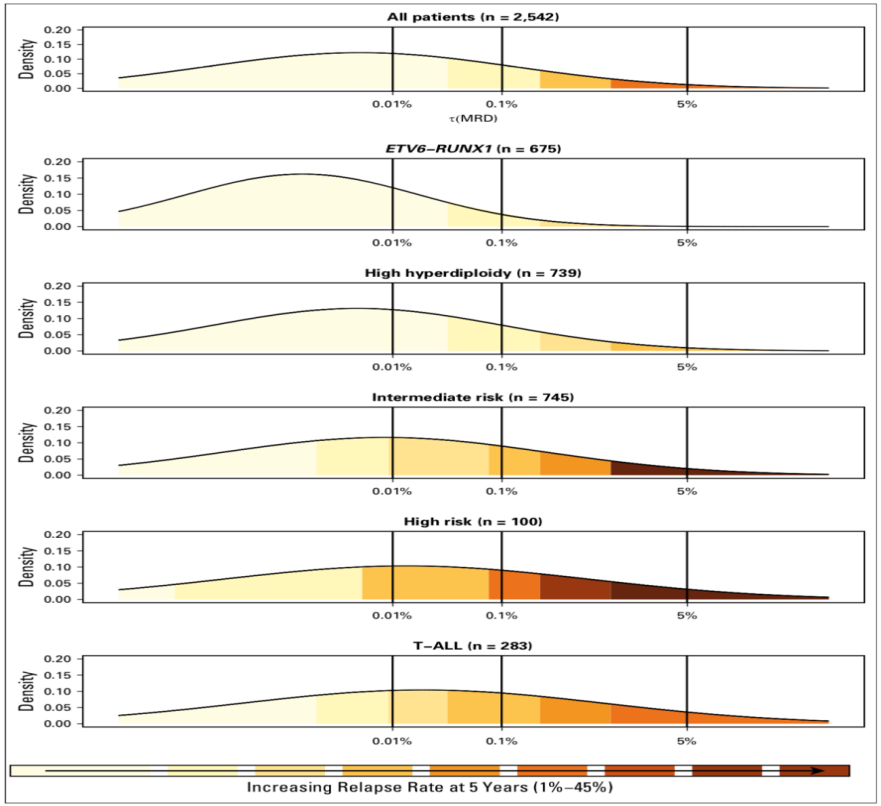
Ribera JM, et al. *Blood.* 2021;137(14):1879-1894.

Value of MRD According to Genetic Subgroups (pediatric ALL)

- **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.

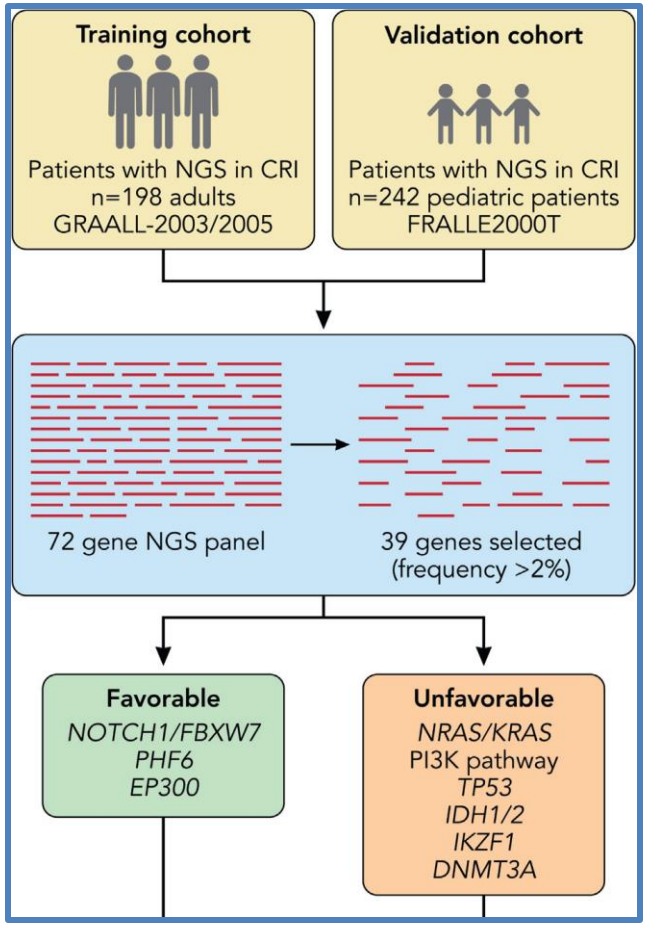
End-Induction NGF MRD Level According to the Genetic Subgroups of BCP ALL

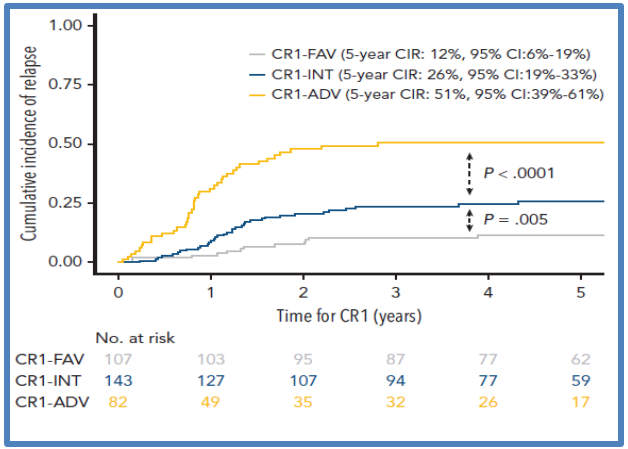
BCP ALL subtype	MRD end Ind-1 (d+35)	
	<0,01%	≥0,01%
B-other (n=53)	53%	47%
Ph-like (n=15)	27%	73%
KMT2Ar (n=15)	53%	47%
Low-hypodiploid (n=9)	33%	67%
PAX5 P80R (n=10)	100%	0%
High-hyperdiploid (n=8)	75%	25%
t(1;19)/TCF3::PBX1 (n=6)	83%	17%

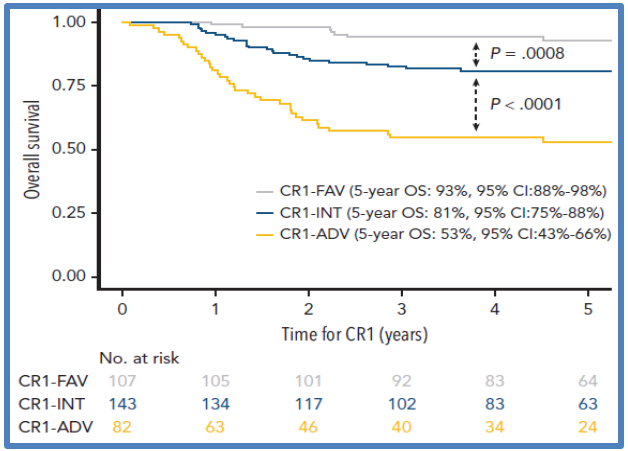
BCP ALL subtype	MRD end Ind-1 (d+35)	
	<0,001%	≥0,001%
B-other (n=53)	40%	60%
Ph-like (n=15)	13%	87%
KMT2Ar (n=15)	33%	67%
Low-hypodiploid (n=9)	33%	67%
PAX5 P80R (n=10)	90%	10%
High-hyperdiploid (n=8)	63%	37%
t(1;19)/TCF3::PBX1 (n=6)	67%	33%

Ribera J, et al. SOHO 2022.

New Risk Classifier for T-ALL





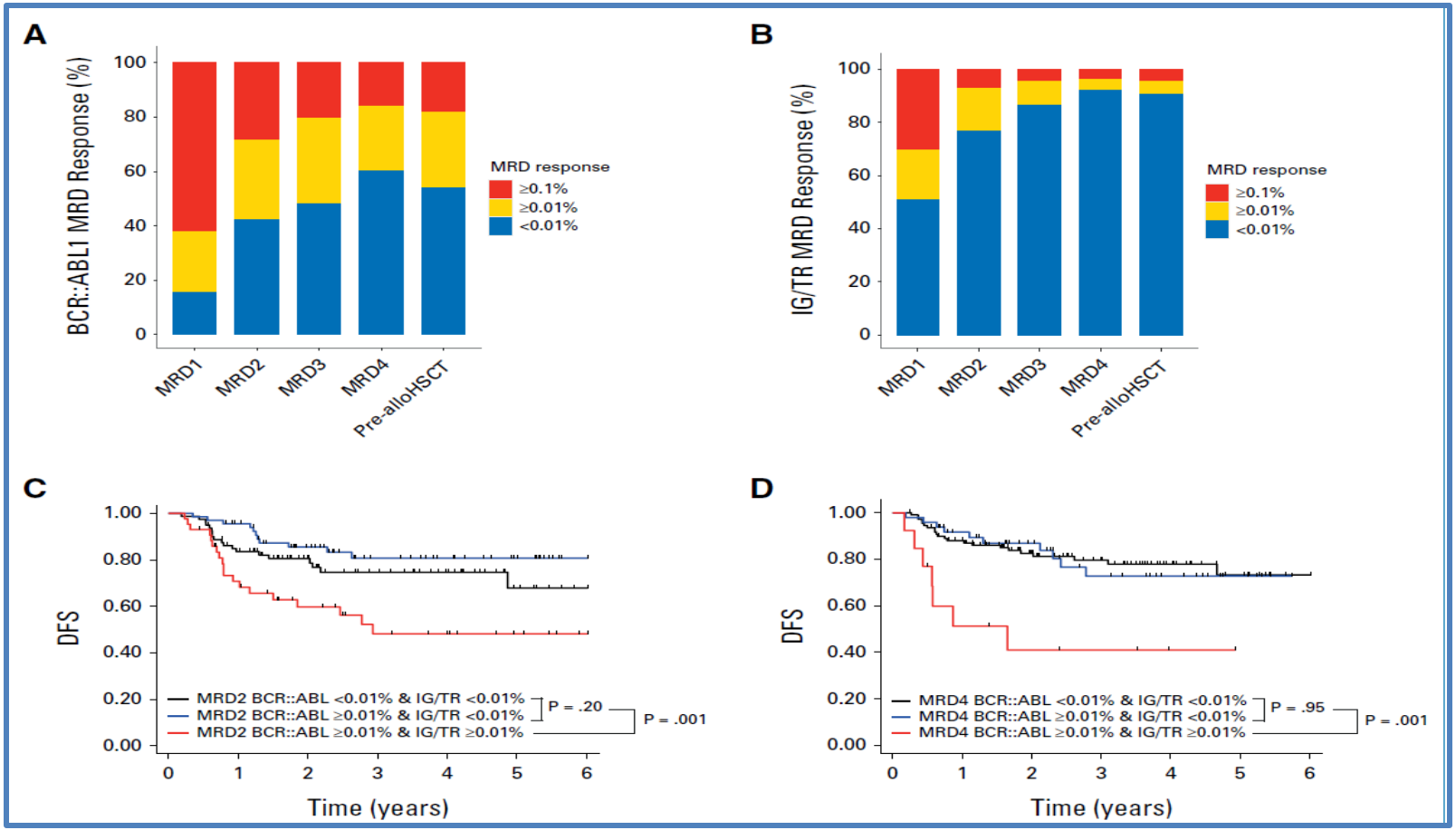


High-Risk classifier

- **WBC** >200 × 10^9/L
- EOI IG/TCR **MRD** >0.01%
- Unfavorable **NGS**

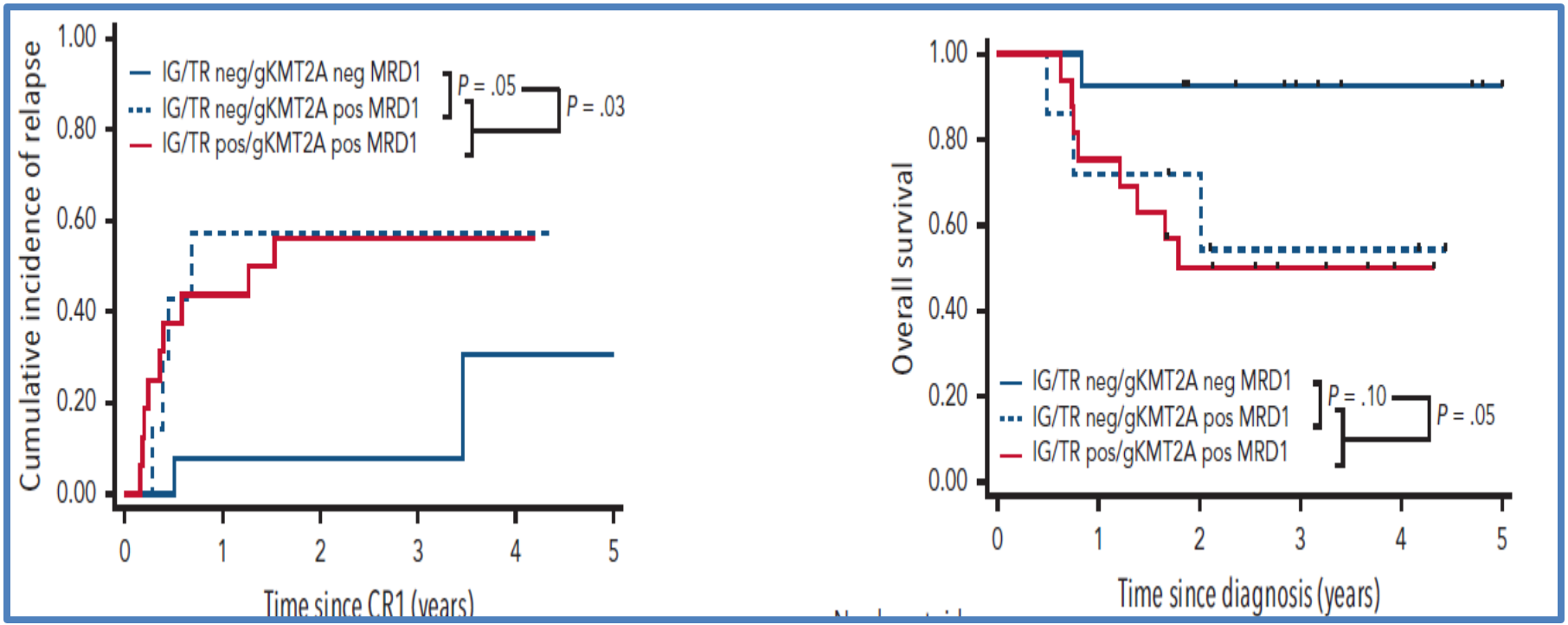
Simonin M, et al. *Blood*. 2024;144:1570-1580.

Ig/TCR PCR Better Than BCR::ABL for Ph+ ALL



Kim R, et al. *J Clin Oncol.* 2024;42:3140-3150.

PCR for KMT2A Better Than PCR for IG/TCR in KMT2Ar ALL

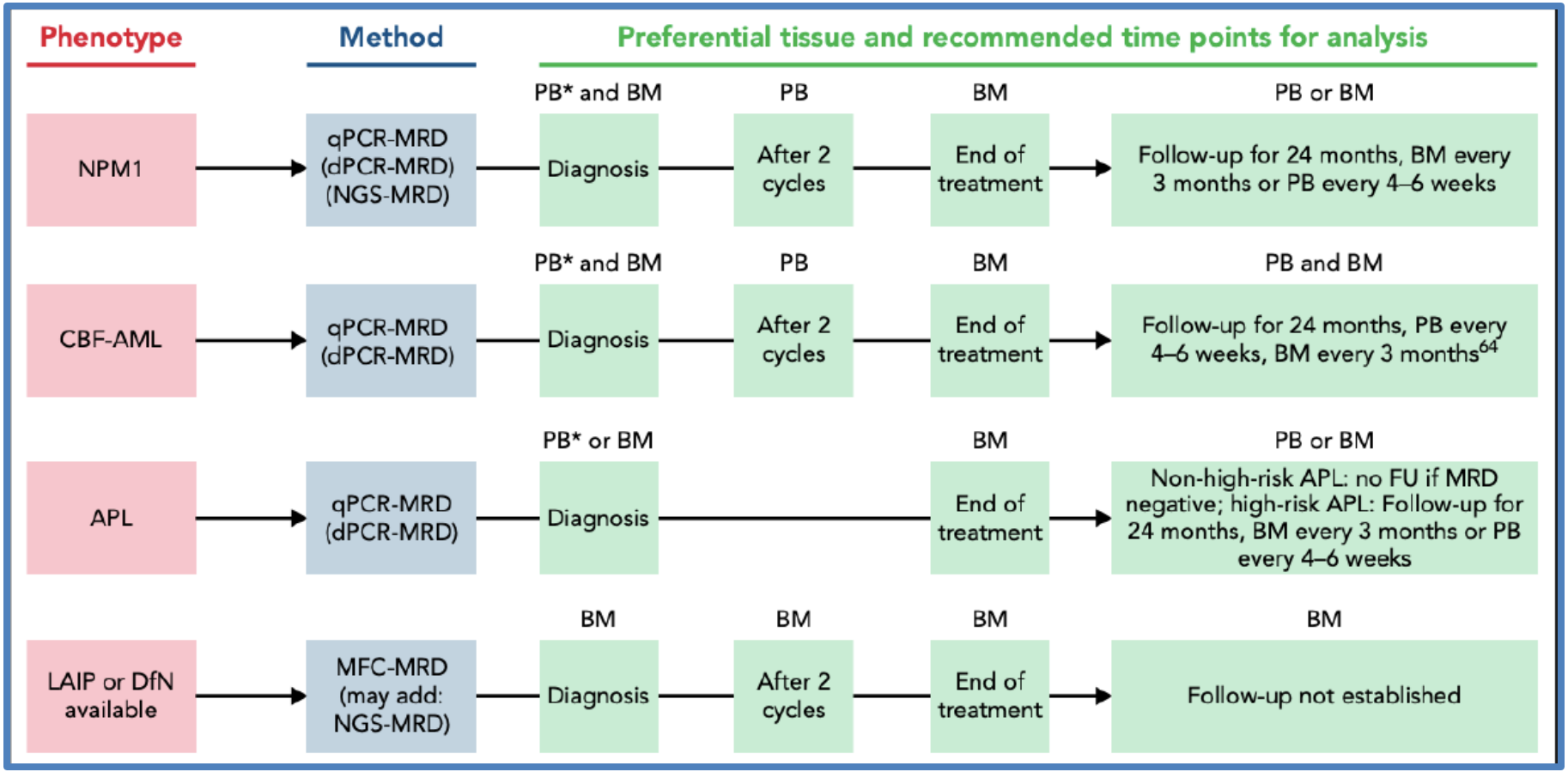


Kim R, et al. *Blood*. 2023;142:1806-1817.

MRD Method and ALL Subtype

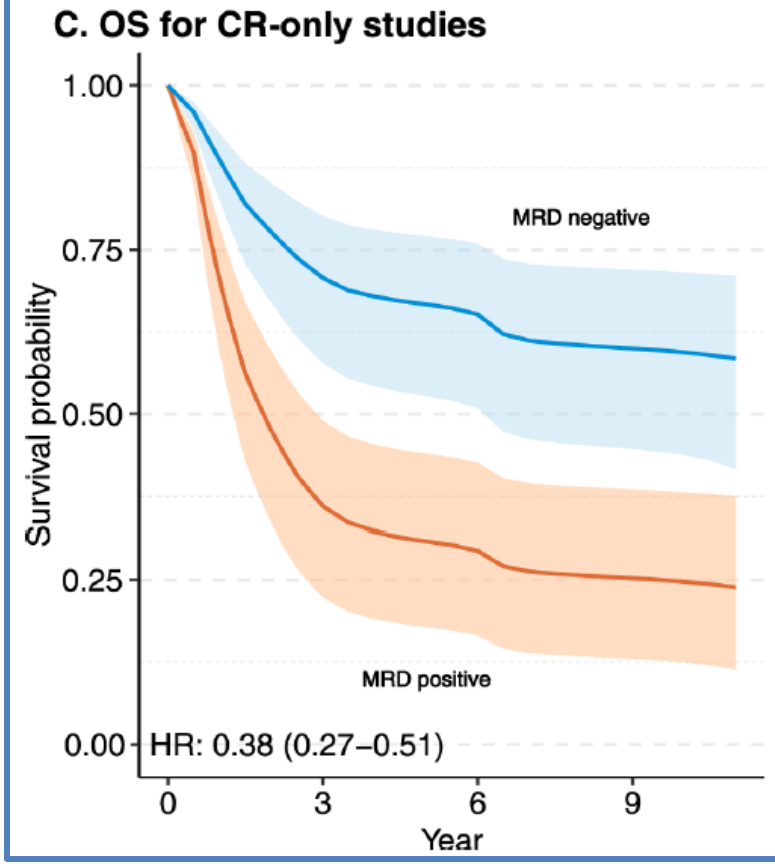
	NGF	Ig/TCR (RT qPCR)	Ig/TCR (NGS)	qPCR BCR::ABL1	qPCR KMT2A::X
Ph–	**OK**	**OK**	**OK**		
Ph+	?	**OK**	**OK**	OK?	
KMT2A r	OK?	OK?	OK?		**OK**
T-ALL	**OK**	**OK**	**OK**		

ELN Recommendations for MRD in AML

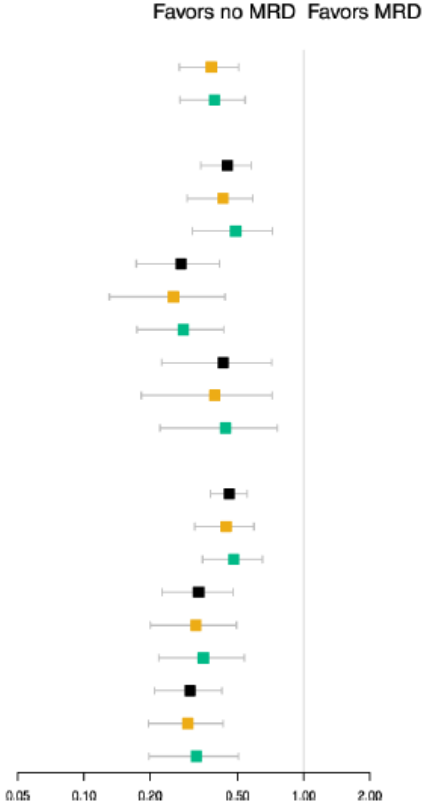


Heuser et al. *Blood.* 2021.

Impact of End-Induction and Consolidation MRD on OS in AML



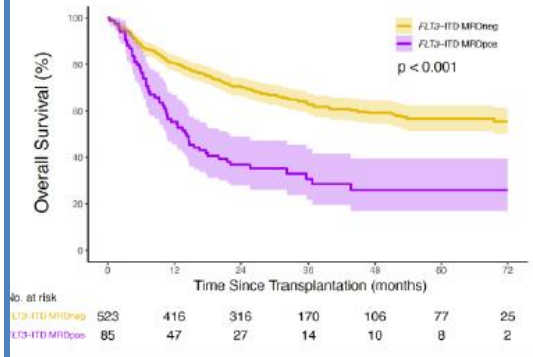
Subgroup	HR (95% CrI)
CR status	
CR only	0.38 (0.27–0.51)
Mixed responses	0.39 (0.27–0.54)
MRD detection method	
MFC	0.45 (0.34–0.58)
CR only	0.43 (0.30–0.59)
Mixed responses	0.49 (0.31–0.72)
PCR	0.28 (0.17–0.41)
CR only	0.25 (0.13–0.44)
Mixed responses	0.28 (0.17–0.43)
Others	0.43 (0.23–0.72)
CR only	0.39 (0.18–0.72)
Mixed responses	0.44 (0.22–0.76)
MRD detection time	
Induction	0.46 (0.38–0.55)
CR only	0.44 (0.32–0.59)
Mixed responses	0.48 (0.35–0.65)
Consolidation	0.33 (0.23–0.48)
CR only	0.32 (0.20–0.49)
Mixed responses	0.35 (0.22–0.54)
After consolidation	0.30 (0.21–0.42)
CR only	0.30 (0.20–0.43)
Mixed responses	0.32 (0.20–0.51)

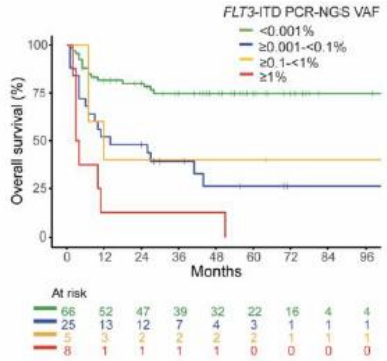


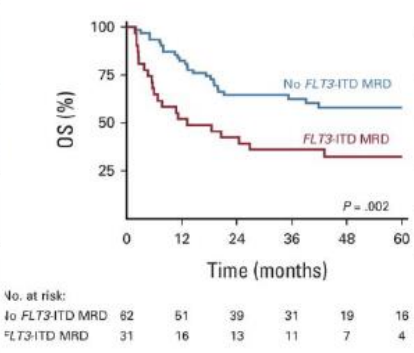
Short N, et al. *Leukemia*. 2022.

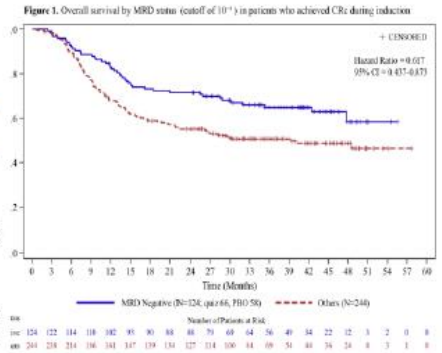
NGS-Based MRD Assessment in FLT3 ITD AML

Study	N	Timepoint	Cohort	Reference
Pre-MEASURE	608	CR1 pre-alloHCT	CIBMTR (111 sites, 2013-2019)	JAMA PMID: 36881031
Loo *et al.*	104	CR1/2 pre-alloHCT	MRC AML17 (n=55, 2009-2014) Alfred/PeterMac (n=49, 2010-2020)	Blood PMID: 35960851
Grob *et al.*	161 (93 alloHCT)	CR1 after induction	HOVON/SAKK trials (HO42A AML, HO102 AML, and HO132)	JCO PMID: 36315929
Erba *et al.*	318	CR1 after induction	QuANTUM-First (Ph3 RCT)	Lancet PMID: 37116523
Levis *et al.*	356	CR1 pre-alloHCT	BMT-CTN 1506 (MORPHO, Ph3 RCT)	JCO PMID: 38471061



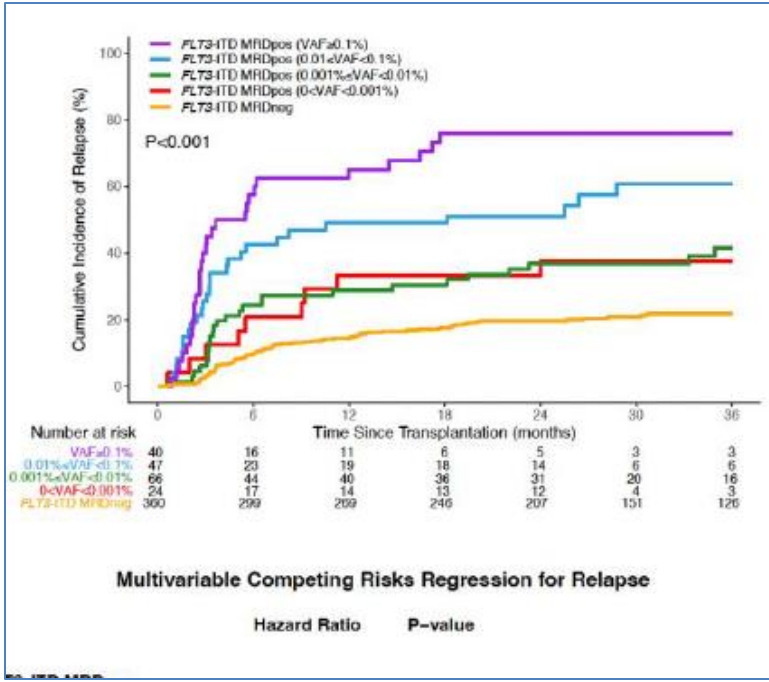


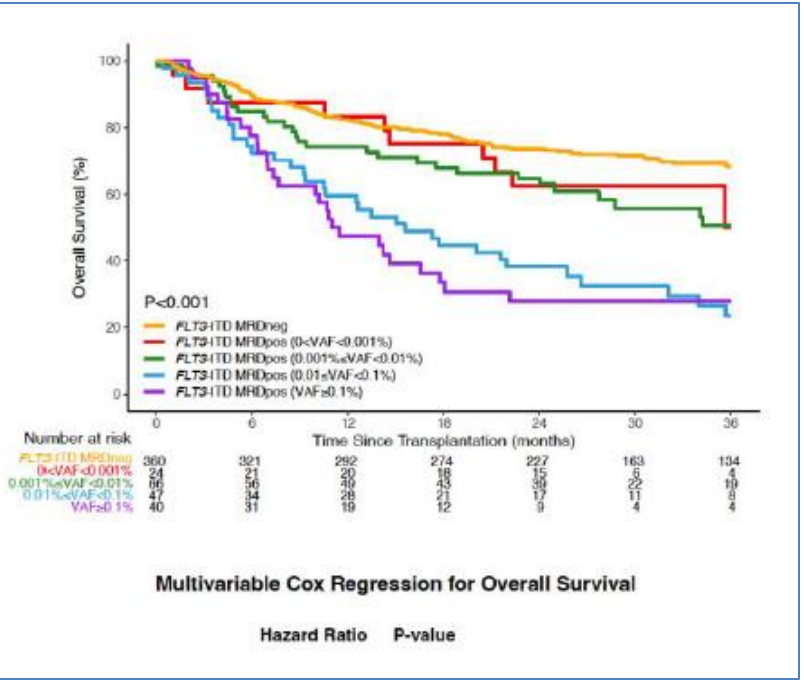




Hourigan C, et al. SOHO 2024.

MRD Burden Before HSCT: The Case of FLT3 ITD AML





Poorest outcomes for FLT3 ITD MRD+ VAF >0.01%

Dillon LW, et al. *JAMA Oncol.* 2024;10:1104-1110.

Potential Uses of MRD in AML

- **Deep quantification of antileukemia efficacy** (*e.g.: log reduction after 2 cycles*)
- **Early relapse detection and intervention during sequential monitoring**
- **Therapeutic assignment** (*e.g.: selection of transplant intensity where otherwise equipoise*)
- **Patient selection for clinical trials** (*e.g.: high risk group of unmet need*)
- **As a surrogate endpoint for overall survival for regulatory approval**

The trouble of MRD as a surrogate endpoint for AML therapy is that it is just not fully standardized

MRD in ALL and AML

- **ALL**
  - Prognostic relevance (most important factor), well standardized, useful as surrogate marker. Additional relevance of WBC count (still resist!) and genetic subtype
- **AML**
  - Prognostic significance in specific subtypes, not well standardized, potential use of surrogate marker

Global Leukemia Academy

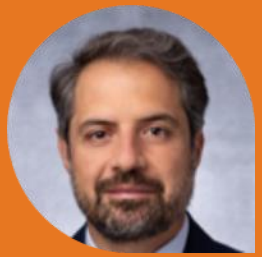
Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Best practices for first-line treatment in ALL

Elias Jabbour



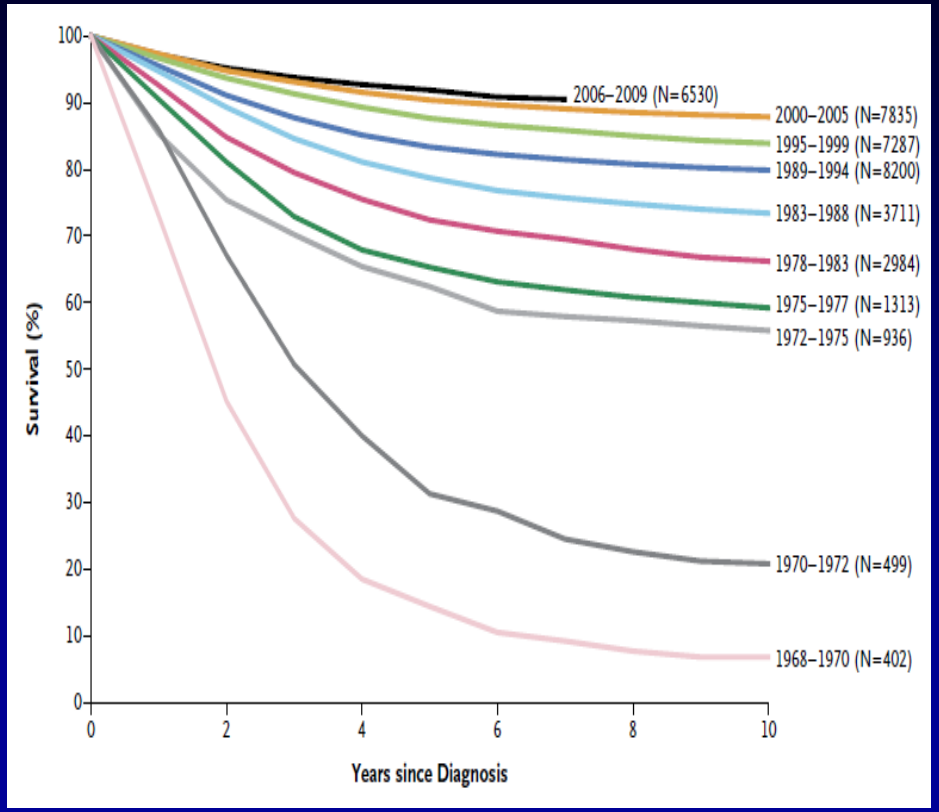
APTITUDE HEALTH®

Integration of Immunotherapy in Newly Diagnosed ALL

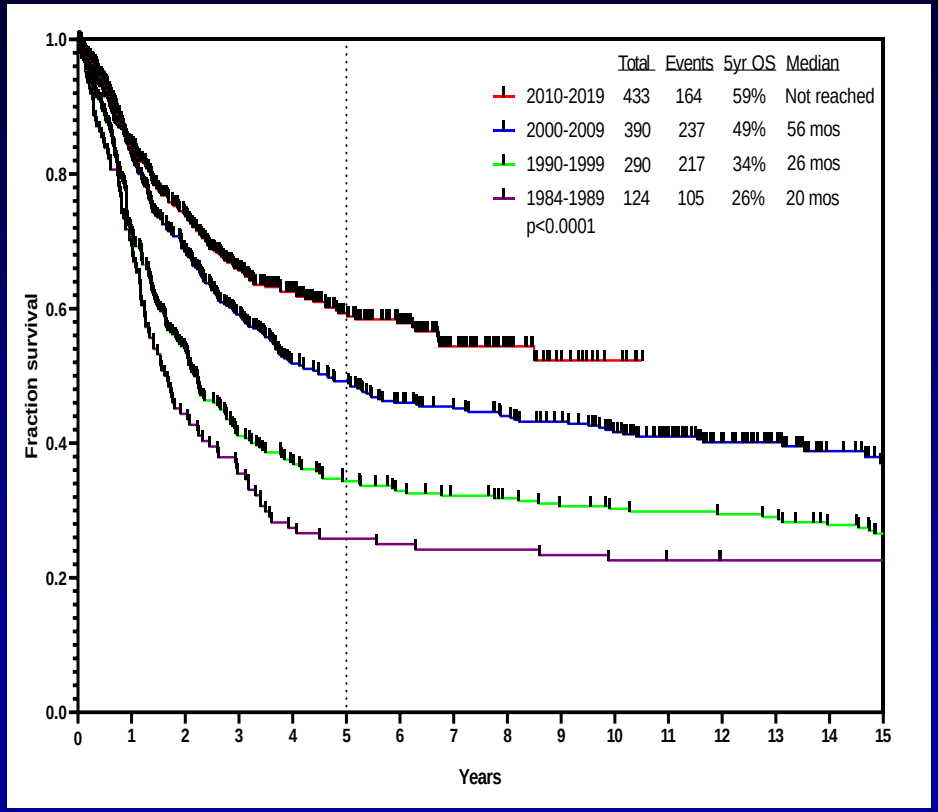
Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

Fall 2024

Survival in Pediatric and Adult ALL with Classical Intensive ChemoRx Regimens

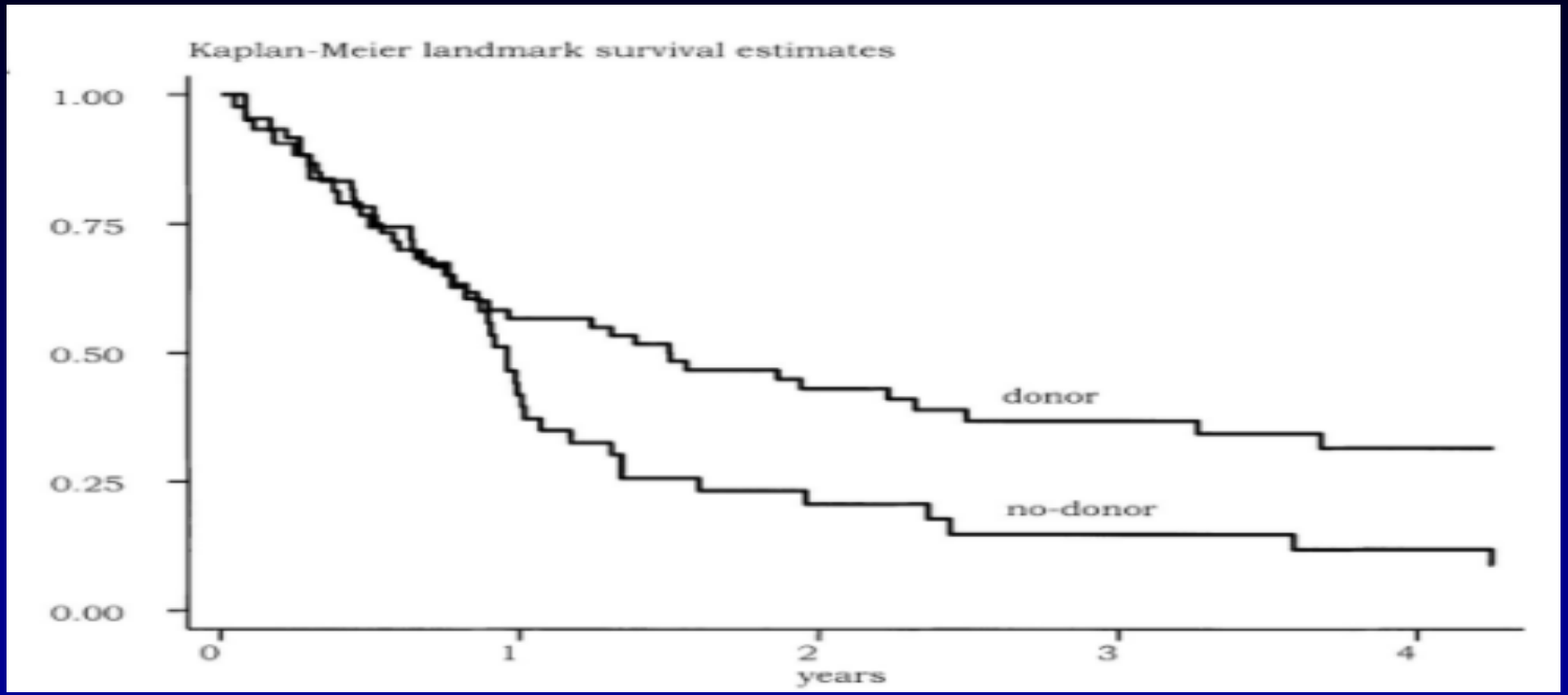


Hunger et al. *N Engl J Med.* 2015;373(16):1541-1552.



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

SCT for Ph+ ALL: Pre-TKI



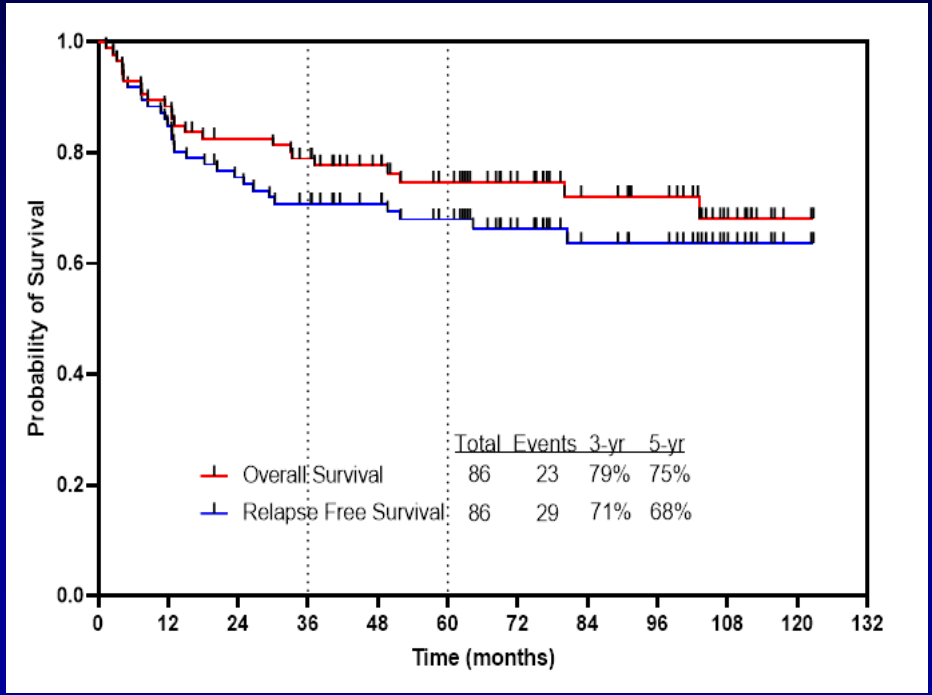
- Donor (n=60) – 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

Dombret H, et al. *Blood.* 2002;100(7):2357-2366.

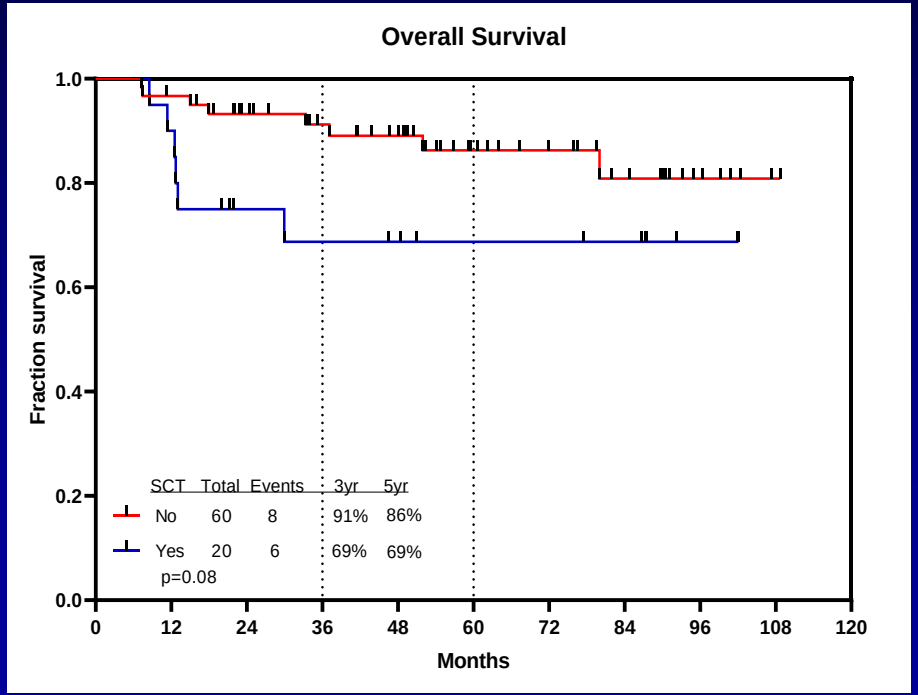
HyperCVAD + Ponatinib in Ph+ ALL

- 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%; 5-yr OS 75%, EFS 68%

RFS and survival



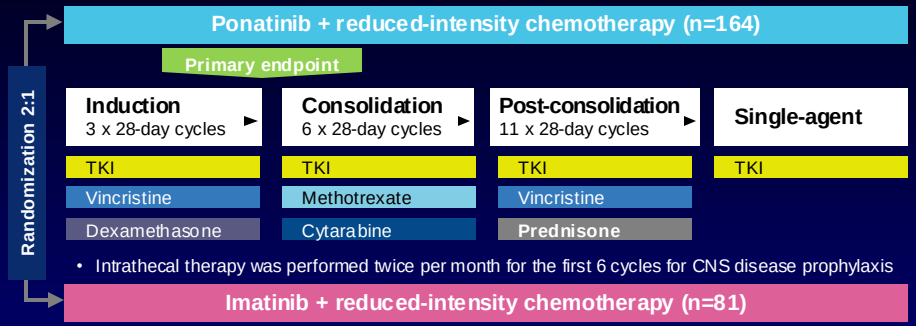
6-month Landmark



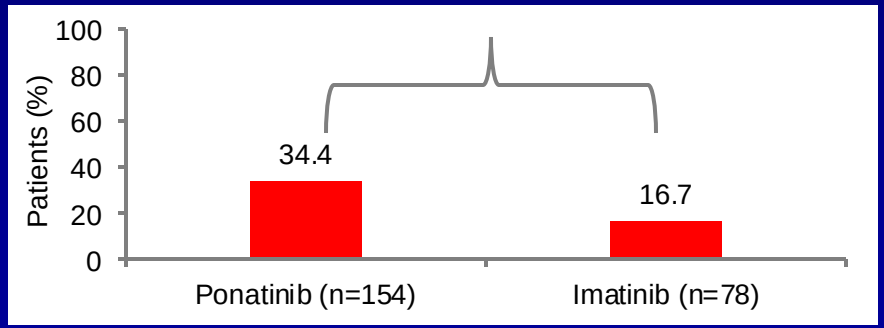
Kantarjian. *Am J Hematol.* 2023;98:493-501.

Ponatinib vs Imatinib With Rx in Ph+ ALL: PhALLCON

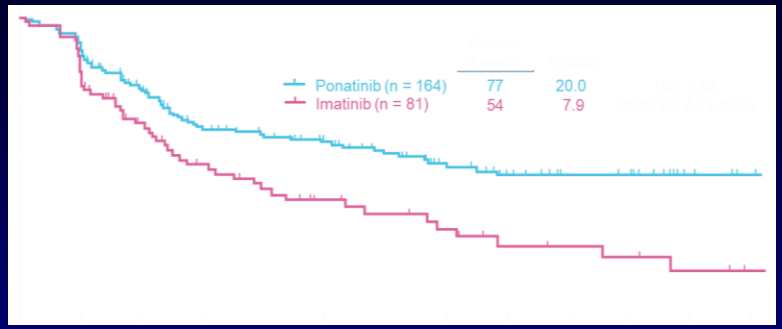
Study design



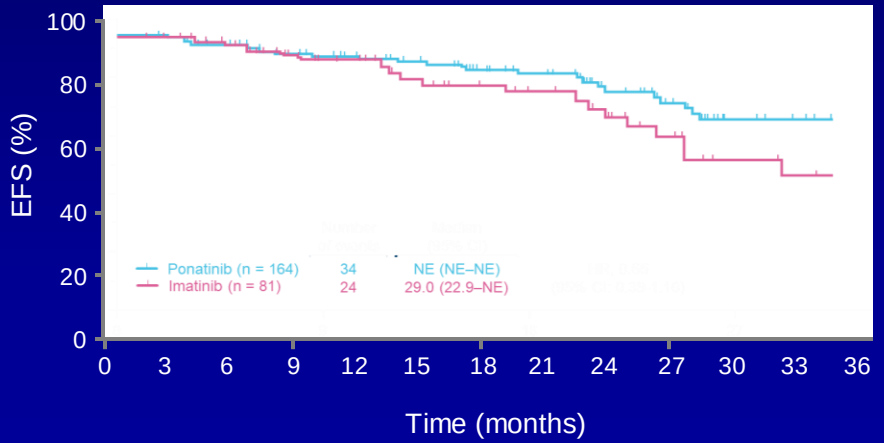
Primary endpoint:
MRD– (MR4) CR at end of induction
RR: 2.06 (95% CI=1.19–3.56)
P = .0021



PFS

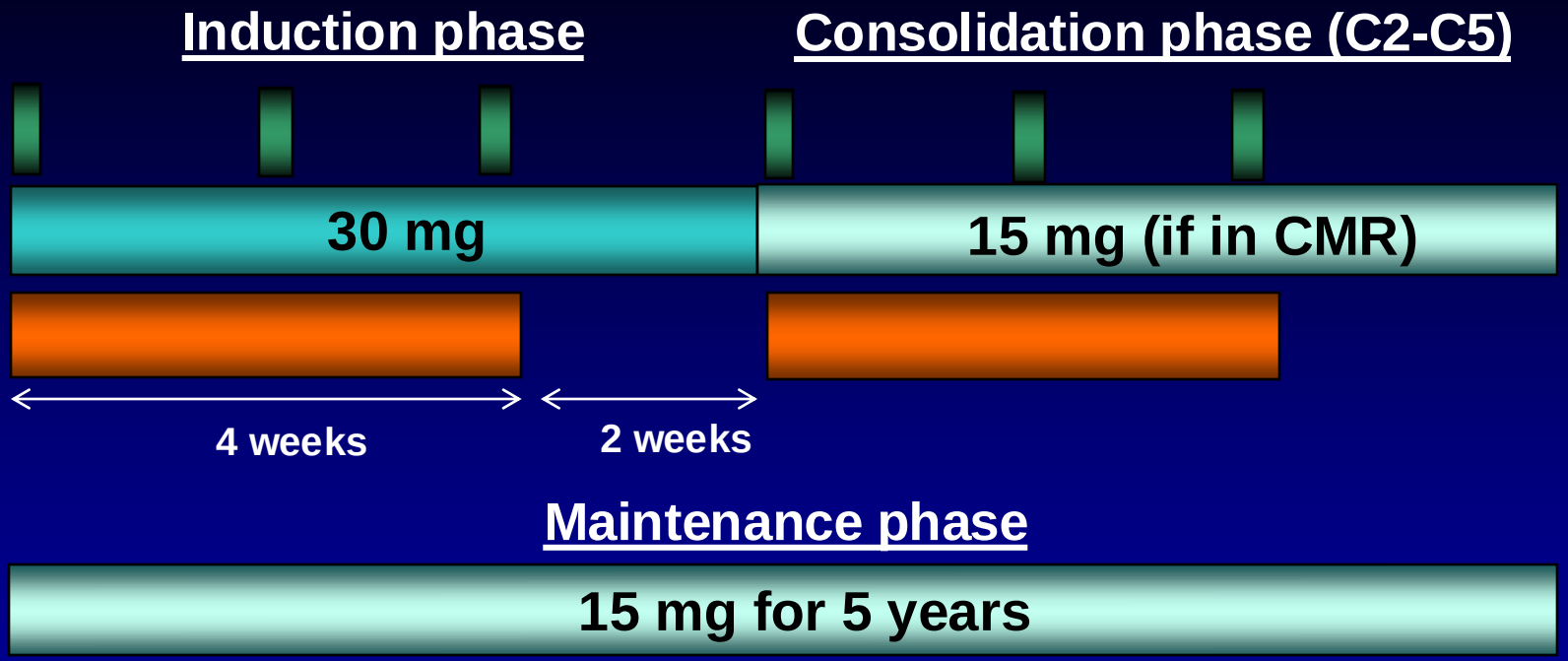


EFS



Jabbour E, et al. *JAMA*. 2024:e244783.

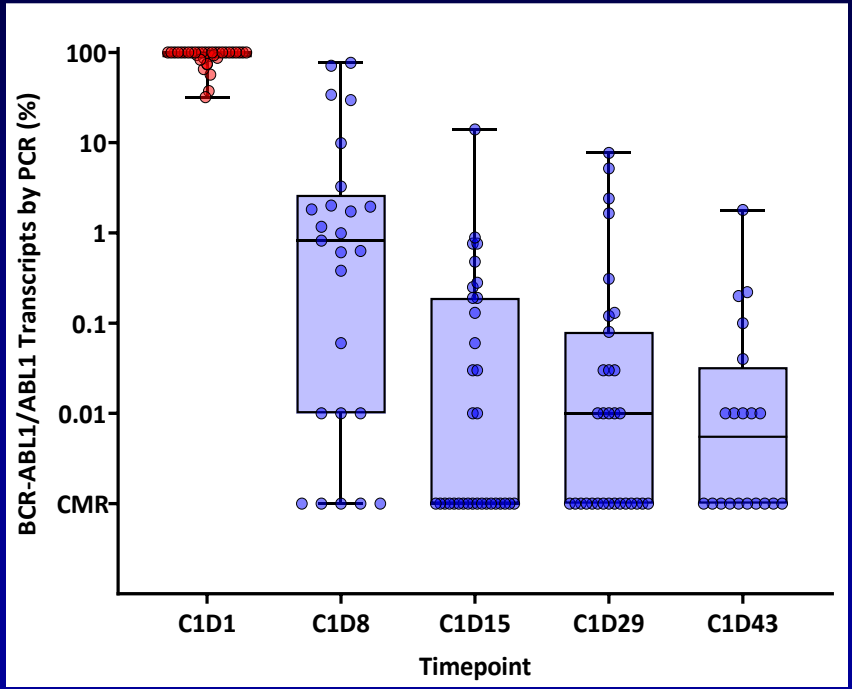
Ponatinib + Blinatumomab in Ph+ ALL: Regimen

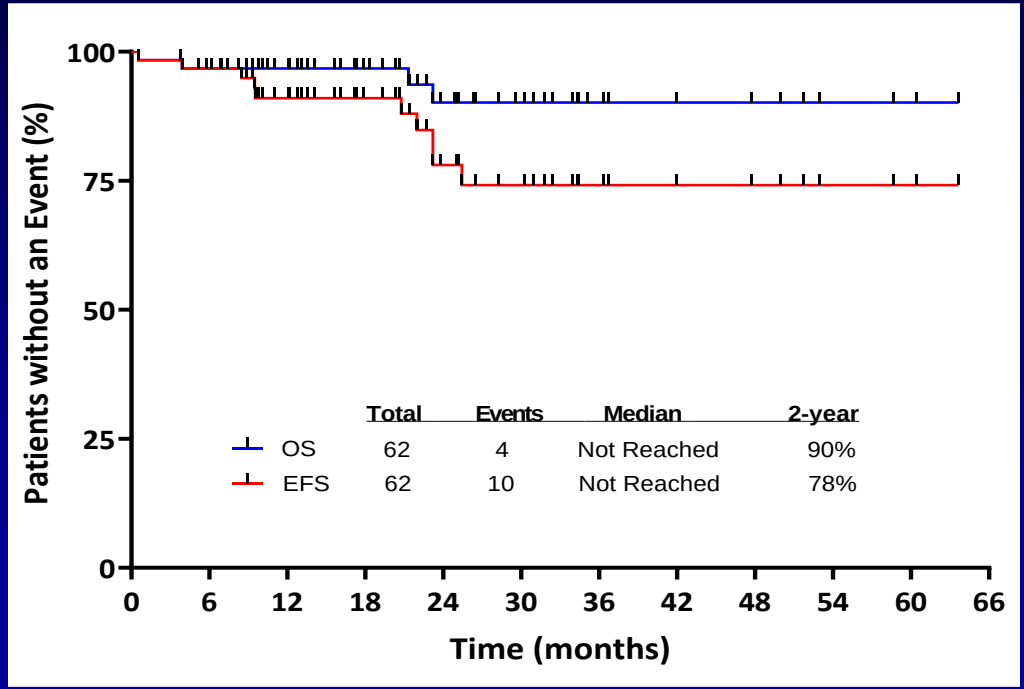


Jabbour E, et al. *Lancet Haematol.* 2023;10(1):e24-e34.

Ponatinib and Blinatumomab in Newly Dx Ph+ ALL

- 62 pts Rx with simultaneous ponatinib 30-15 mg/D and blinatumomab ×5 courses. 12-15 ITs
- Only 2 pt had SCT(3%); Median F/U 17 mos
- CR/CRi 98% (CR 95%); CMR 84% (67% after C1); NGS-MRD negativity 94%
- 2-yr EFS 78%, OS 90%. 7 relapses (all p190): 4 CNS, 1 CRLF2+ (Ph-), 2 systemic. 5/7 WBC >75k





Jabbour E, et al. *Lancet Haematol.* 2023;10(1):e24-e34.

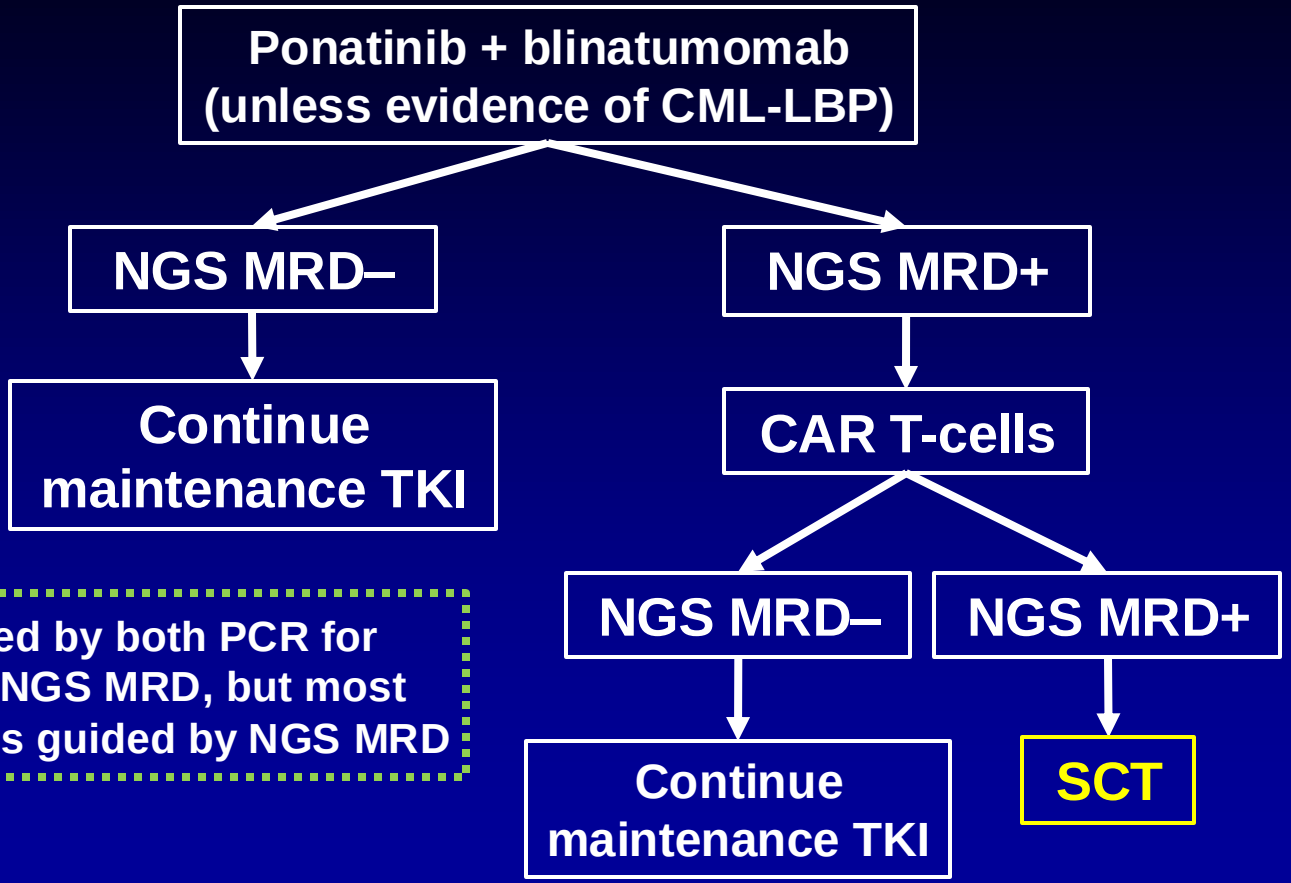
Haddad. *Blood.* 2023;142:abstract6 2827.

Ponatinib vs Dasatinib + Blinatumomab in Ph+ ALL

Parameter	Pona+Blina (n=62; 5 blina)	Dasa+Blina (n=63; 2+blina)	Dasa+ Blina (n=24; 3 blina)
Median age (yrs)	58	54	73
% PCR neg % NGS-clonoSEQ neg	84 94	93 (+PNQ)	63
% 4-yr OS	90	82	75
% allo SCT	3	48	5
Relapses (CNS)	7 (4)	9 (4)	8 [3 T315I]

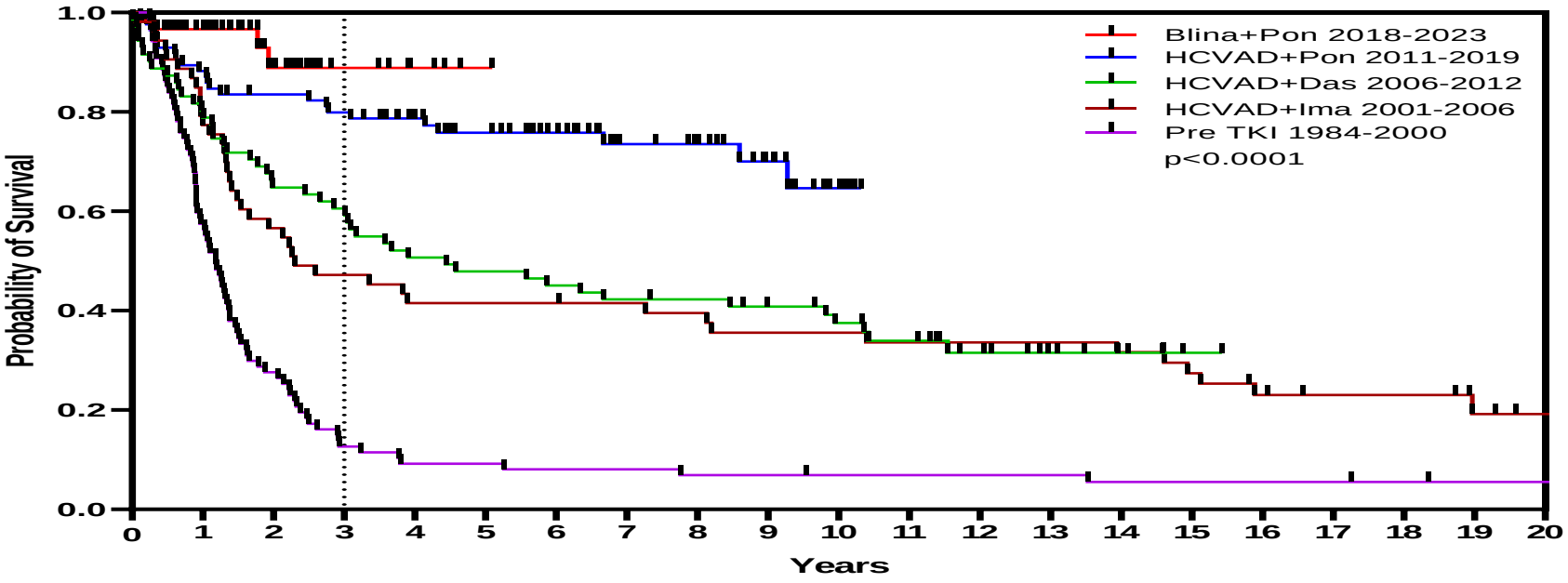
Jabbour E, et al. *Lancet Haematol.* 2023;10(1):e24-e34. Foa. *J Clin Oncol.* online, December 23; 2023. Advani. *Blood.* 2023;142:abstract 1499.

Research Rx Algorithm for Ph+ ALL



MRD is assessed by both PCR for *BCR::ABL1* and NGS MRD, but most treatment decisions guided by NGS MRD

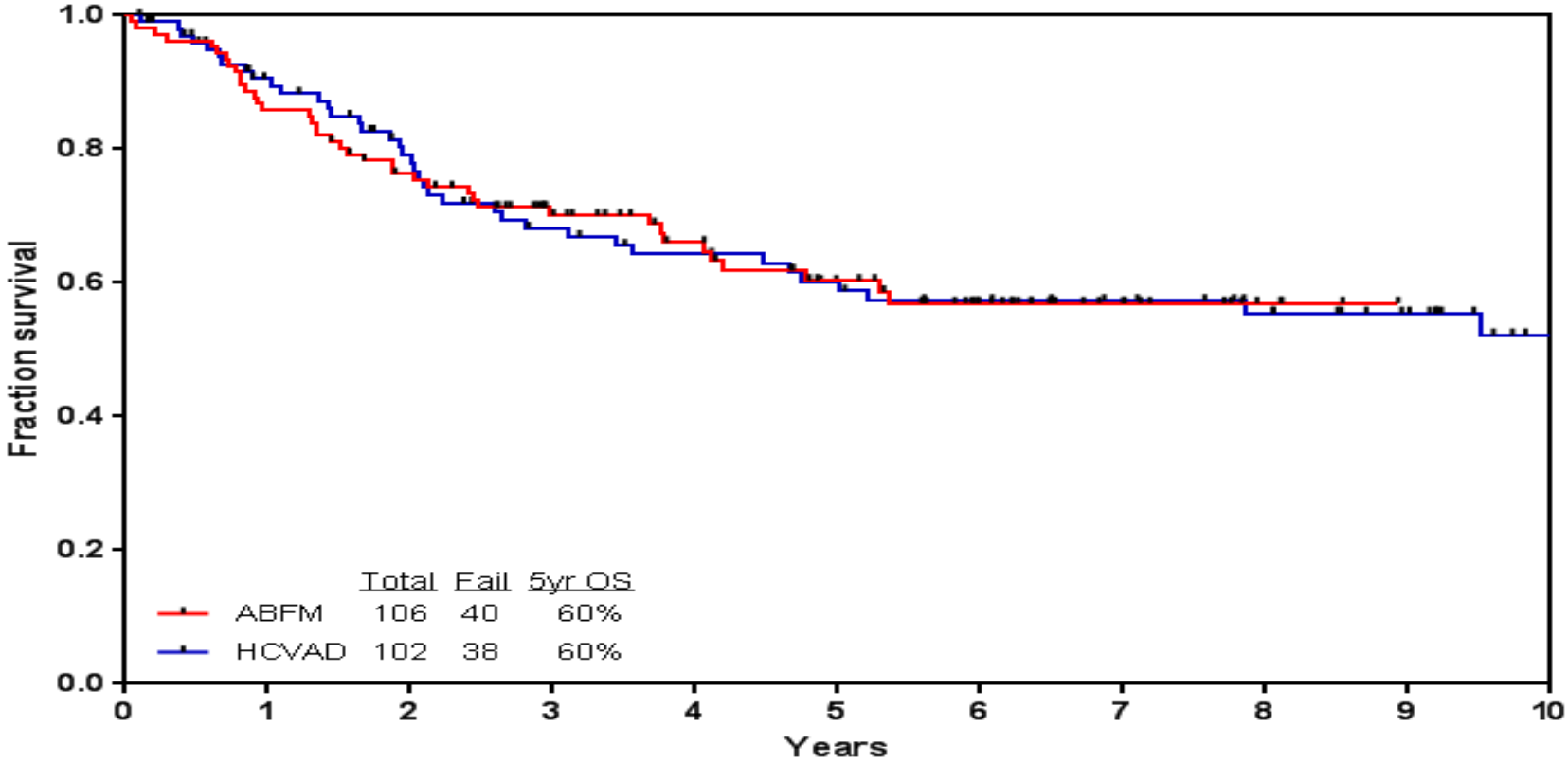
Ph+ ALL: Survival by Decade (MDACC 1984-2023)



	Total	Events	3yr OS	5yr OS	Median
Blina+Pon 2018-2022	62	4	89%	—	Not reached
HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
Pre TKI 1984-2000	87	83	13%	9%	14 mos

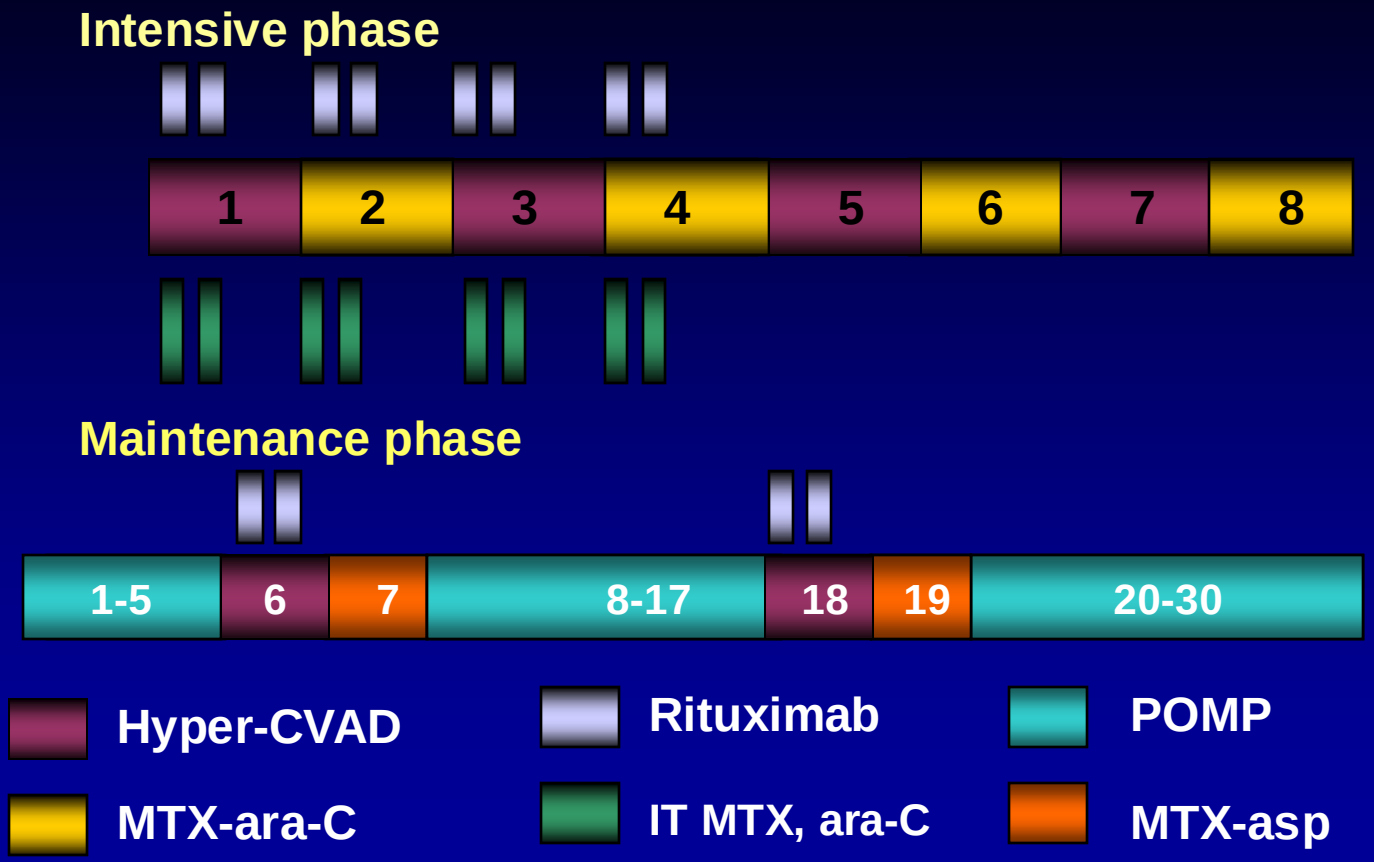
p<0.0001

Hyper-CVAD vs ABFM: Overall Survival



Rytting. *Cancer.* 2014;120:3660-3668; Rytting. *Am J Hematol.* 2016;91:819.

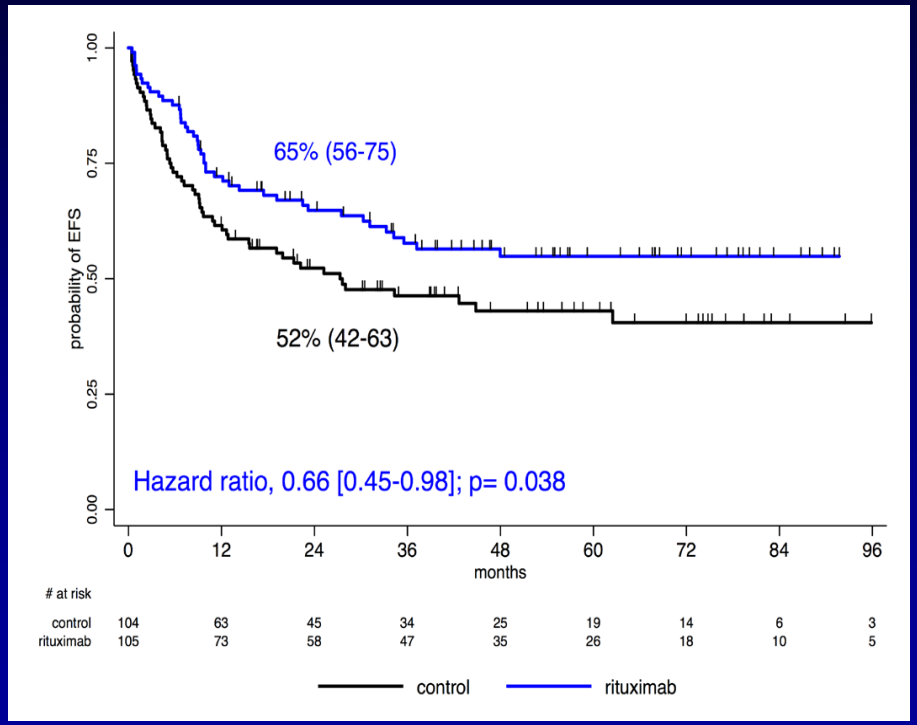
Hyper-CVAD + Rituximab in Precursor B-ALL

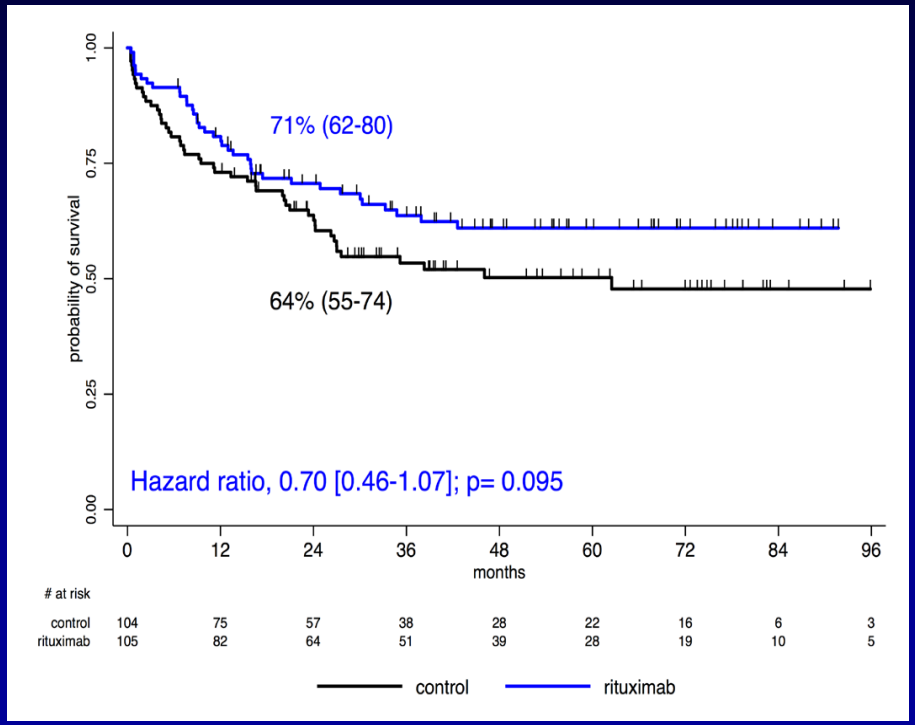


Thomas. *J Clin Oncol.* 2010;28:3880-3889.

Chemo Rx +/- Rituximab: Results of the Randomized GRAALL-R 2005 in Pre–B-ALL

- Median follow-up 30 months

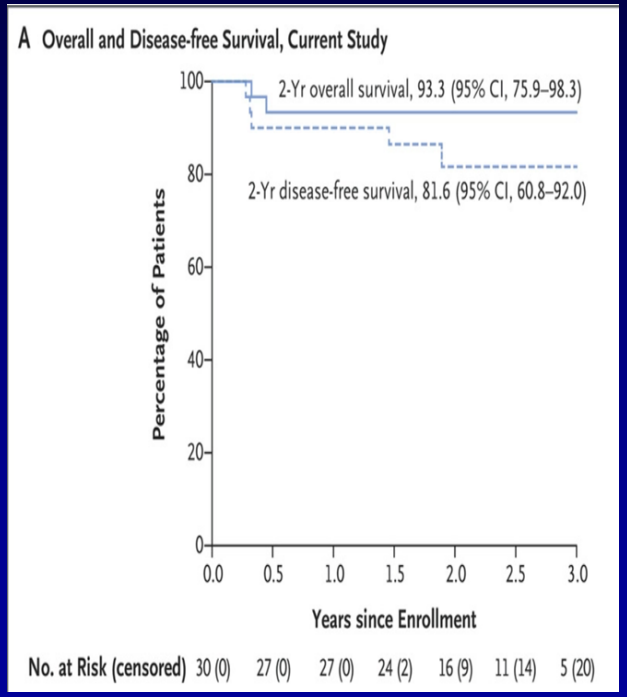


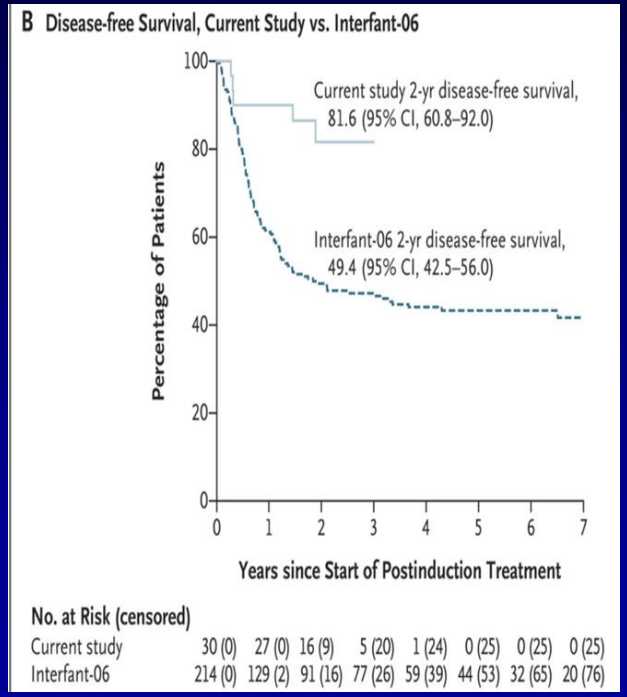


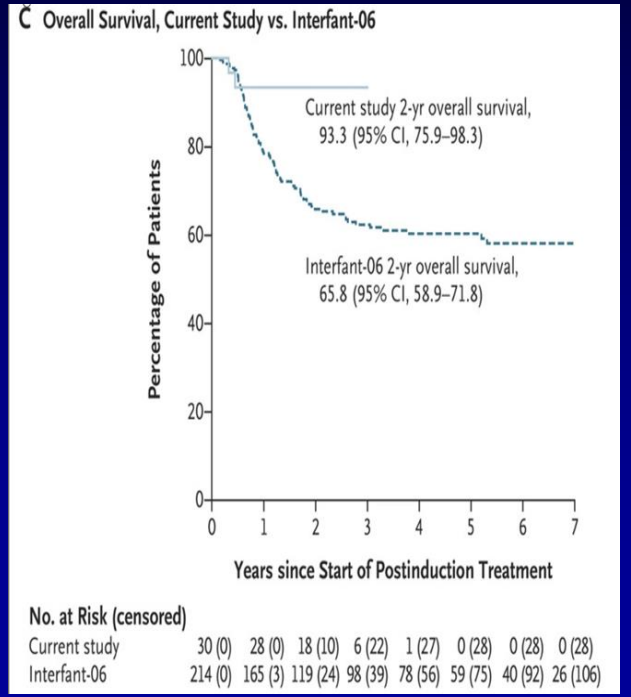
Maury. *N Engl J Med.* 2016;375:1044-1053.

ChemoRx + Blina in Newly Dx KMT2A-Rearranged ALL

- 30 infants age <1 yr Rx with chemoRx induction, then 1 course blina consolidation (15 mcg/m^2 ×28), then chemoRx continuation



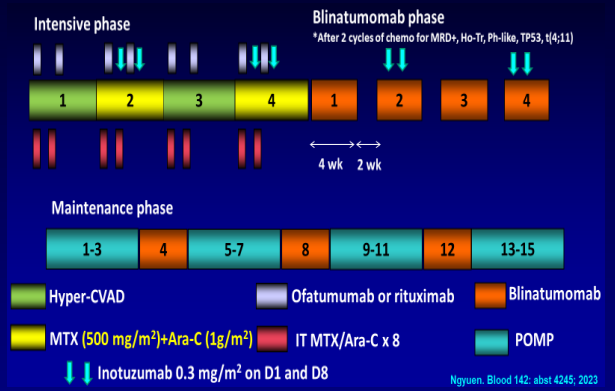


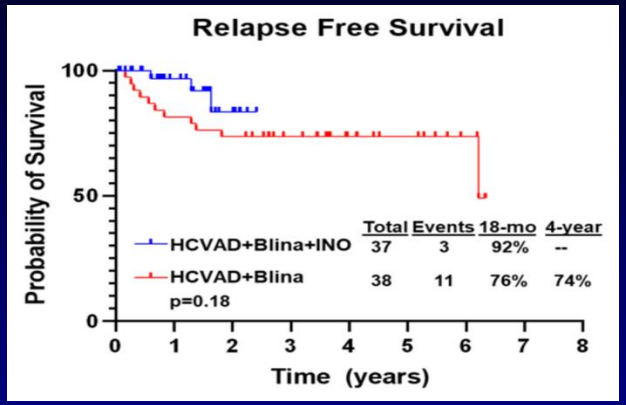


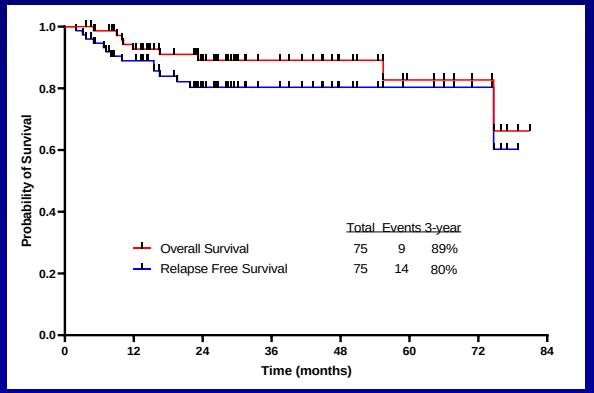
Vam der Sluis. NEJM 388:1572-1581; 2023

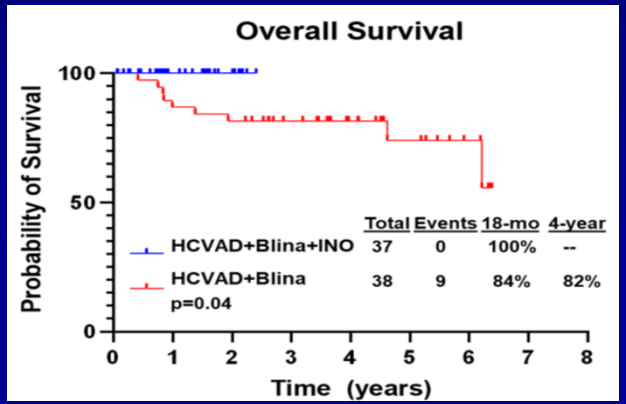
Hyper CVAD-Inotuzumab → Blina in Newly Dx Adult ALL

- 75 pts; median age 33 yrs (18-59); Median F/U 26 months (1-77)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 73%; 60-day mortality 0%; 24 (32%) allo-SCT

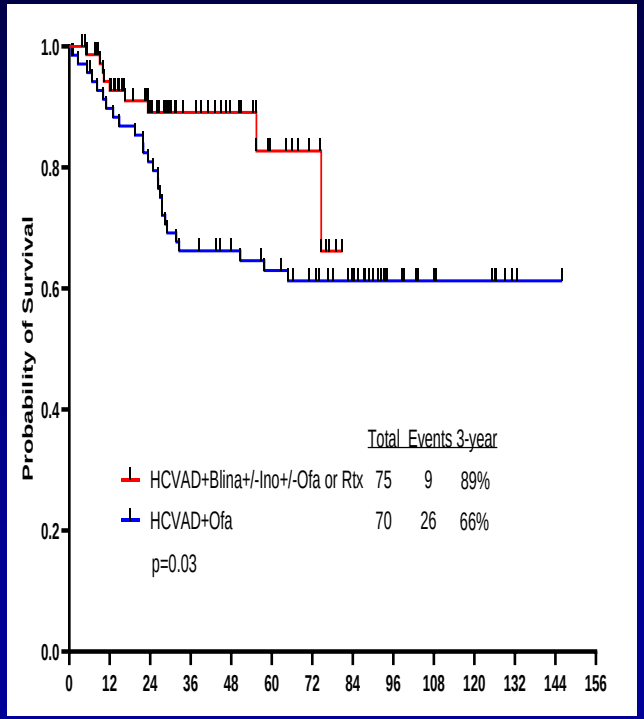








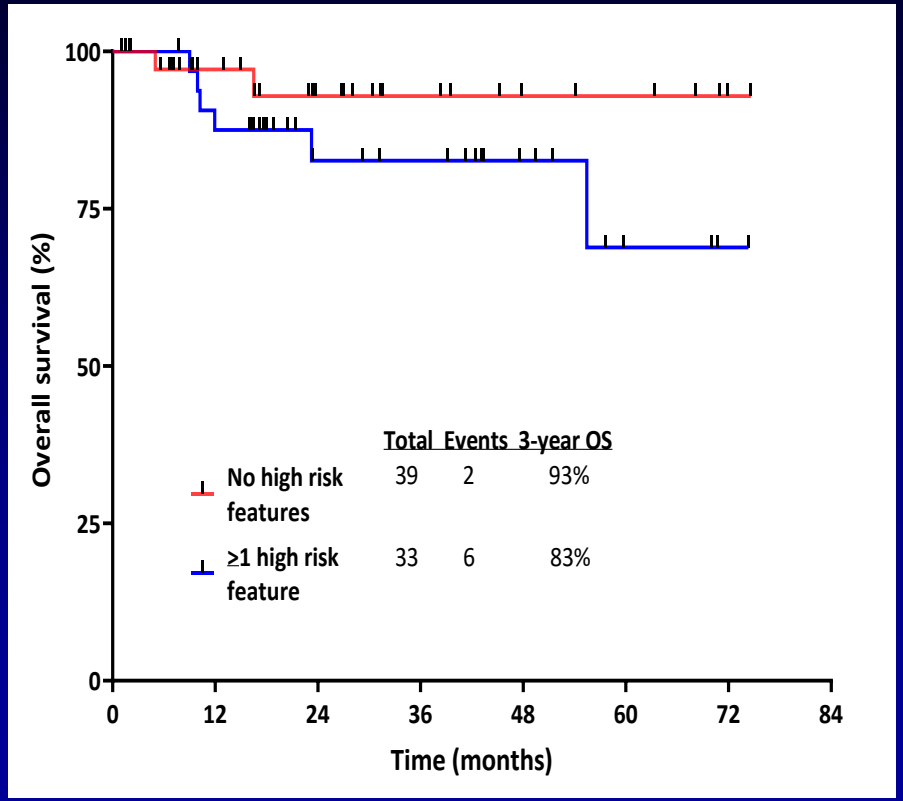
Overall Survival



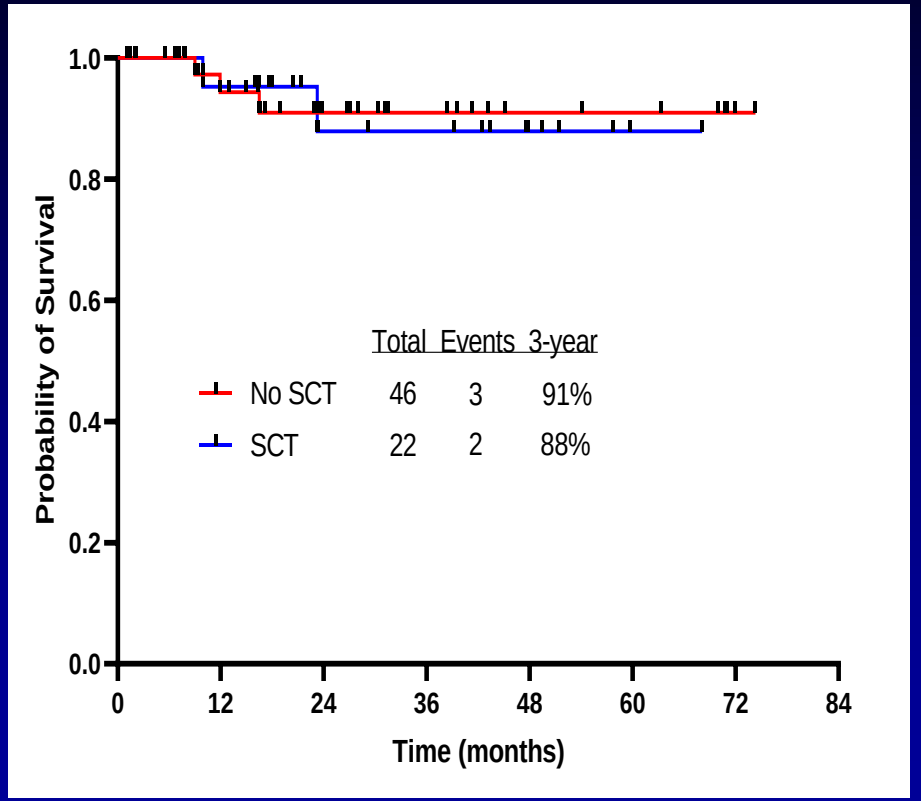
Nguyen. *Blood.* 2023;142:abstract 4245.

Hyper-CVAD + Blinatumomab + Inotuzumab in B-ALL

Outcome by ALL Risk

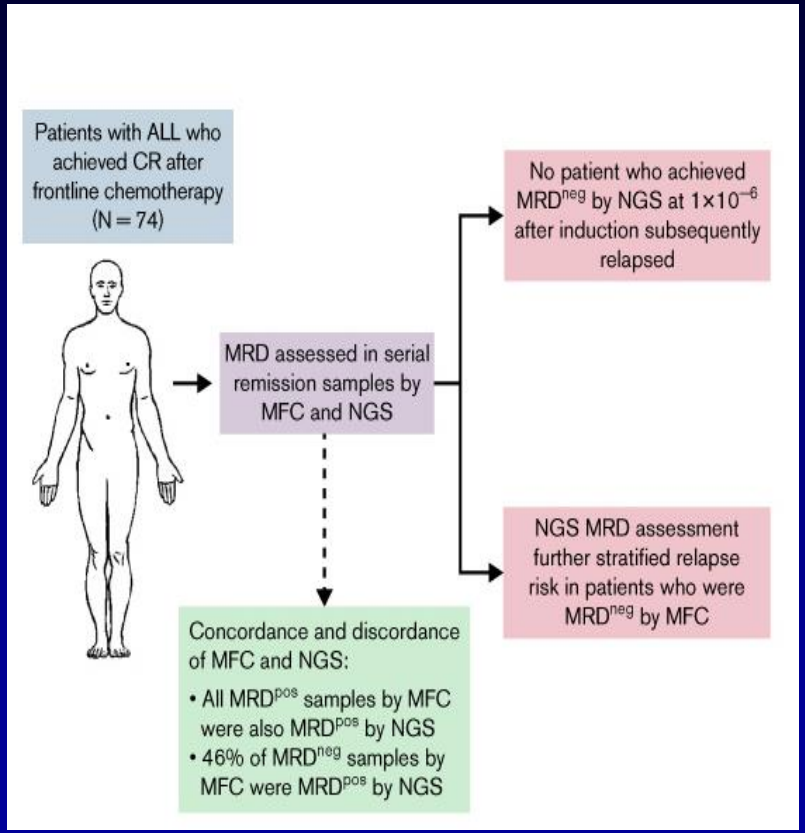


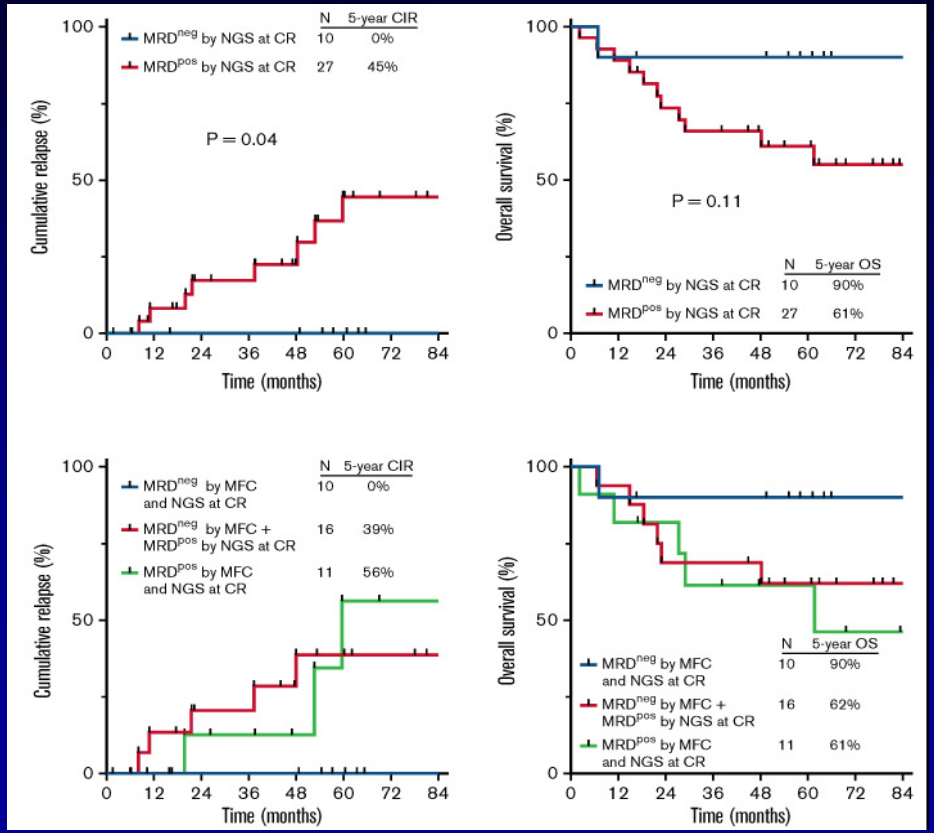
Outcome by ASCT (5-mo landmark)



Jabbour E, et al. *Lancet Haematol.* 2023;9:e878-e885.

Outcome Prediction by NGS MRD Better Than MFC MRD in Pre–B-ALL





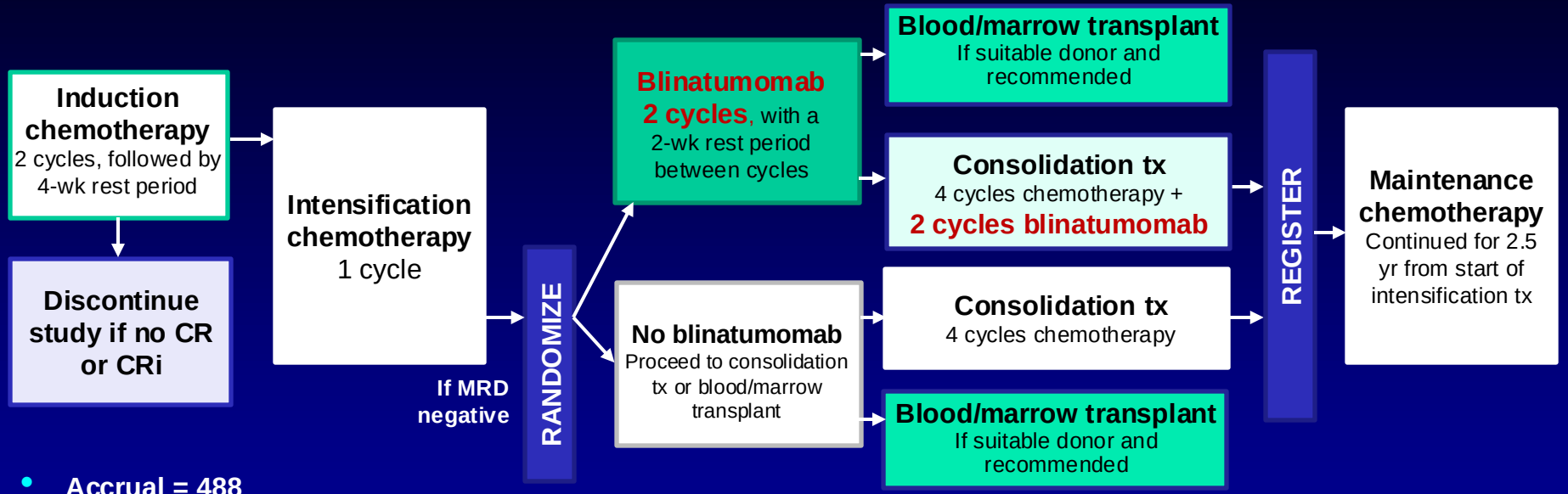
Short. *Blood Adv.* 2022;6:4006-4014.

Frontline Blinatumomab and Inotuzumab Combinations in Adult Newly Dx ALL

	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
HCVAD-blina-inotuzumab	Blinatumomab and Inotuzumab	75	33 (18-59)	100	95	89 (4-yr)
GIMEMA LAL1913	Blinatumomab	149	41 (18-65)	88	93	71 (3-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)

Jabbour E, et al. *Lancet Haematol.* 2023;9:e878-e885; Chiaretti. *Blood.* 2023;142:abstract 826; Boissel. *Blood.* 2021;140:abstract 1232; Fleming. *Blood.* 2021;138:1224.

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



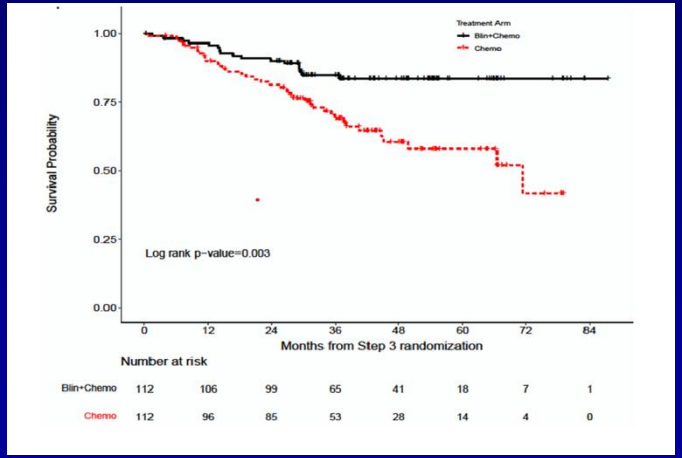
- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

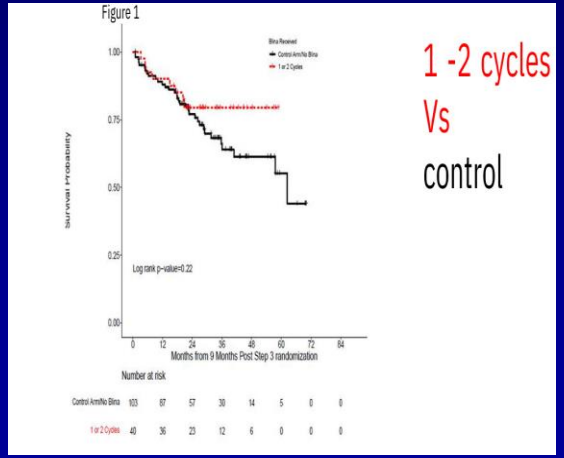
Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

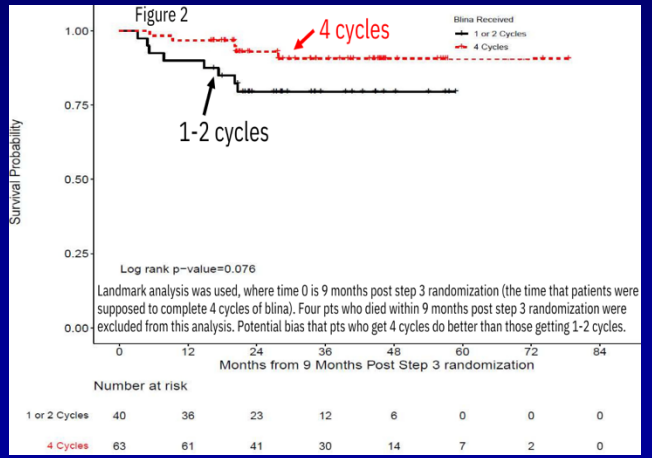
E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD–: Outcomes by Number of Cycles

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

# cycles	121
1	12
2	32
3	4
4	**63 (52%)**

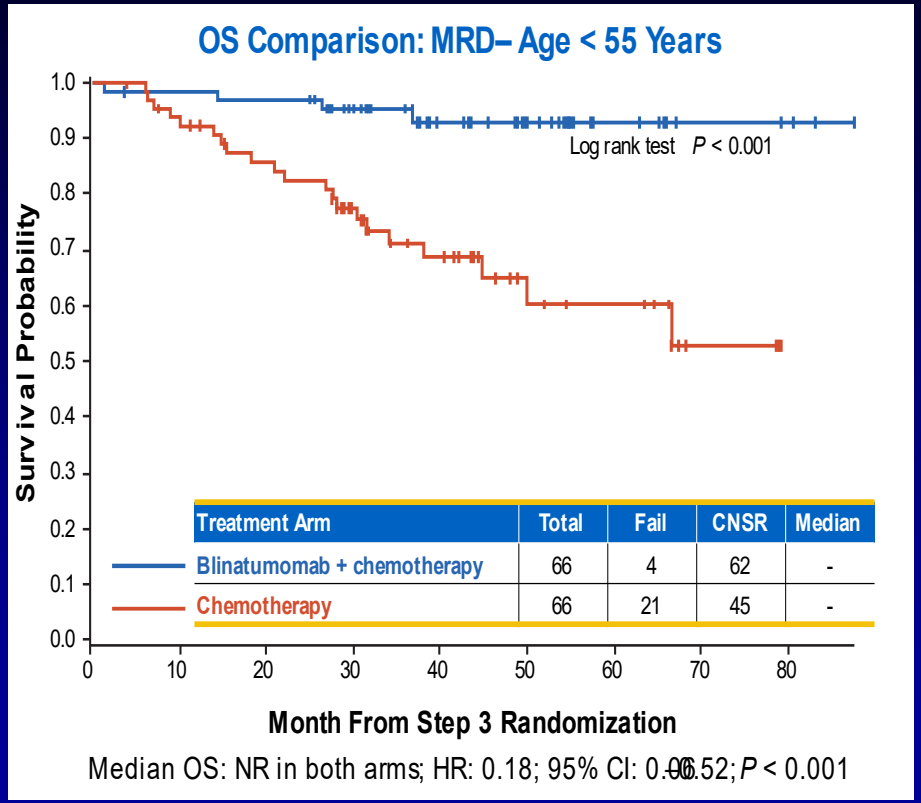


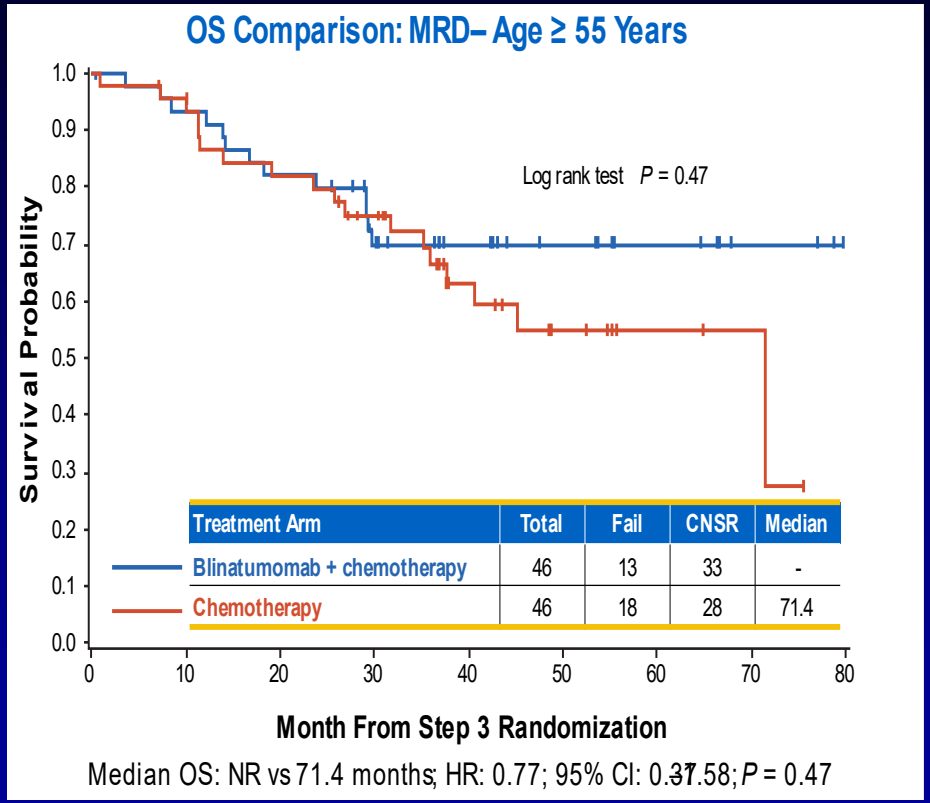




Luger. *Blood.* 2023;142:abstract 2877.

E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD–: Outcomes by Age

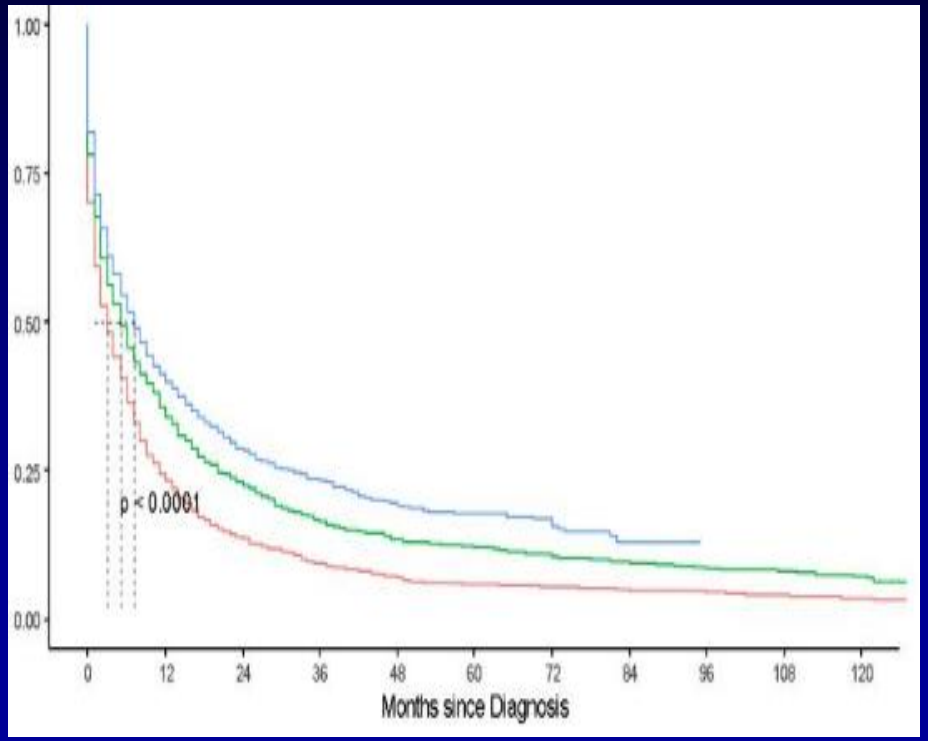


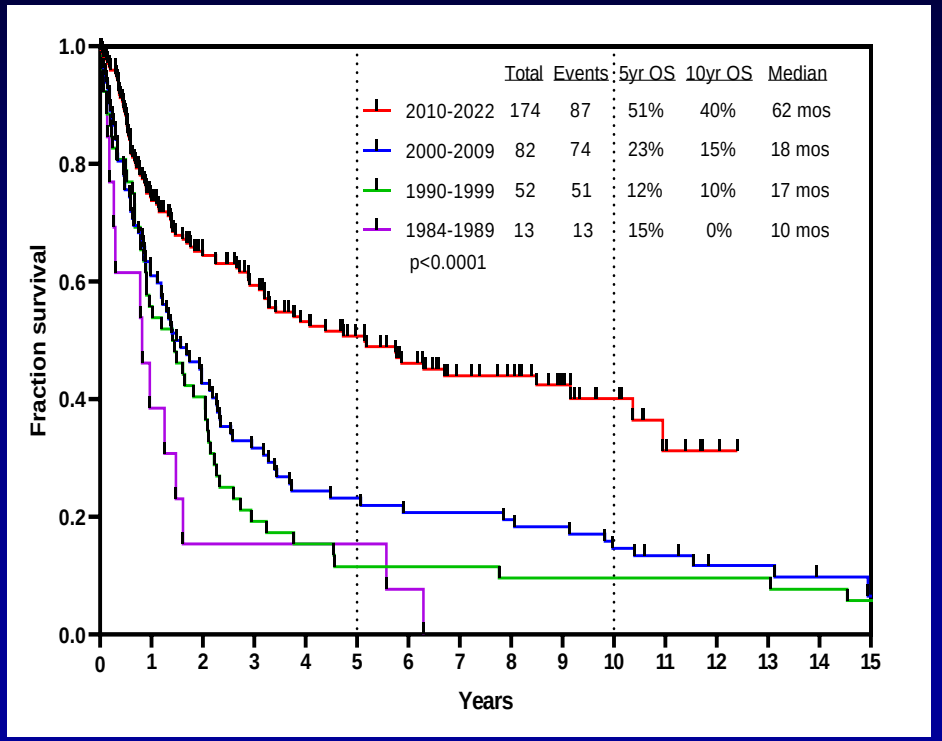


Mattison R, et al. EHA 2023. Abstract S115.

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

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

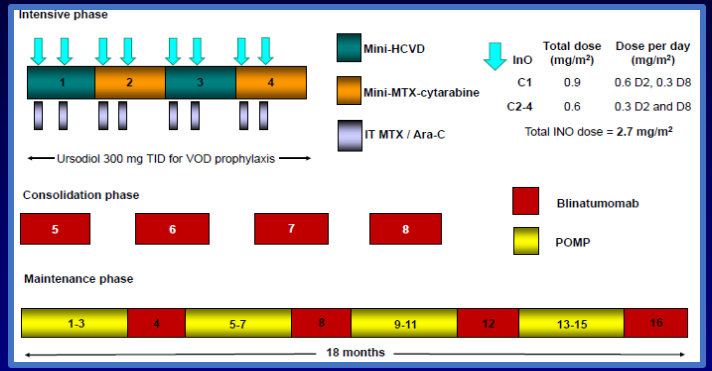




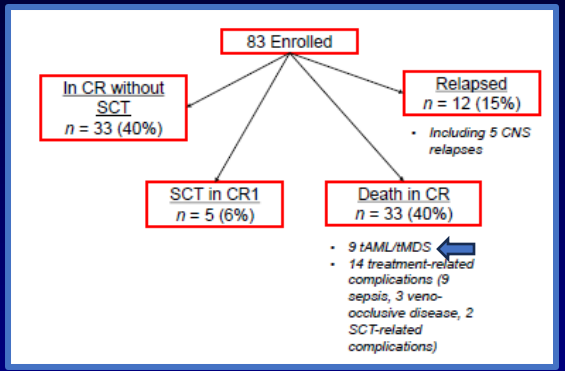
Gupta. *Blood.* 2022;140:abstract 1379.

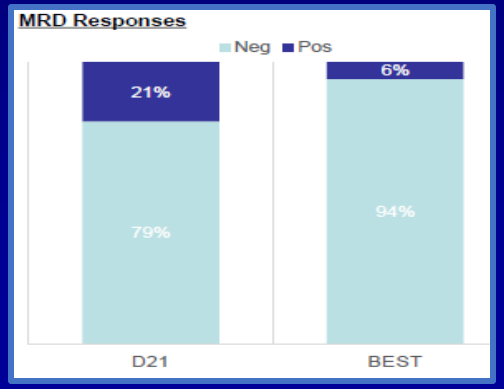
Mini-HCVD + INO ± Blina in Older ALL (N=83)

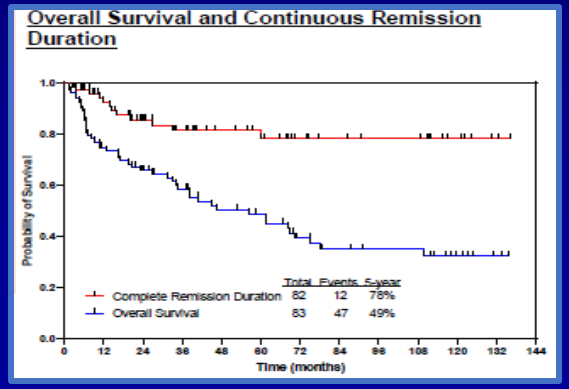
- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: *TP53* 39%; Ph-like 18%; poor cytogenetics 23%
- ORR 99% (CR 90%); MRD negativity 94% (79% at CR)



Characteristic	Category	N (%) / Median [range]
Age (years)	≥70	68 [60 - 87] 28 (34)
Cytogenetics	Diploid HeH Ho-Tr Tetraploidy Complex t(4;11) Misc IM/ND	27 (33) 5 (6) 12 (14) 3 (4) 3 (4) 1 (1) 16 (19) 16 (19)
CD19 (%)		99.6 [26-100]
CD22 (%)		96.9 [27-100]
CD20	≥20%	46/76 (61)
Ph-like ALL		9/50 (18)
TP53 mutation		25/64 (39)





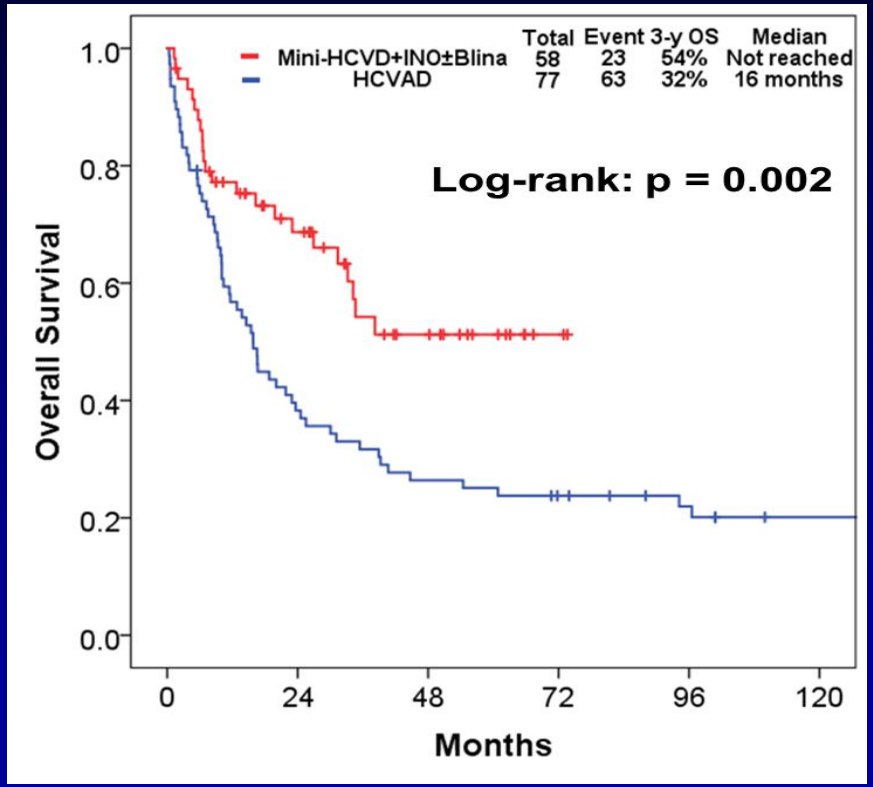


- Median F/U 88 months
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; 6%)
- Death due PD/NR: 12/83 (15%); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (11%); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: 33/83 (40%); 11/28 (39%) in pts ≥70 yrs
- 14/33 deaths (42%) Rx related (9 sepsis, 3 VOD, 2 ASCT)

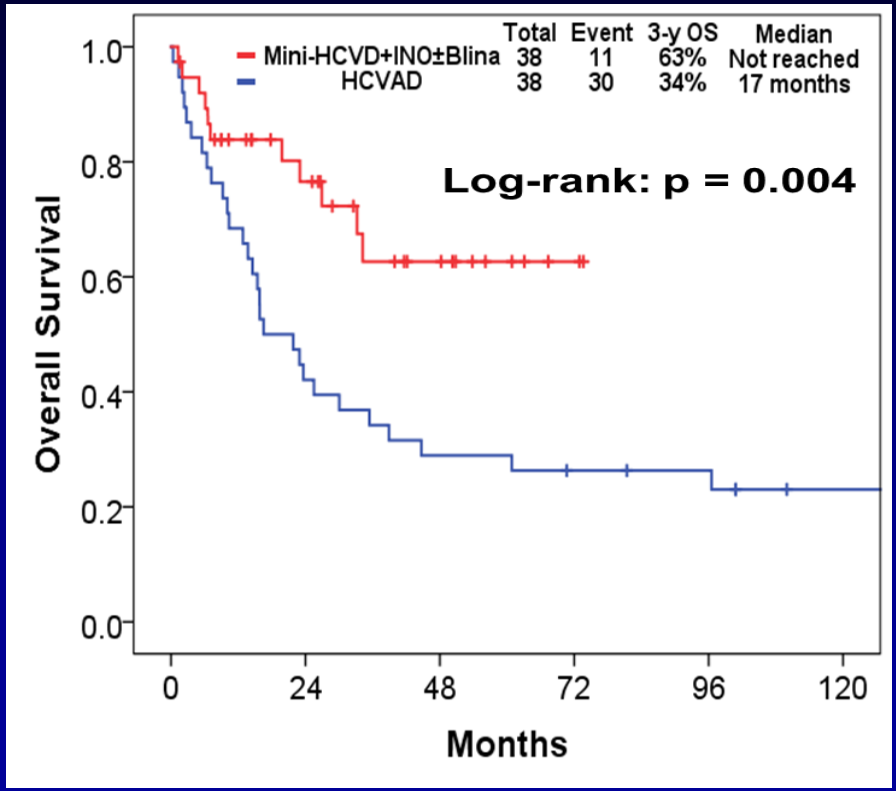
Jen. *Blood.* 2023;142:abstract 2878.

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

Pre-matched



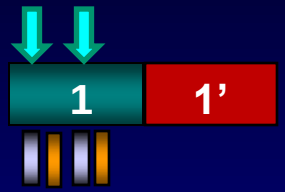
Matched



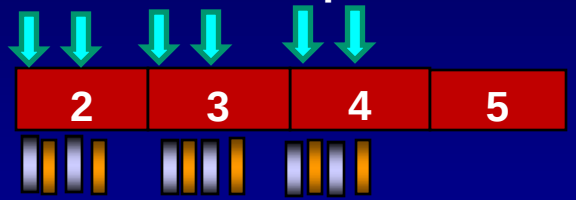
Jabbour E, et al. *Cancer*. 2019;125(15):2579-2586.

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

Induction (D1-14)



Consolidation phase



Maintenance phase

Dexa 20 mg D1-4 and VCR 1 mg D4

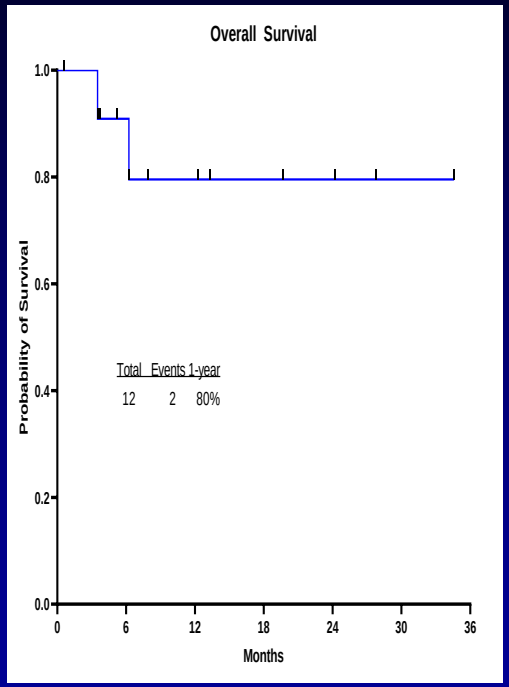
Blinatumomab

IT MTX, Ara-C Rituximab if CD20+

1' Blinatumomab for 2 weeks

INO*	Total dose (mg/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



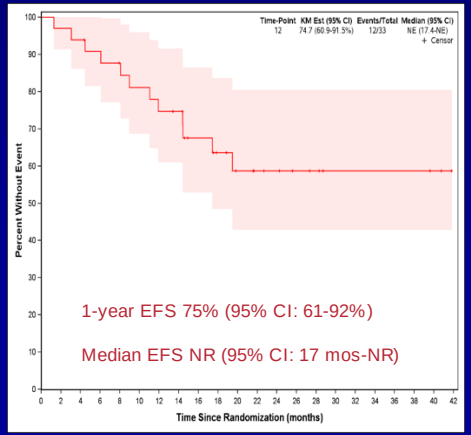
*Ursodiol 300 mg tid for VOD prophylaxis

Chemo Rx-Free Inotuzumab + Blinatumomab in Pre–B-ALL (Alliance A 041703)

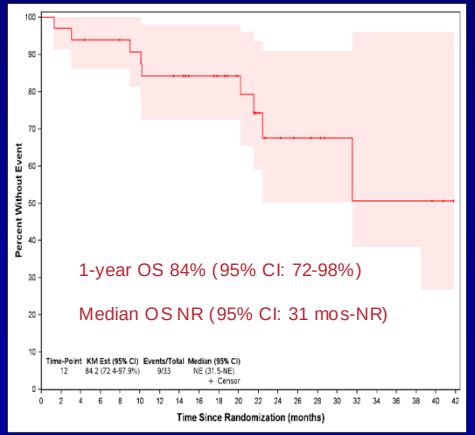
- 33 pts; median age 71 yrs (60-84). Median CD22 92%. F/U 22 months
- Induction: INO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 & 15 (1.8 mg/m^2)
- Maintenance: If CR-CRi INO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) ×2 then BLINA ×2
- If no CR-CRi—BLINA 28 mcg/D ×21 then ×28 ×3
- IT ×8
- CR 85% post INO ×3; cumulative CR 97%
- 1-yr EFS 75%; 1-yr OS 84%
- 9 relapses; 2 deaths in CR. 9 deaths, 6 post relapse

	Induction with Inotuzumab (IA/B/C)	Consolidation with Blinatumomab
Cumulative CR (CR+CRh+CRi)	28/33 (85 %)	32/33 (97 %)
CR	15/33 (45%)	19/33 (58 %)
CRh	11/33 (33 %)	12/33 (36 %)
CRi	2/33 (6 %)	1/33 (3 %)
Refractory	3/33 (9 %)#	-

EFS

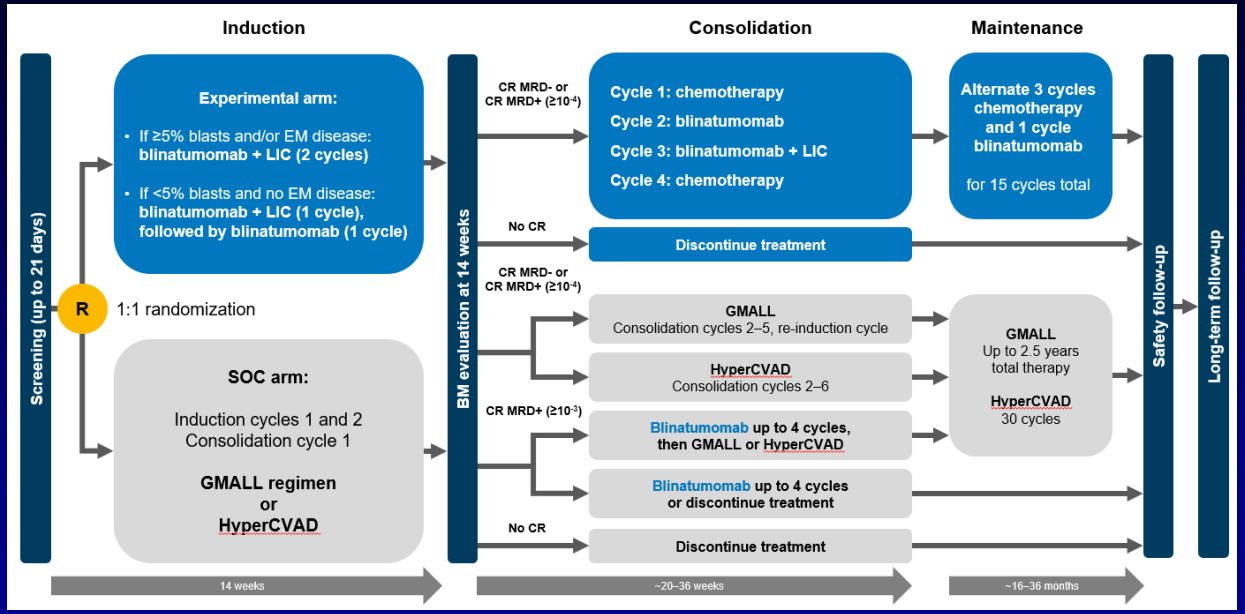


OS



Wieduwilt. *HemaSphere.* 2023;7:abstract S117.

Blina + Low-Intensity ChemoRx in Older Pre-B ALL: Golden Gate Safety Run-In Results of Phase III



Characteristic	N=10
Age, median (range), years	69 (57–77)
≥70, n (%)	4 (40)
≥55 to <70, n (%)	6 (60)
>40 to <55, n (%)	0

Response	After cycle 1 (N=10)	After cycle 2 (N=10)
Disease response available, n	10	9
Complete remission	10	8
MRD response	9	7
MRD complete response	7	5
MRD nonresponder	1	1
CRh	0	0
CRi	0	0
Blast-free hypoplastic or aplastic BM without CRh or CRi	0	0
Nonresponse	0	0
Relapse	0	1
PD	0	0
PR	0	0

- 10 pts; median age 69 yrs (57–77); 40% ≥70 yrs
- 9/10 had molecular response after C1; 7/10 MRD-negative CR
- No grade ≥3 CRS or ICAN

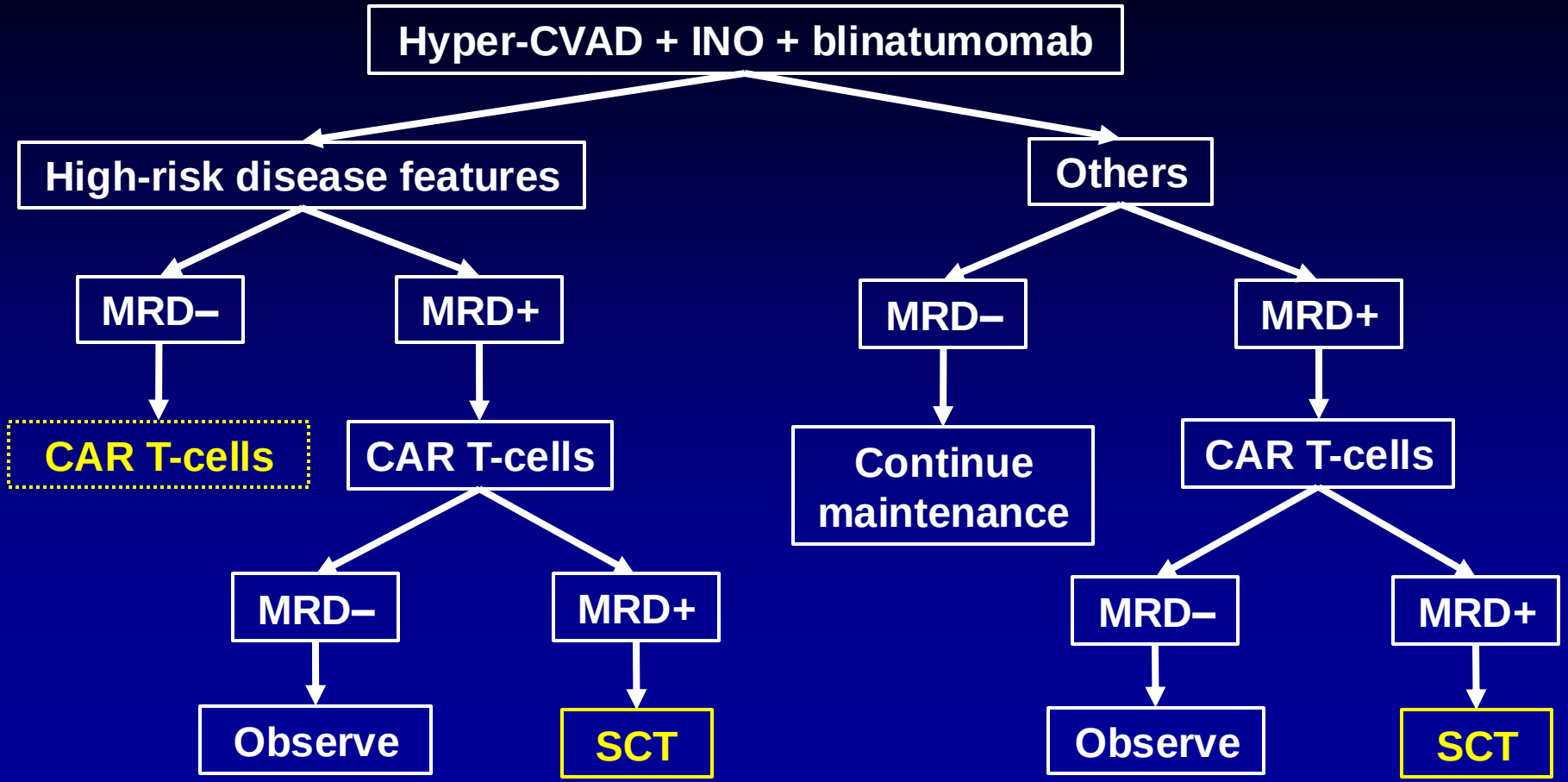
Jabbour E, et al. ASH 2022; Abstract 2732; NCT04994717. Available at https://clinicaltrials.gov/ct2/show/NCT04994717. Accessed January 2024.

Frontline Blina and Inotuzumab Combinations in Newly Dx Older ALL

	Agent	N	Median Age, yr (range)	CR, %	MRD negativity, %	OS, % (x yr)
Mini-HCVD–inotuzumab–blinatumomab[1]	Blinatumomab and inotuzumab	83	68 (60–87)	90	94	49 (5 yr)
SWOG 1318[2]	Blinatumomab	31	73 (66–86)	66	92	37 (3 yr)
EWALL-INO[3]	Inotuzumab	131	69 (55–84)	88	57	54 (2 yr)
GMALL Bold[4]	Blinatumomab	50	65 (56–76)	85	82	67 (3 yr)
INITIAL-1[5]	Inotuzumab	43	64 (56–80)	100	71	73 (3 yr)
Alliance[6]	Ino + Blina	33	71 (60–84)	97	--	67 (2 yr)

1. Jen WY, et al. *Blood.* 2023;140:abstract 2878; 2. Advani AS, et al. *J Clin Oncol.* 2022;40:1574-1582; 3. Chevallier P, et al. *Blood.* 2022;140:abstract 2724; 4. Goekbuget N, et al. *Blood.* 2023;140:abstract 964; 5. Stelljes M, et al. *J Clin Oncol.* 2023; 6. Wieduwilt M, et al. *HemaSphere.* 2023;7:abstract S117.

Research Algorithm for Ph-Negative B-ALL in 2024+



ALL 2024+: Conclusions

- Significant improvements across all ALL categories
- Ph-positive ALL
  - Ponatinib > imatinib --- evaluating newer TKI (olverembatinib, asciminib)
  - Blina-ponatinib: 3-year OS 90%, rarely allo-SCT
  - CNS relapses: 15 IT vs systemic chemotherapy in WBC >70K
- Incorporation of Blina/INO in FL therapy highly effective and improves survival
  - HCVAD-blina-ino: 3-year OS 88%
  - Mini-HCVD-INO in older ALL: 5-year OS 50%
  - Exploring chemotherapy-free approach to reduce death in CR in older ALL
- Early eradication of MRD predicts best overall survival
  - NGS > FCM in Ph-negative ALL, NGS > PCR in Ph-positive
- Antibody-based Rxs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather complementary
  - CAR T as consolidation post Blina/Ino based regimen
- Future of ALL Rx
  - 1) less chemotherapy and shorter durations
  - 2) combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22, CD79
  - 3) SQ blinatumomab
  - 4) CAR Ts CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT

Thank You

Elias Jabbour MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX
Email: ejabbour@mdanderson.org
Cell: 001.713.498.2929

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

Nicola Gökbuget

APTITUDE HEALTH®

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

Nicola Gökbuget, MD
Goethe University Hospital, Department of Medicine II, Frankfurt
GMALL Study Coordinator

UNIVERSITÄTS KLINIKUM FRANKFURT
GOETHE-UNIVERSITÄT

GMALL
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

DKTK German Cancer Consortium

uct Universitäres Centrum für Tumorerkrankungen Frankfurt
University Cancer Center

MED2

FRANKFURT CANCER INSTITUTE

AYA Patients With ALL

- **Definition of AYA**
- **Generally promising approaches**
- **Why and which specific approaches for AYA**

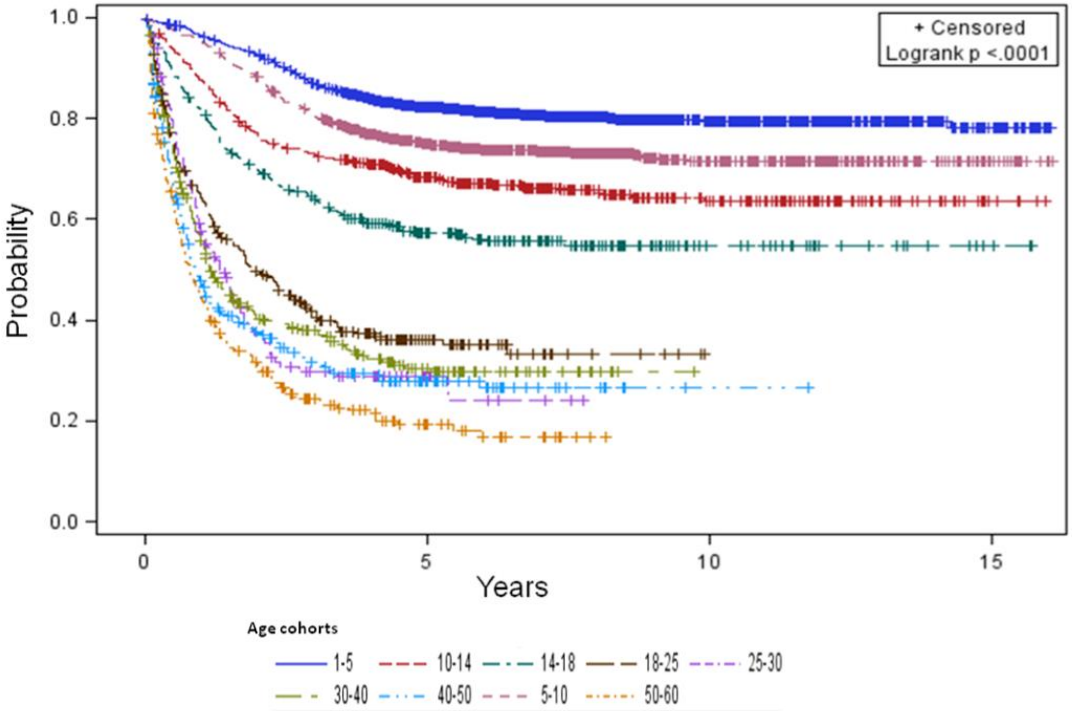
Role of Age in ALL

Children - Adolescents - AYA - Young Adults Adults - Elderly - Frail

Gökbuget 10/2024

Treatment Results in ALL Depend on Age: Children vs Adults

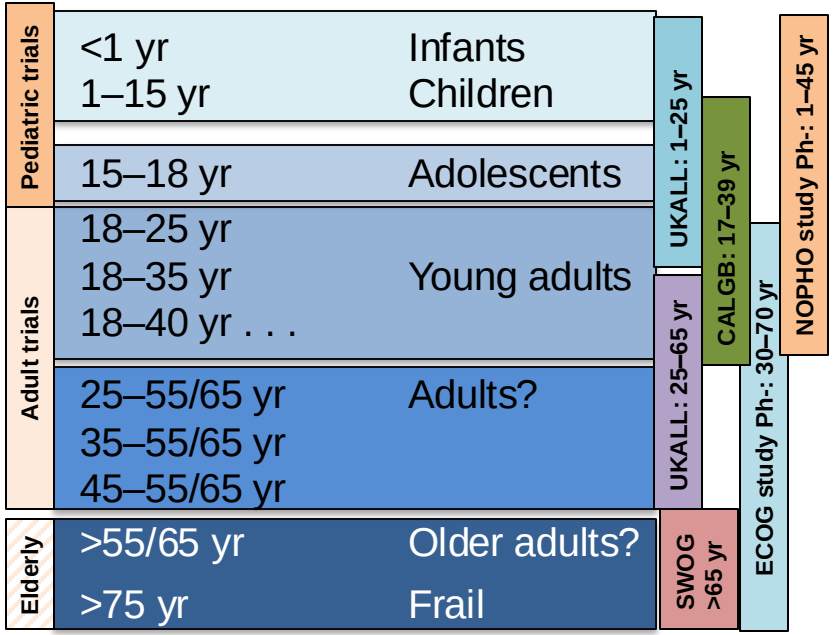
Chiaretti S, et al. *Haematologica.* 2013;98.



Essential factors for decreasing survival with increasing age

- Lower dose-intensity and higher risk of complications
- Increasing proportion of patients with high-risk features
  - Pro B-ALL
  - *MLL*-rearranged ALL
  - Hypodiploid ALL
  - Early T-ALL
  - (Ph positive)
- Unknown factors of disease biology

What Is the Meaning of “Young” and “Old” in the ALL World?



Age cuts are not evidence based, eg

- Toxicity of chemotherapy in general
- Toxicity of defined compounds
- Tolerability of SCT
- Psychosocial factors

Severe consequences, eg

- Non-comparability of clinical trials
- Label for tisa-cel up to 25 yr
- Label for brexu-cel from 26 yr
- Broad age group of "so-called" adults (40–80?) without clear treatment strategy
- Next: Label for blina in MRD neg for 30–70 yr?

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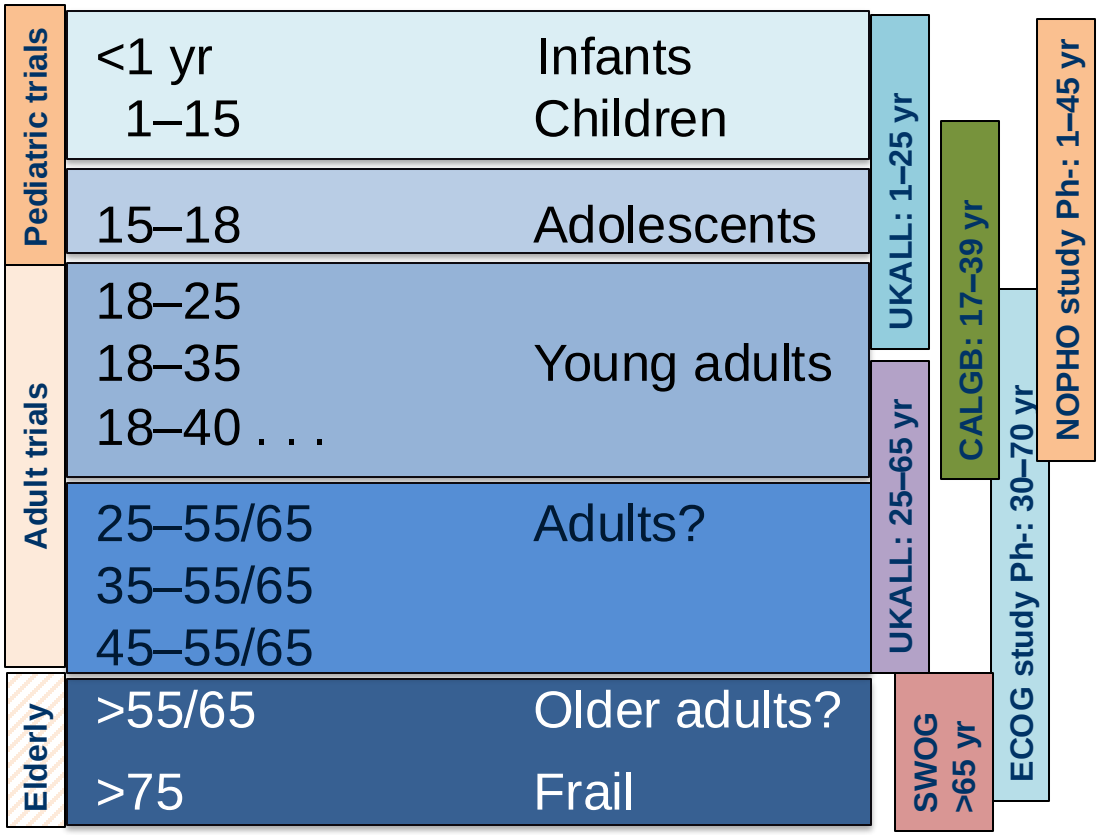
Definition of Target Population: What Is the Meaning of "Young" in the ALL World?



GMALL procedure

Full pediatric protocols? **<18 yr**

Adapted pediatric protocols? **<56 yr**

Reduced pediatric protocols **<76 yr**

Elements of pediatric protocols

Suggestion for a Rational Definition to Decipher Younger and Older Adults

Younger	Older
• Usually 18 to 55–65 yr • No severe comorbidities • In principle, suitable for ped-based therapy (contraindications for individual drugs are acceptable) • In principle, suitable for SCT • Good ECOG before ALL onset	• Usually >55–65 yr • Often severe comorbidities or syndromes • May have limitations in terms of ECOG before ALL and/or in ADL

Flexible age definitions should be used that are based on predefined criteria in clinical trials

Gökbuget 10/2024

AYA Patients With ALL

- **Definition of AYA**
- **Generally promising approaches**
  - **Risk stratification**
- **Why and which specific approaches for AYA**

Diversity of Adult ALL

At first diagnosis

1. **Clinical**
   - Bone marrow involvement
   - Extramedullary involvement
   - Blood counts
   - Age
   - ECOG status
   - Comorbidities
2. **Biological**
   - Subtype
   - Genetic aberrations
     - Translocations
     - Other genetic aberrations like mutations, deletions
     - Aberrant gene expression
     - Gene polymorphisms

During first-line treatment

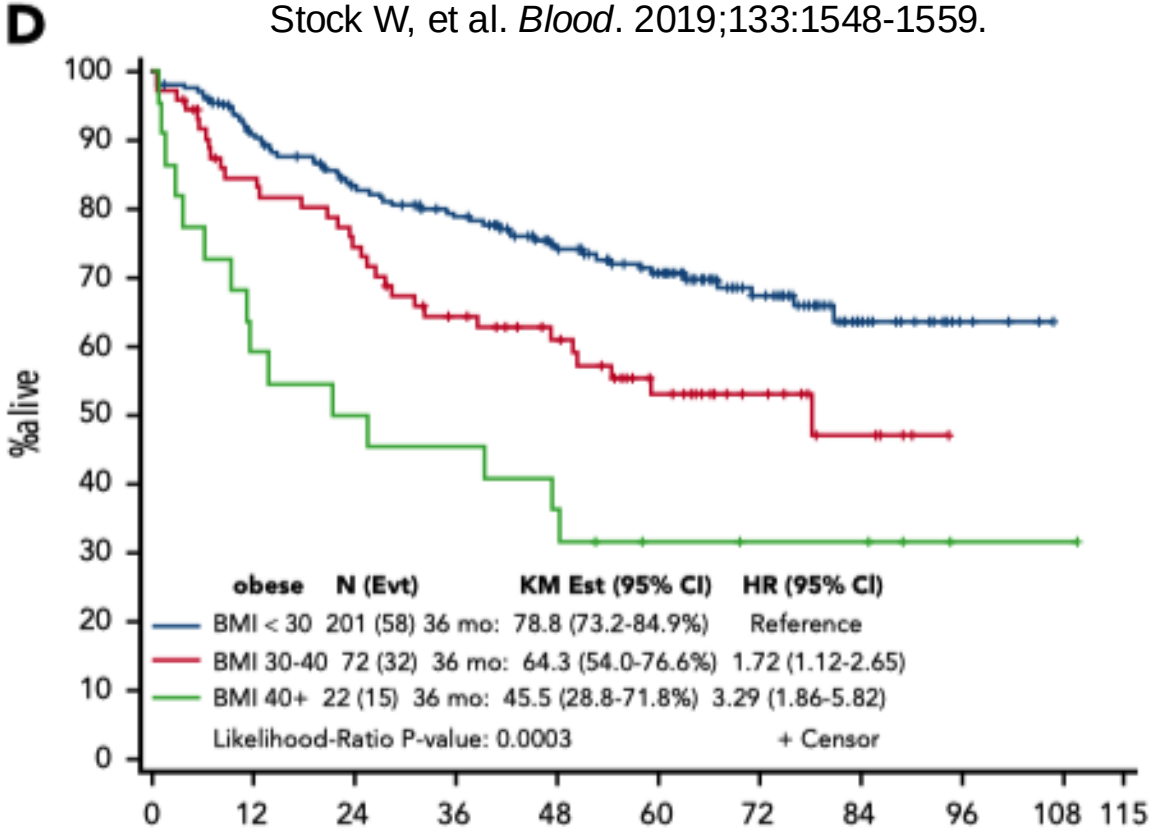
1. **Cytologic response**
2. **Molecular response**
3. **Clinical toxicities/complications**

Risk factors for

- Non-response
- Complications
- Early death
- Death in CR
- Molecular failure
- Relapse
- Late complications

Prognostic Impact of Obesity: Pediatric Regimen in AYA (17–39 yr)

Stock W, et al. *Blood*. 2019;133:1548-1559.



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- Early death
- Death in CR
- Molecular failure
- Relapse
- Late complications

Comorbidities and Early Death in Patients ≥55 Years

Wermann WK, et al. ASH 2018. Abstract 660.

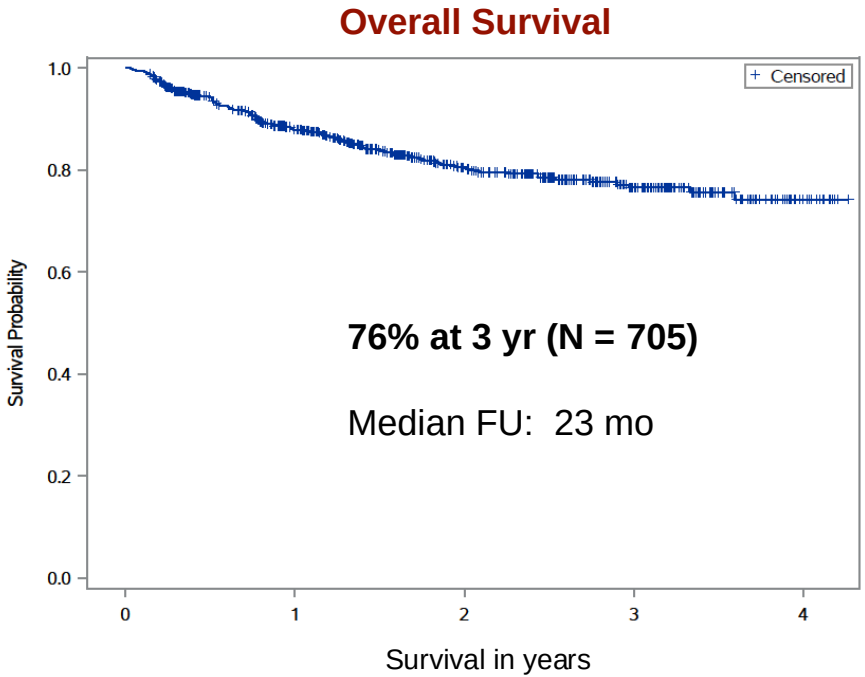
Score	HCT-CI (“Sorror”)		CCI (“Charlson”)
Evaluable	312		328
Early death	13%		12%
LR (0)	**7%**	**Score “0”**	**9%**
IR (1–2)	**13%**	**Score “1–2”**	**12%**
HR (3)	**15%**	**Score “≥3”**	**35%**

AYA Patients With ALL

- **Definition of AYA**
- **Generally promising approaches**
  - **Pediatric-based adult-adapted therapy**
- **Why and which specific approaches for AYA**

GMALL Trial 08/2013: Overall Survival

Gökbuget N, et al. ASH 2021. Abstract 362.



Best From Both Worlds: “Pediatric” and “Adult” Approaches

Pediatric

ALL typical drugs
Vincristine, steroids, asparaginase
Methotrexate
Reinduction

Cyclic sequential block therapy
Intensive CNS prophylaxis
Consequent maintenance

Risk-adapted treatment including MRD
Reduction of SCT indications

↓ Intensive chemo in Ph+/less SCT

Protocol adherence including relapse therapy
Treatment within multicenter study groups

Adult

ALL typical drugs
Vincristine, steroids
Methotrexate lower doses
Reinduction
PEG-asparaginase individualized

↓Cyclic block therapy including “AML” cycles
Intensive CNS prophylaxis
↑ Consequent maintenance

Risk-adapted treatment including MRD
↑ Reduction of SCT indications

Low-intensity chemo + TKI including third gen
Integration of immunotherapy in first line

↑ Protocol adherence
↑ Treatment within multicenter study groups

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Further Treatment Optimization in Younger Patients With ALL

- **Asparaginase intensification**
- **Rituximab in CD20-positive ALL**
- **Targeted therapy in molecular failure**
- **Integration of immunotherapy in first line**

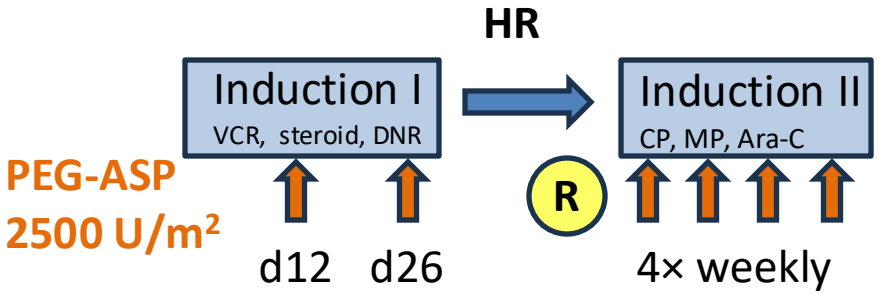
Impact of Intensification of Asparaginase in Pediatric ALL

Pieters R, et al. *Cancer.* 2011;117:238-249.

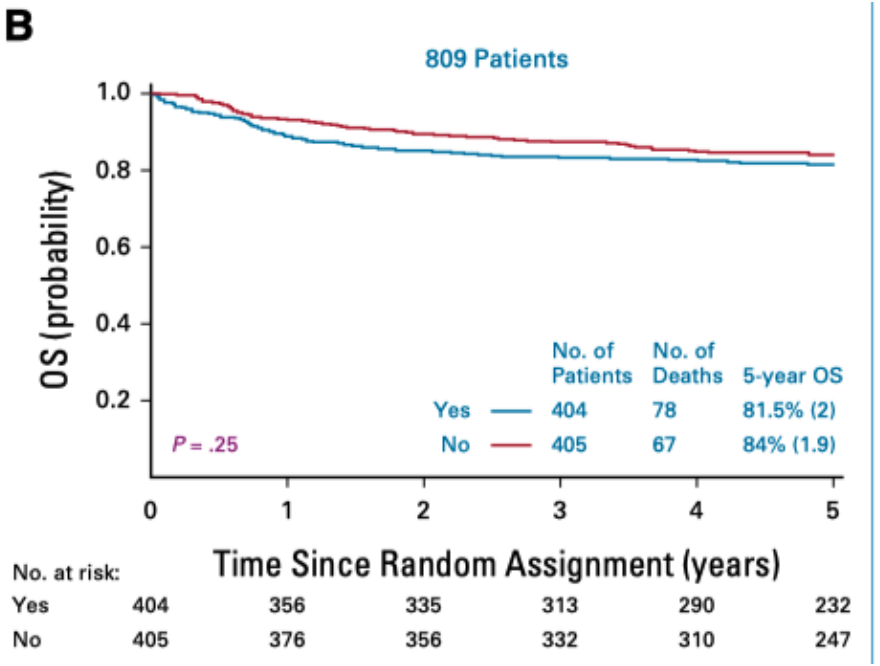
	EFS with less intensive Asp	EFS with more intensive Asp	difference	reference
Erwinase vs Coli Asp EORTC-CLG 58881	60%	73%	significant	Duval 2002
Erwinase vs Coli Asp DFCI 95-01	78%	89%	significant	Moghrabi 2007
20 extra wks of Asp IBFM/IDH ALL91	79%	88%	significant	Pession 2005
20 extra wks of Asp in IRG AIEOP ALL91	72%	76%	not sign	Rizzari 2001
20 wks of Asp in T-ALL POG 8704	55%	68%	significant	Amylon 1999
20 wks of Asp in T-NHL POG 8704	64%	78%	significant	Amylon 1999
Shorter or longer than 25 wks of Asp DFCI 91-01	73%	90%	significant	Silverman 2001

PEG-Asparaginase Intensification in Pediatric ALL

Conter V, et al. *J Clin Oncol*. 2024;42:915-926.



Adverse Reactions	AR (including life-threatening[a] AR) With PEG-ASNASE	AR (including life-threatening[a] AR) Without PEG-ASNASE
No. of patients with AR	81 (22.2)	39 (8.9)
P	<.001	
No. of AR	93 (25.5)	41 (9.3)
Infectious	32 (8.8)	17 (3.9)
Pancreatic	18 (4.9)	2 (0.5)
Thrombotic (including cerebral)	10 (2.7)	4 (0.9)
Hepatic	7 (1.9)	4 (0.9)
Neurologic/psychologic	10 (2.7)	10 (2.3)
Gastrointestinal	1 (0.3)	0
Metabolic/endocrine	0	1 (0.2)
Drug-related allergic reactions	15 (4.1)	0
Skeletal	0	1 (0.2)
Other/not classifiable	0	2 (0.4)



No effect on outcome
No effect on MRD

Correlation of Selected Grade III/IV Induction Toxicities With BMI

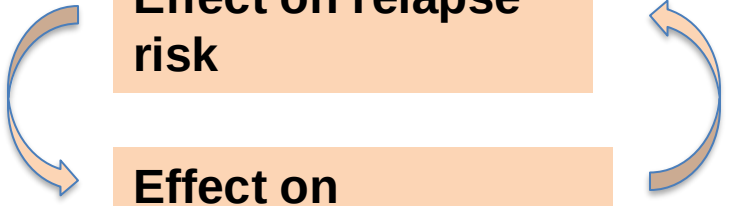
Advani AS, et al. *Blood Adv*. 2021;5:504-512.

Toxicity	**<30**	**30–40**	**>40**
N	197	71	21
Non-hematologic	77%	80%	86%
Hepatic toxicity	**31%**	**52%**	**62%**
Infection	22%	27%	43%
ALT	**24%**	**35%**	**52%**
AST	7%	24%	29%
Hyperbilirubinemia	**12%**	**31%**	**48%**
Pancreatitis	2%	3%	9%
Hyperglycemia	26%	39%	48%

Goals of Asparaginase Therapy

1. **Asparagine depletion for defined time periods**
   - Interval or continuous?
   - Dosing?

2. **Avoidance of severe toxicities**
   - Identification of high-risk patients
   - Identification of high-risk treatment elements
   - Surveillance and supportive care
   - Individualization of dosing and/or intervals



3. **Goal**
   - Right dose to achieve a defined period of asparaginase activity (ie, asparagine depletion for a defined time)

Further Treatment Optimization in Younger Patients With ALL

- **Asparaginase intensification**
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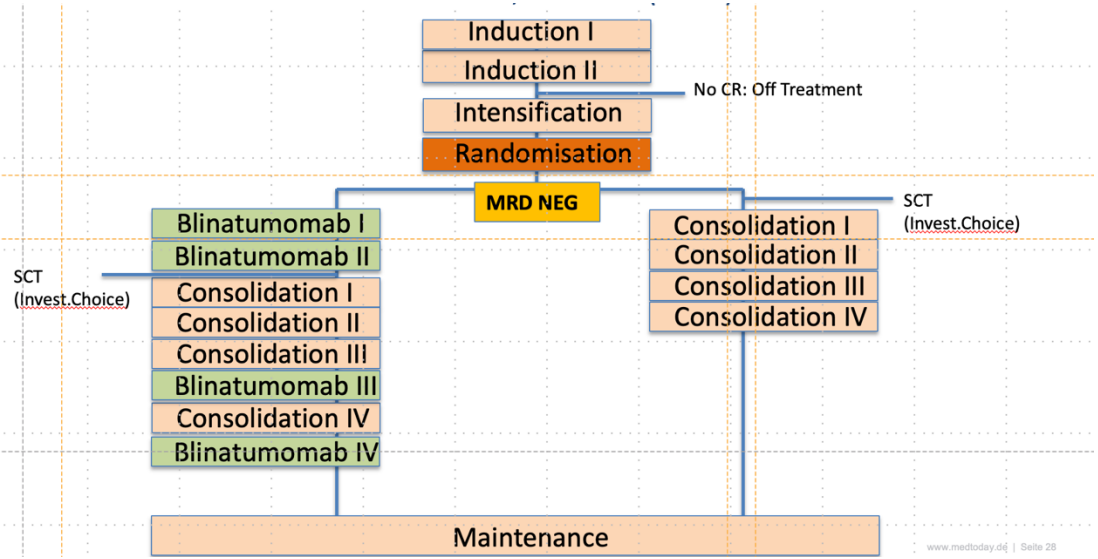
Randomized Trial With Blinatumomab Consolidation in De Novo ALL

Litzow MR, et al. ASH 2022. Abstract LBA-1.



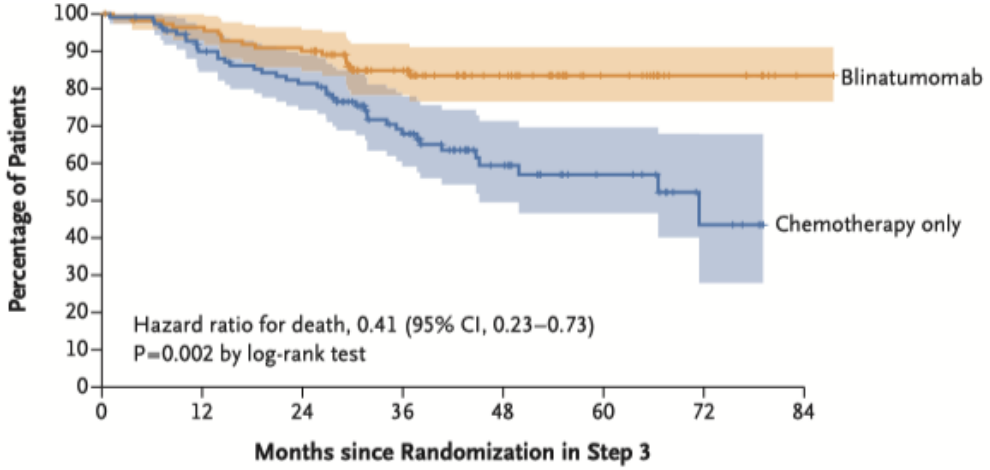
Recruitment: 2013–2019 (6 yr)
Data cutoff: 9/2022 (med FU: 43 mo)
772 screened (screen failure, mostly *BCR-ABL*+)
488 included (1 T-ALL, 6 *BCR-ABL*+)
481 eligible
224 randomized for (MRD negative)

Key features

Median age:	51 (30–70) yr
CR/CRi:	81%
MRD neg:	224 (57%)
SCT CR1:	Around 20% (invest. choice)

ECOG 1910: Overall Survival in MRD-Negative Patients

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



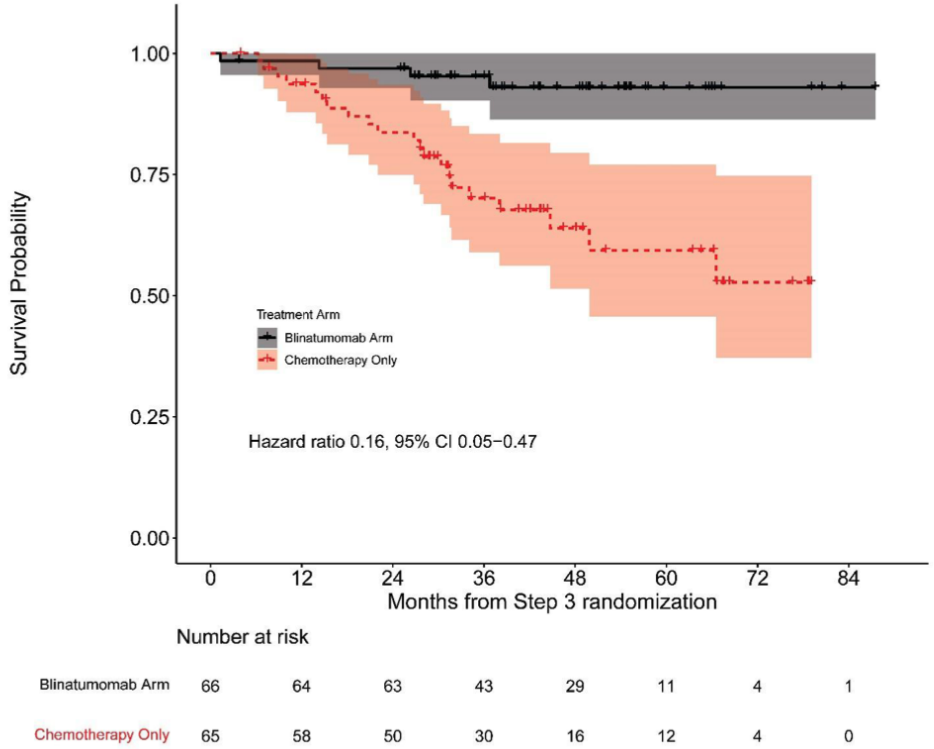
No. at Risk								
Blinatumomab	112	106	99	65	41	19	8	1
Chemotherapy only	112	96	85	53	28	15	5	0

	Blina	Comparator
N	112	112
Death	17 (15%)	40 (36%)
Death relapse	8 (7%)	31 (28%)
Death CR*	9 (8%)	7 (6%)
Unknown	0	2

*Largely from infection.

ECOG 1910: Overall Survival in MRD-Negative Patients 30–55 yr

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



	Blina	Comparator
N	66	65
Death	4 (6%)	21 (36%)
Death relapse	2 (3%)	15 (28%)
Death CR*	2 (3%)	5 (6%)
Unknown		1

*Largely from infection.

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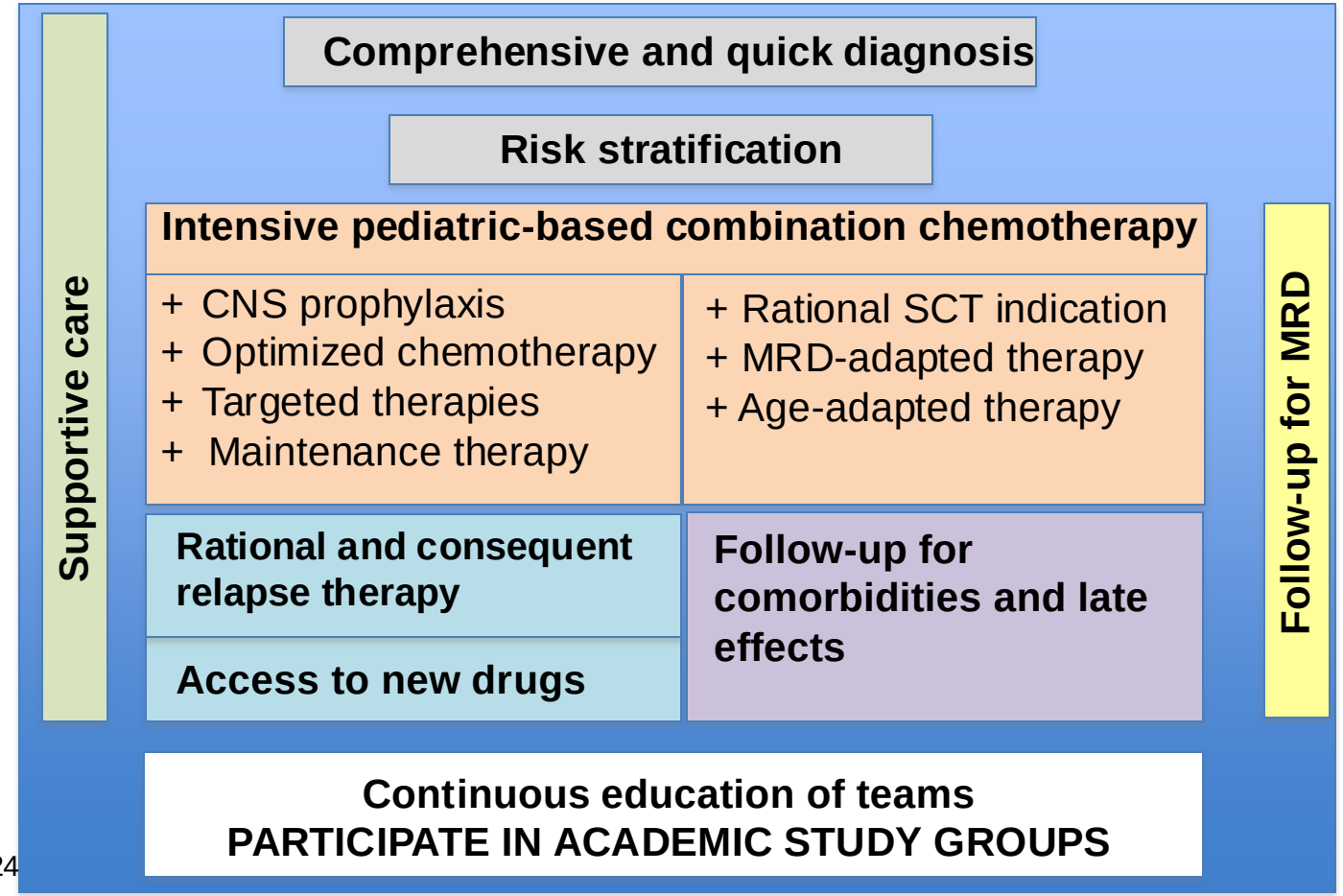
Modern Management of ALL for All Age Groups



AYA Patients With ALL

- **Definition of AYA**
- **Generally promising approaches**
- **Why and which specific approaches for AYA**

UKALL 2003 in Children and Young Adults

Hough R, et al. *Br J Haematol.* 2016;172:439-451.

Impact of Age on SAE Frequency

Age Group	<5 yr	5–9 yr	10–15 yr	16–24	
Pancreatitis	**1%**	**2%**	**3%**	**3%**	**<> 10 yr**
Bacterial infection	**8%**	**6%**	**12%**	**15%**	
Septicemia	**5%**	**4%**	**8%**	**8%**	
MTX encephalopathy	**5%**	**7%**	**15%**	**12%**	
Mucositis	**1%**	**1%**	**3%**	**3%**	
Hyperglycemia	**1%**	**1%**	**3%**	**3%**	
CNS thrombosis	**1%**	**2%**	**3%**	**4%**	
Other thrombosis	**<1%**	**<1%**	**1%**	**3%**	**Increasing with age**
Steroid psychosis	**<1%**	**1%**	**<1%**	**2%**	
Any infection	**17%**	**14%**	**19%**	**27%**	
Avascular necrosis	**<1%**	**2%**	**15%**	**12%**	**More frequent in adolescence**

Major Toxicities and Cause of Death

Rausch CR, et al. *Cancer*. 2019;126:1152-1160.

Relapse is the major cause of death!

All cycles
Cytopenia
Infections

Methotrexate
- Mucositis
- Renal failure

Maintenance
- Adaptations according to blood counts and liver toxicity

Long-term effects
- Osteonecrosis

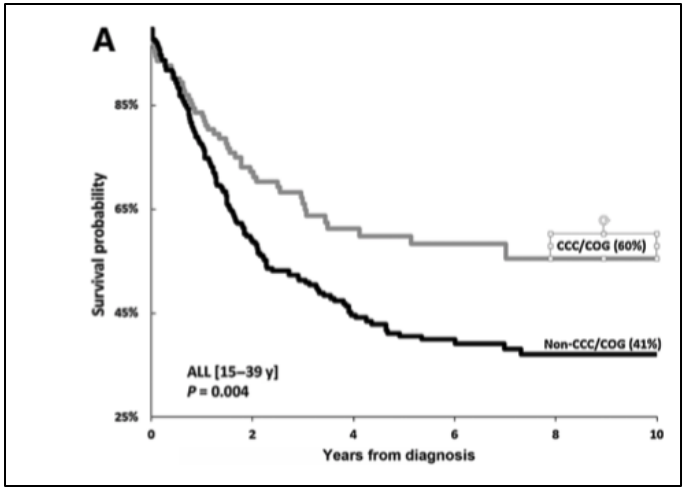
Important
- **Experience**
- **Local logistics**
- **Supportive care**
- **Handling recommendations for toxicities**
- **Continuous education of all teams**

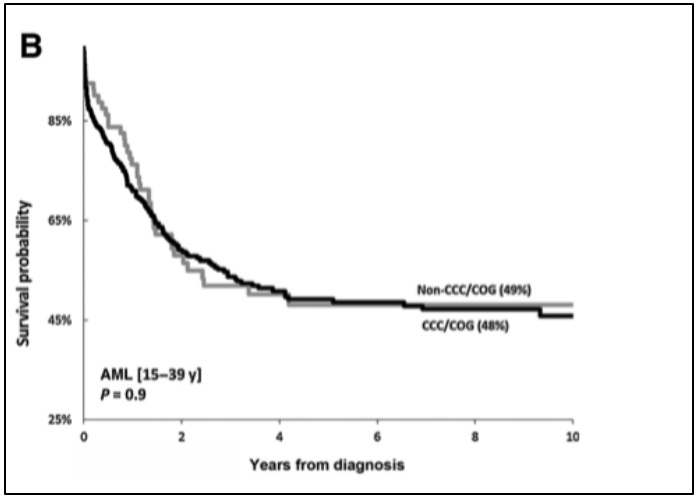
Center Effect on Outcome of Adult ALL

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

Patient cohort: AYA; 15–39 yr
NCI-designated CCC or COG sites vs rest
N = 1,380 ALL
N = 490 AML

Peds: CCC/COG Adult: CCC	Peds: COG Adult: Non-CCC	Peds: Non-COG Adult: Non-CCC
N=3 • UCLA / Jonsson • City of Hope • USC / Norris / Children's Hospital Los Angeles	N=3 • Harbor UCLA • Kaiser Permanente Southern California • Cedars-Sinai	N=89





Center Effect on Outcome of Adult ALL

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

Table 2. Patient characteristics overall and by treatment site

	Acute lymphoblastic leukemia			
	Total (*n* = 1,380)	**CCC/COG (*n* = 809)**	**Non-CCC (*n* = 571)**	***P***
Age				
1–14 years	978 (70.9%)	687 (84.9%)	291 (51.0%)	<0.001
15–21 years	190 (13.8%)	96 (11.9%)	94 (16.5%)	
22–39 years	212 (15.4%)	26 (3.2%)	186 (32.6%)	
Gender				
Female	573 (41.5%)	335 (41.4%)	238 (41.7%)	0.9
Male	807 (58.5%)	474 (58.6%)	333 (58.3%)	
Race/ethnicity				
NHW	275 (19.9%)	182 (22.5%)	93 (16.3%)	0.02
African American	49 (3.6%)	26 (3.2%)	23 (4.0%)	
Hispanic	962 (69.7%)	541 (66.9%)	421 (73.7%)	
Asian/Pacific Islander	94 (6.8%)	60 (7.4%)	34 (6.0%)	
Insurance				
Private	712 (51.6%)	423 (52.3%)	289 (50.6%)	0.2
Public	605 (43.8%)	356 (58.8%)	249 (43.6%)	
Uninsured	63 (4.6%)	30 (3.7%)	33 (5.8%)	
SES				
High	170 (12.3%)	105 (13.0%)	65 (11.4%)	0.6
Middle	758 (54.9%)	444 (54.9%)	314 (55.0%)	
Low	452 (32.8%)	260 (32.1%)	192 (33.6%)	
Distance to nearest CCC/COG (miles)				
Median (IQR)	7.0 (6.0)	6.8 (6.4)	7.3 (5.1)	0.5
Mean (SD)	8.5 (6.7)	8.7 (7.5)	8.3 (5.2)	

In 22- to 39-year-olds, public/uninsured (ALL: *P* = .004; AML <.001), African American/Hispanics (ALL: *P* = .03), and 30- to 39-year-olds (ALL: *P* = .03) were less likely to use CCC/COG.

Do We Need AYA-Specific Therapy Protocols?

No

- Current "adult" protocols are pediatric based, yield good results, and integrate immunotherapy
- Future treatment decisions to be based on age and comorbidities
- Center experience of utmost importance

What do we need?

- Better care for all adult patients with ALL by specialized sites
- Recruitment into clinical trials
- Specific offers for AYA patients (suboptimal in pediatric and adult sites)
- Joint pediatric-adult trials for rare entities

Global Leukemia Academy

Q&A

APTITUDE HEALTH®

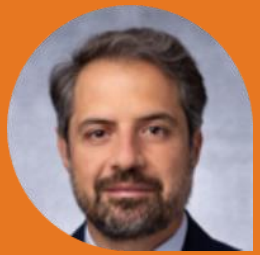
Global Leukemia Academy

ALL case-based panel discussion

Case 1 ALL: Anjali Cremer (Germany)

Case 2 ALL: Fabian Lang (Germany)

Moderator: Elias Jabbour



APTITUDE HEALTH®

Global Leukemia Academy

Case 1

Anjali Cremer

APTITUDE HEALTH®

Clinical Case:
B-ALL in an Elderly Patient

Global Leukemia Academy EU Meeting

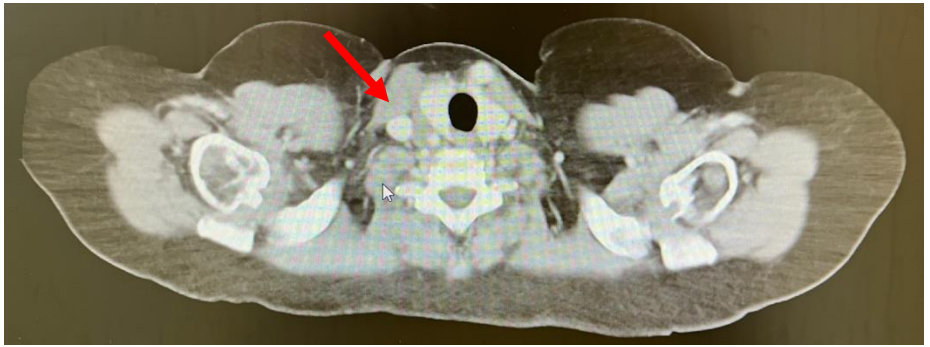
Dr med Anjali Cremer
University Hospital Frankfurt
Department of Hematology/Oncology

October 16–17, 2024

Clinical characteristics

- Female, 62 y
- Presents with exertional dyspnea since 4 days, pain in her lower calves
- CT scan: mass around right A. carotis and infiltration of M. sternocleidomastoideus

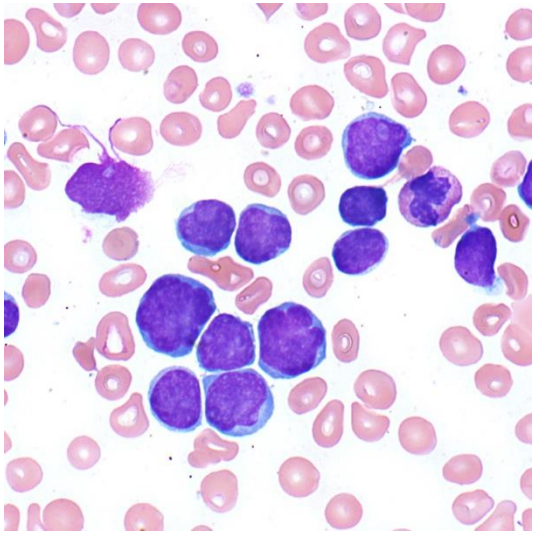
Bestimmung	Wert	Flag	Status	Vorwert vom	Einheit	Referenzbereich
Laborkennung						
LaborKennung	ZIMZL		T.Val.			
Hämatologie						
Leukozyten	120.71	++	M.Val		/nl	3.96 - 10.41
Erythrozyten	2.14	--	M.Val		/pl	3.96 - 5.16
Hämoglobin	6.7	--	M.Val		g/dl	11.6 - 15.5
Hämatokrit	18.8	--	M.Val		%	34.6 - 45.3
MCV	87.9		M.Val		fl	80.0 - 95.5
MCH	31.3		M.Val		pg	26.1 - 32.6
MCHC	35.6	+	M.Val		g/dl	31.9 - 35.5
Red Cell Distribution Width	16.3	+	M.Val		%	12.1 - 14.8
MPV	9.2		M.Val		fl	9.2 - 12.5
Thrombozyten	68	--	M.Val		/nl	176 - 391



Prof Vogl, Frankfurt

Bone marrow cytology

Blasts	67%
Cellularity	Hypercellular
Megakaryopoiesis	Normal
Promyelocytes	1%
Myelocytes	1%
Granulocytes	1%
Eosinophils	1%
Monocytes	1%
Erythroblasts	10%
Plasma cells	5%
Lymphoids	11%



www.cap.org

Immunophenotype

CD45 dim	86%
CD19+	99.2%
CD79a+	97.2%
CD34+	8%
CD10-	0.2%
CD19+20+	0.3%
cyIgM-	1%
CD38dim	1%
CD58+	10%
CD66c-	5%
CD34+CD22+	3.2%

MRD and cytogenetics

Probennummer	Index-Marker	Inhibition	Albumin-kopien	MRD-Wert (korrigiert)	Material Abnahme	Material Eingang	Art des Materials	Anlass (incl. Einsender)
D-24-00011	1;2		1.1E+05	7E-01	25.12.2023	29.12.2023	pB	Primärdiagnose
D-24-00012	1;2		4.1E+04	6E-01	27.12.2023	29.12.2023	KM	Primärdiagnose

- Cytogenetics: *KMT2A-AF4* (t[4;11])

Risk factors

High leukocyte counts	>30 G/l B-cell precursor ALL
Subtype	Pro B, early T, mature T
Late CR	>3 weeks (after Induction II)
Cytogenetics/Molecular aberrations	t(9;22) – *BCR/ABL* t(4;11) – *KMT2A/AFF1*
Minimal residual disease (MRD)	MRD level >10^{-4} MRD increase >10^{-4} after previous CR

Question 1

How would you classify the risk level of this disease?

A. Standard risk
B. High risk

High leukocyte counts	>30 G/l B-cell precursor ALL
Subtype	Pro B, early T, mature T
Late CR	>3 weeks (after Induction II)
Cytogenetics/Molecular aberrations	t(9;22) – *BCR/ABL* t(4;11) – *KMT2A/AFF1*
Minimal residual disease (MRD)	MRD level >10^{-4} MRD increase >10^{-4} after previous CR

Question 1 – Answer

How would you classify the risk level of this disease?

A. Standard risk
B. High risk

High leukocyte counts	>30 G/l B-cell precursor ALL
Subtype	Pro B, early T, mature T
Late CR	>3 weeks (after Induction II)
Cytogenetics/Molecular aberrations	t(9;22) – *BCR/ABL* t(4;11) – *KMT2A/AFF1*
Minimal residual disease (MRD)	MRD level >10^{-4} MRD increase >10^{-4} after previous CR

Overview GMALL study protocol

This slide contains data shown exclusively to the live audience

Treatment

12/2023: Primary diagnosis – pro-B ALL, MRD: 7E-01

12/2023: Prephase GMALL elderly study protocol (dexamethasone, cyclophosphamide, methotrexate IT)

1/2024: Induction I (vincristine, idarubicin IT. Triple: dexamethasone IT, cytarabine IT, MTX IT)

> blast persistence, MRD positive 2E-01

2/2024: Induction II (cyclophosphamide, cytarabine IT triple)

> hCR, MRD positive 6E-03

3/2024: Consolidation I (MTX reduced on 63% due to BMI, PEG-asparaginase)

4/2024: Consolidation II: cytarabine IT triple

> hCR, MRD positive 6E-04

6/2024: Blinatumomab salvage I > paused due to neurotoxicity

> hCR, MRD positive 9E-05

8/2024: Blinatumomab salvage II > patient develops neurotoxicity again and dexamethasone treatment was started

9/2024: Planned allogeneic stem cell transplantation MUD

Question 2

How would you have decided regarding blinatumomab treatment and observed neurotoxicity before alloTx?

A. Continue with blinatumomab in a lower dose with parallel dexamethasone treatment

B. Stop treatment and proceed to alloTx

Question 2 – Answer

How would you have decided regarding blinatumomab treatment and observed neurotoxicity before alloTx?

A. Continue with blinatumomab in a lower dose with parallel dexamethasone treatment

B. Stop treatment and proceed to alloTx 

Treatment

- MRD before Blina: 9×10^{-5}
- Blinatumomab was only tolerated by the patient under dexamethasone 40 mg/d due to ongoing neurotoxicity
- High infection risk under continuous Dexa treatment, which might interfere with planned allogeneic HSCT

MRD levels over the course of treatment

Proben-nummer	unters. Marker	Hin-weis‘	Albumin-kopien	MRD-Wert (kumulativ)	Material Abnahme	Material Eingang	unters. Material	Zeitpunkt (laut Einsender)
D-24-00011	1;2		1.1E+05	7E-01	25.12.2023	29.12.2023	pB	Primärdiagnose
D-24-00012	1;2		4.1E+04	6E-01	27.12.2023	29.12.2023	KM	Primärdiagnose
D-24-01254	1;2		1.0E+05	2E-01	26.01.2024	27.01.2024	KM	nach Ind. I
D-24-03224	1;2		9.6E+04	6E-03	08.03.2024	12.03.2024	KM	vor Kons. I
D-24-06547	1;2		1.0E+05	6E-04	17.05.2024	21.05.2024	KM	Verlauf
D-24-09202	1;2		8.3E+04	2E-04	12.07.2024	13.07.2024	KM	vor Reinduktion
D-24-09868	1;2		5.0E+04	9E-05	25.07.2024	26.07.2024	KM	Verlauf
D-24-11123	1;2		1.1E+05	positiv <1E-04	23.08.2024	24.08.2024	KM	nach Blina

Central MRD Reference Lab Kiel, M. Brüggemann.

Global Leukemia Academy

Case 1 – Discussion

Anjali Cremer

APTITUDE HEALTH®

Global Leukemia Academy

Case 2

Fabian Lang

APTITUDE HEALTH®

Male patient, 35 years old

- 12/2020 primary diagnosis: common B-ALL
  - Initial blood count: leukocytes 114,600/yL; Hb 10 g/dL; thrombocytes 342,000/yL
  - Bone marrow: 70%–80% lymphatic blast infiltration
  - Immunology: CD19, CD10, CD34, CD79a, CD22, TdT positive
  - Cytogenetics: 46 XY t(9;22)(q34;q11) -4
    45 XY der(7;16)(q10;p10), t(9;22)(q34;q11) -11
    46 XY r(7)(p11q21), t(9;22)(q34;q11) -4
    46 XY -10
  - Molecular genetics: *BCR::ABL1* positive

- Comorbidities
  - Diabetes mellitus type 2

Treatment course: Male patient, 35 years old

Male patient, 35 years old, refractory disease after Cons 1

Which therapeutic option would you choose?

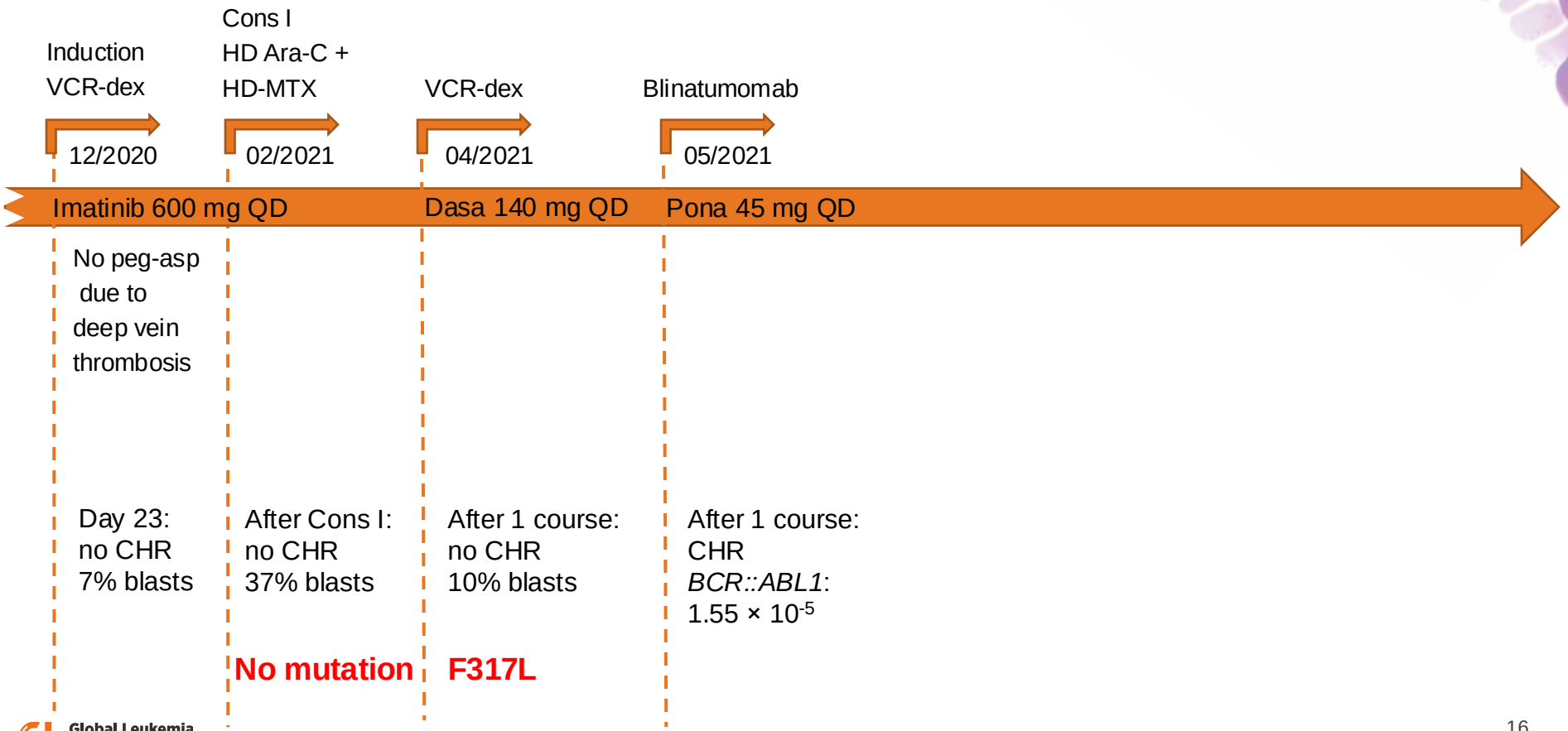
- Switch to ponatinib 45 mg QD
- Switch to dasatinib 140 mg QD + VCR-dex
- Blinatumomab + ponatinib 45 mg QD
- Blinatumomab + dasatinib 140 mg QD

Male patient, 35 years old, refractory disease after Cons 1

Which therapeutic option would you choose?

- Switch to ponatinib 45 mg QD
- **Switch to dasatinib 140 mg QD + VCR-dex**
- Blinatumomab + ponatinib 45 mg QD
- Blinatumomab + dasatinib 140 mg QD

Treatment course: Male patient, 35 years old



Male patient, 35 years old, hCR after blina + pona, *BCR::ABL1*: 1×10^{-5}

Which therapeutic option would you choose?

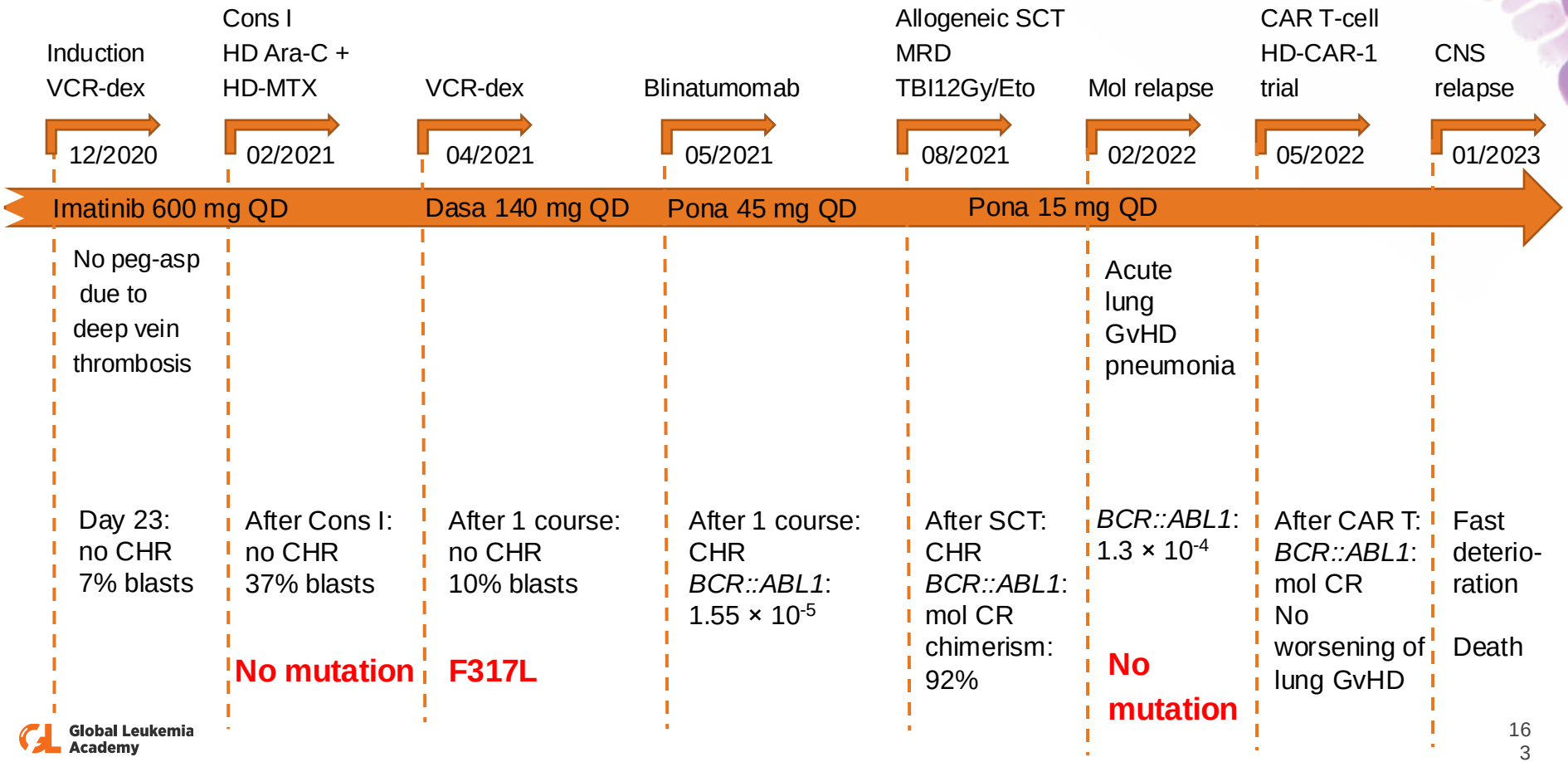
- Continue blinatumomab + ponatinib
- Ponatinib 45 mg QD
- Allogeneic SCT
- CAR T-cell therapy

Male patient, 35 years old, hCR after blina + pona, *BCR::ABL1*: 1×10^{-5}

Which therapeutic option would you choose?

- Continue blinatumomab + ponatinib
- Ponatinib 45 mg QD
- **Allogeneic SCT**
- CAR T-cell therapy

Treatment course: Male patient, 35 years old



Main messages/questions from this case

- Up-front resistant disease is difficult to treat to reach durable remission
- Relapse despite allogeneic SCT in optimal MRD setting
- CAR T-cell therapy effective, but not durable
- Multiple relapse despite continuous TKI therapy
- Efficacy of immunotherapy?
- How to prevent CNS relapse after CAR T-cell therapy?

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Case 2 – Discussion

Fabian Lang

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BREAK

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Genetic characterization and risk stratification of AML; role of *FLT3* and *IDH* in AML and special considerations for young and fit patients

Naval Daver

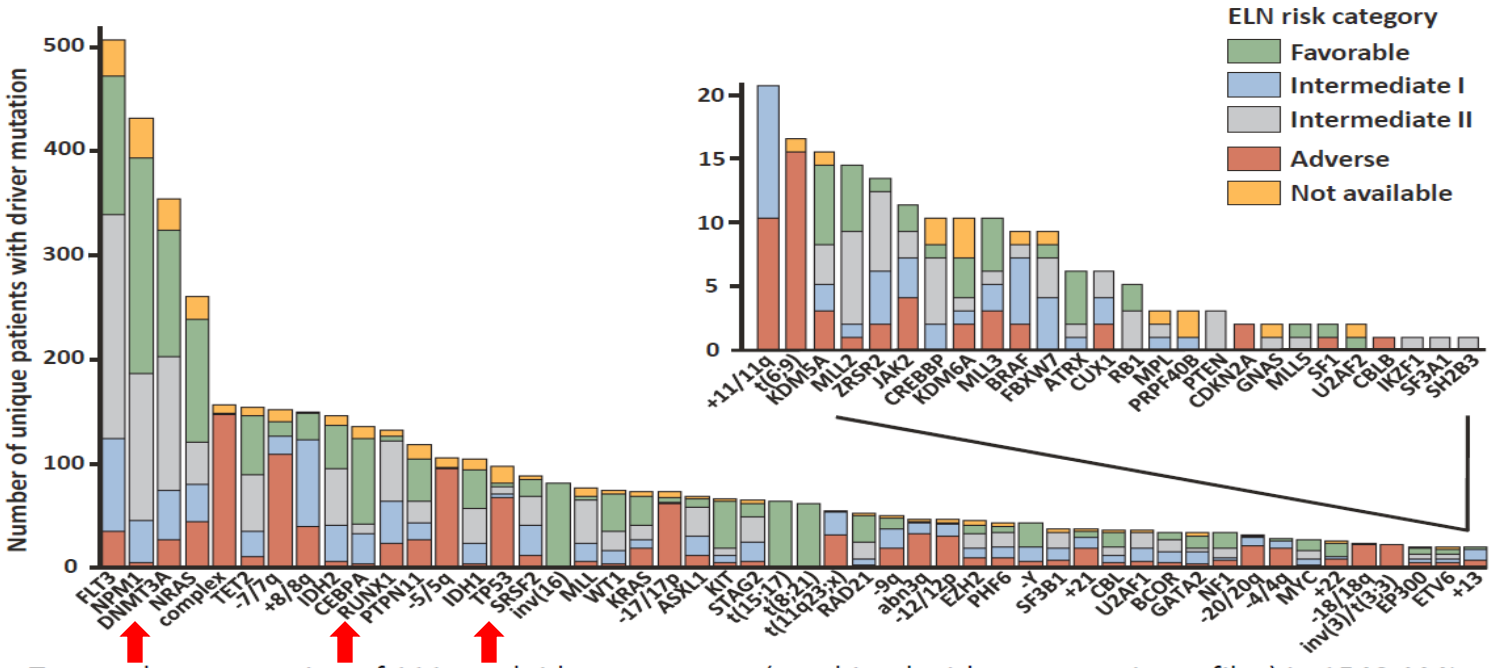
APTITUDE HEALTH

Optimizing the Incorporation of Targeted Therapies in the Treatment of AML

GLA JAPAC August 2024

Naval Daver, MD
Director, Leukemia Research Alliance Program,
Professor of Medicine
Department of Leukemia
MD Anderson Cancer Center

Major advances in understanding the cytogenetic and mutational landscape of AML



- Targeted resequencing of 111 myeloid cancer genes (combined with cytogenetic profiles) in 1540 AML
- 5236 driver mutations (i.e., fusion genes, copy number alterations, gene mutations) involving 77 loci
- 6 genes mutated in >10% pts; 13 genes 5–10% pts; 24 genes 2–5% pts; 37 genes <2% pts

Papaemmanuil E, et al. *N Engl J Med*. 2016;374:2209-2221.

Using genomics to improve AML prognostication and AlloSCT decisions

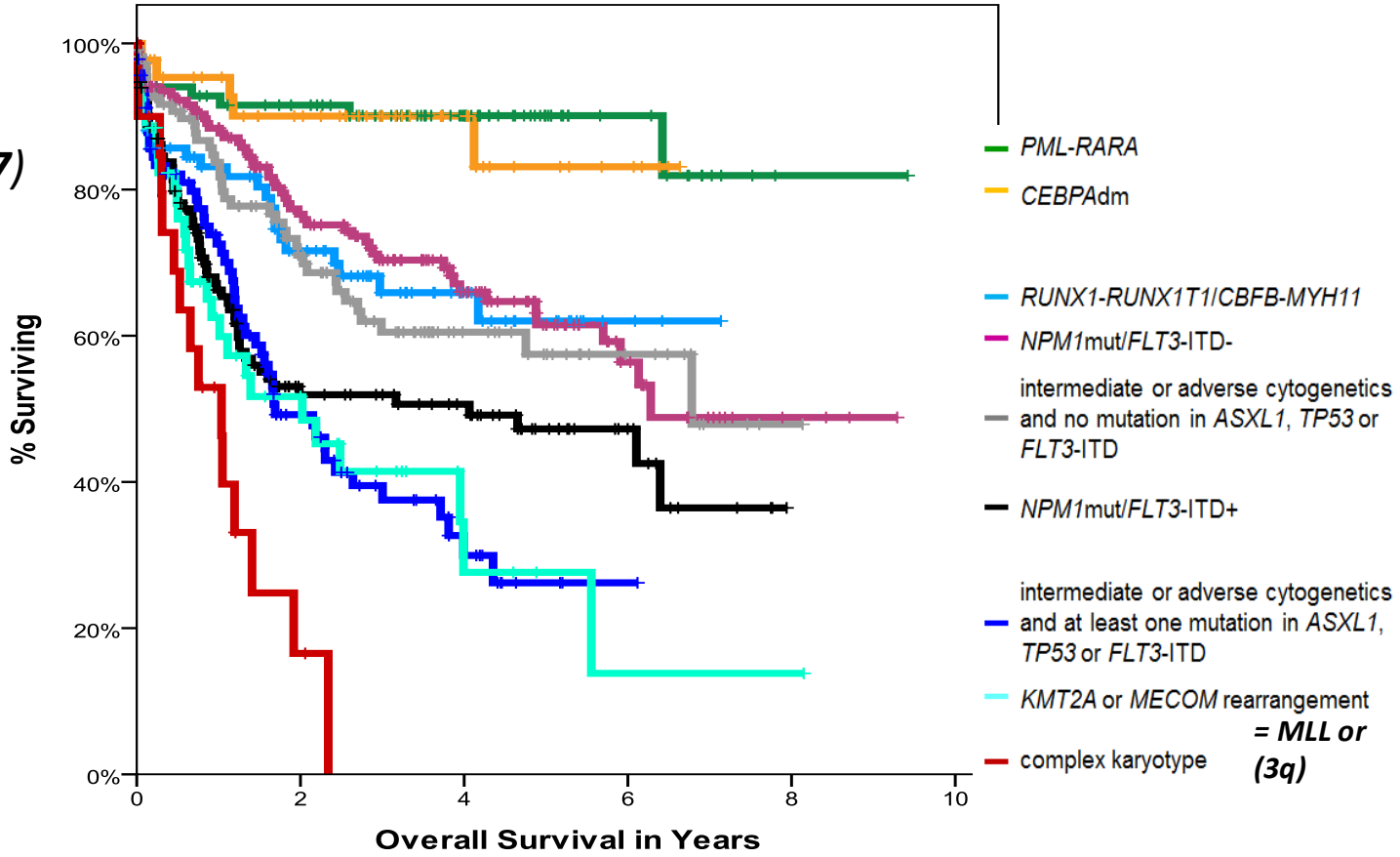
APL:

PML-RARA = t(15;17)

Core-binding factor (CBF) leukemias:

RUNX1-RUNX1T1 = t(8;21)

CBFB-MYH11 = inv(16) or t(16;16)



Haferlach C, et al. Blood. 2016;128(22):286.

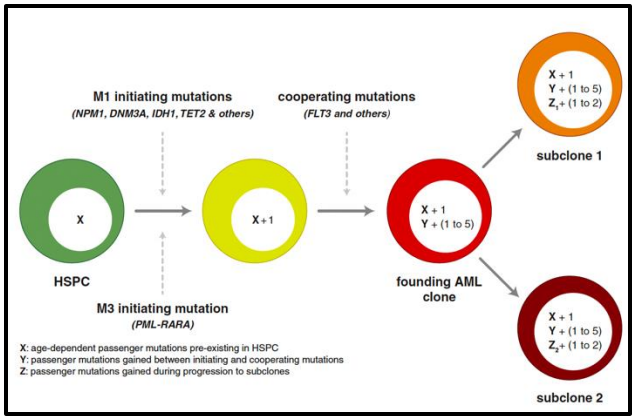
Using genomics to improve AML therapy

- ***FLT3* mutations – add FLT3 inhibitor (midostaurin, sorafenib, quizartinib, gilteritinib), consider allo-SCT**
- ***IDH1/2* mutations – add IDH inhibitor: enasidenib (AG-221/IDH2 inhibitor), ivosidenib or olutasidenib (IDH1 inhibitors)**
- ***MLL*r (*KMT2A*r) – Menin inhibitors (Syndax, Kura, Sumitomo, J&J, BMF, and others)**
- ***NPM1* mutation in diploid CG – Menin inhibitors, Ara-C sensitivity, VEN sensitivity**
- ***TP53* mutation – consider decitabine 10 days, new agents (APR, CD47), IO therapies, early referral to allo-SCT**
- ***RAS* mutations – no targetable therapies in AML, common resistance pathway to VEN, FLT3i, IDHi therapies; consider clinical trials**

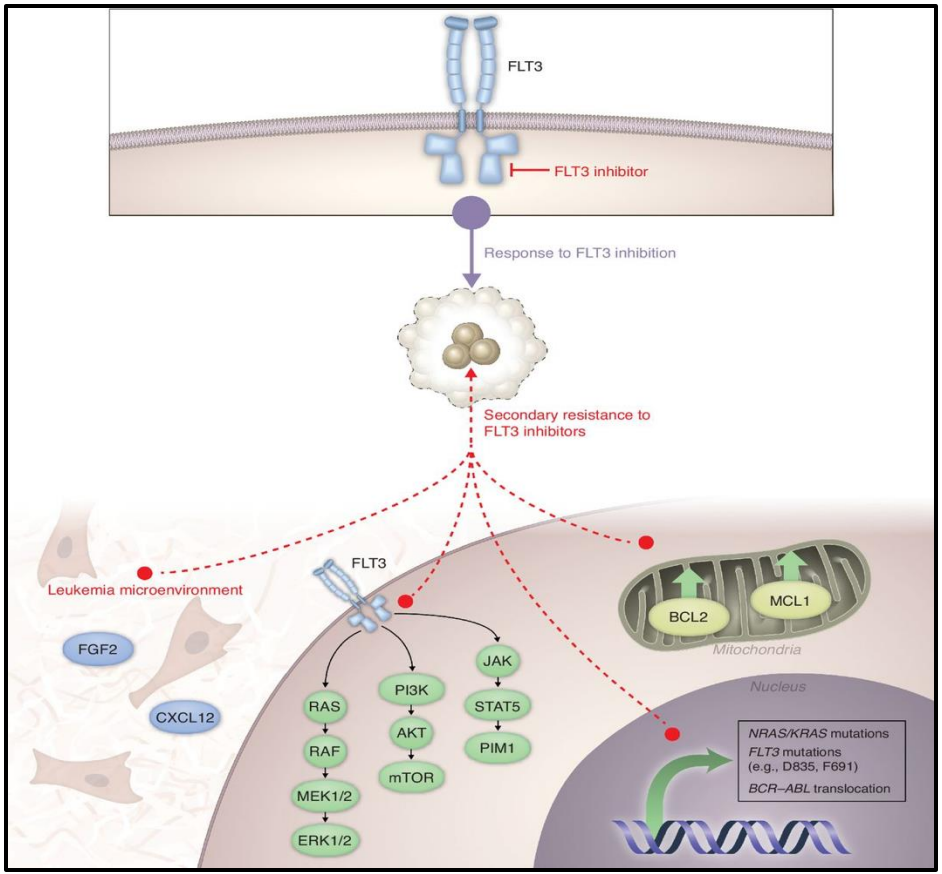
1. Targeting *FLT3* Mutations

Combination approaches may help overcome heterogenous mechanisms of resistance: Many *FLT3* relapses are *FLT3*wt and *FLT3* is almost always a late hit

PTPN11
NPM1
DNMT3A
WT1



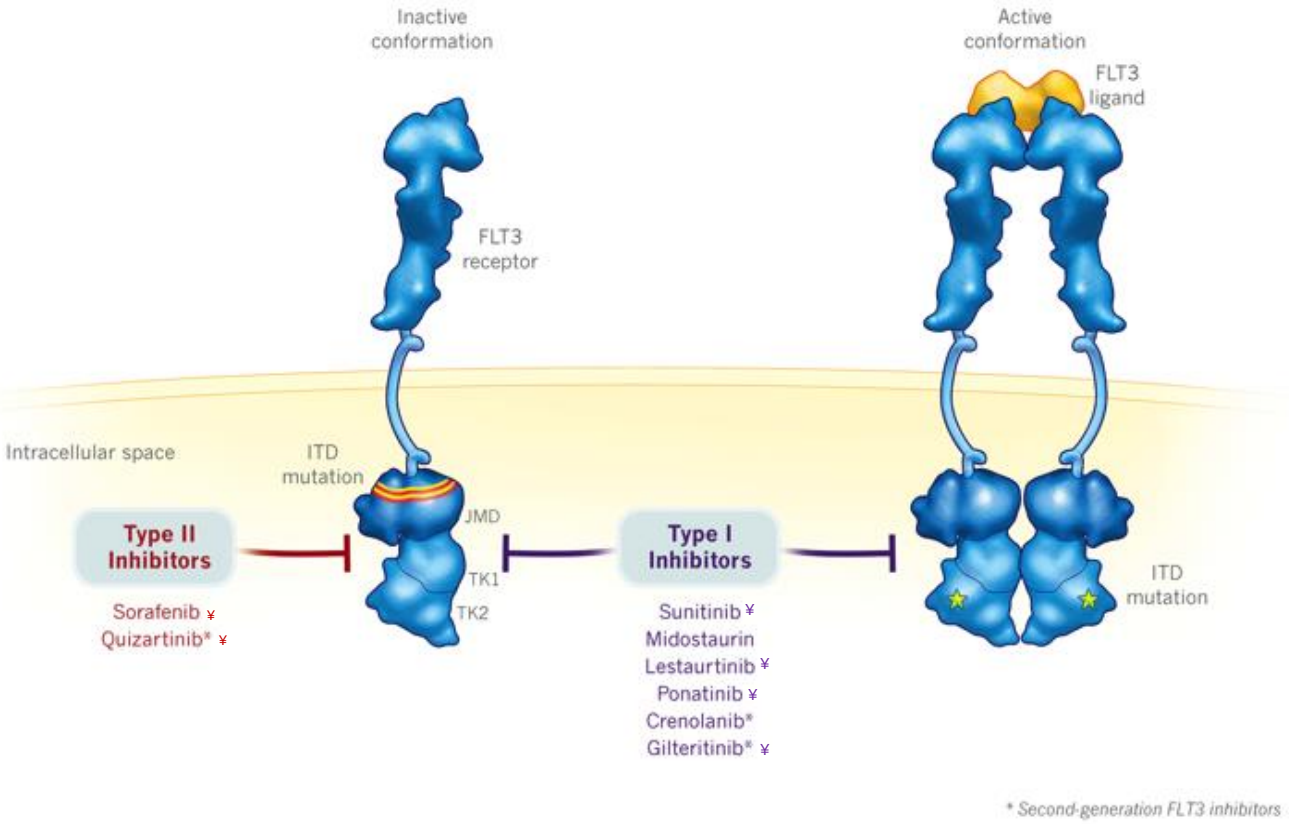
FLT3-ITD
NPM1
DNMT3A
WT1



- *FLT3* mutations are late hits and frequently subclonal
- Can be gained or lost at relapse/progression

Short N….Daver N., Cancer Discov. 2020 Apr;10(4):506-525

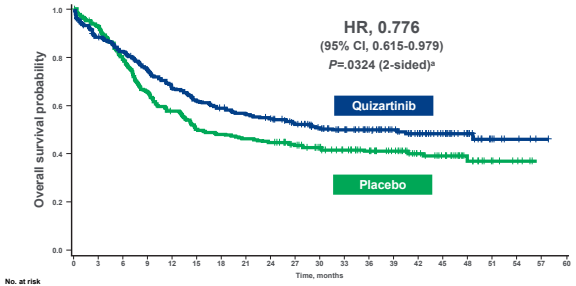
Type 1: Bind receptor "active" conformation near ATP pocket or activation loop: ITD and TKD
Type 2: Bind receptor "inactive" conformation near ATP pocket – ITD only

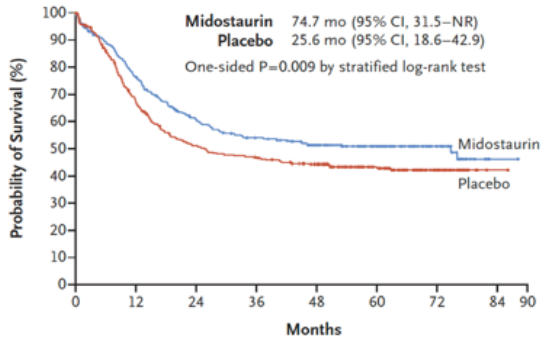


Daver N et al, Leukemia. 2019 Feb;33(2):299-312

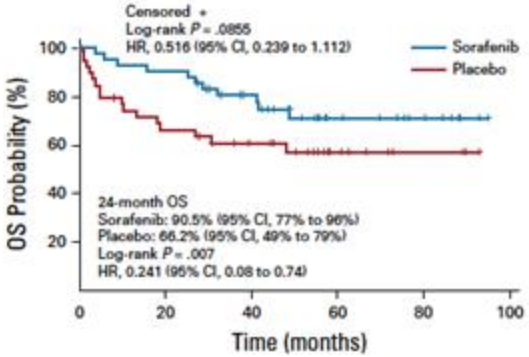
FLT3 inhibition improves survival in fit patients across the treatment spectrum

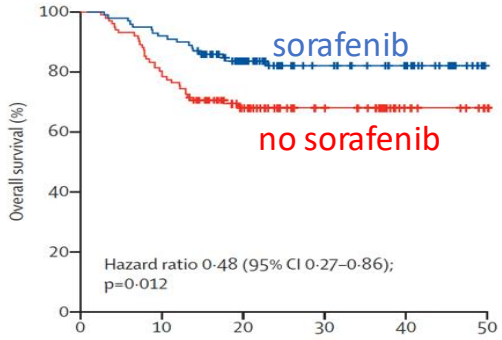
Newly diagnosed, intensive chemotherapy + TKI/placebo



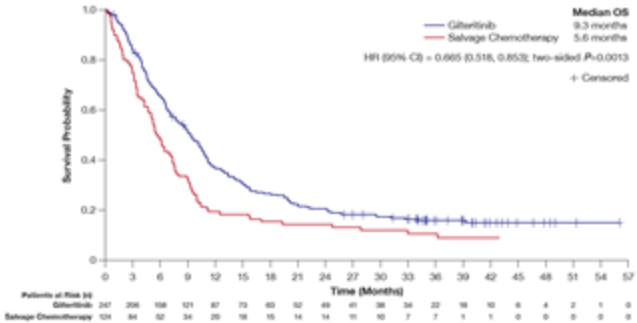


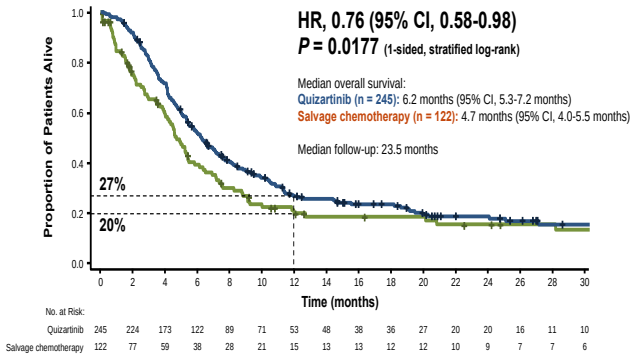
TKI maintenance after alloHSCT (sorafenib 2 studies)





Relapsed/Refractory single agent TKI vs chemotherapy

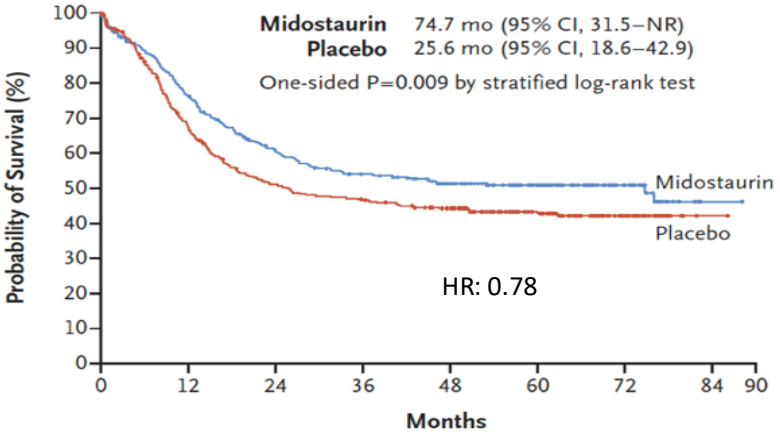




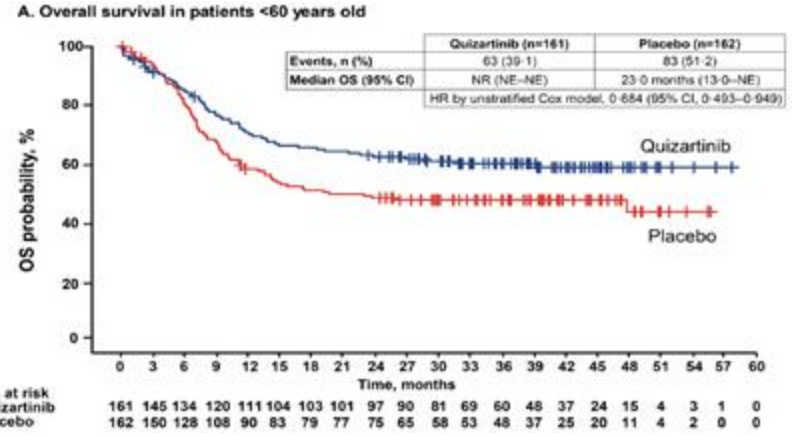
Erba HP, et al. EHA 2022, abstract S100;Stone RM, et al. N Engl J Med. 2017;377(5):454-464; Burchert A, et al. J Clin Oncol. 2020;38(26):2993-3002; Xuan Y, et al. Lancet Oncol. 2020;21(9):1201-1212; Perl AE, et al. Blood. 2022;139(23):3366-3375; Cortes JE, et al. Lancet Oncol. 2019;20(7):984-997.

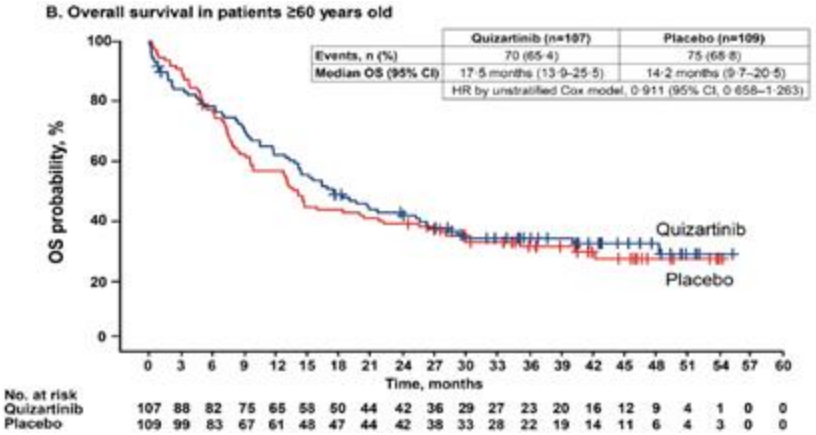
Younger patients (<60 years) particularly benefit from quizartinib

RATIFY, all <60 years old and 25% *FLT3*-TKD: 4-yr OS 51%



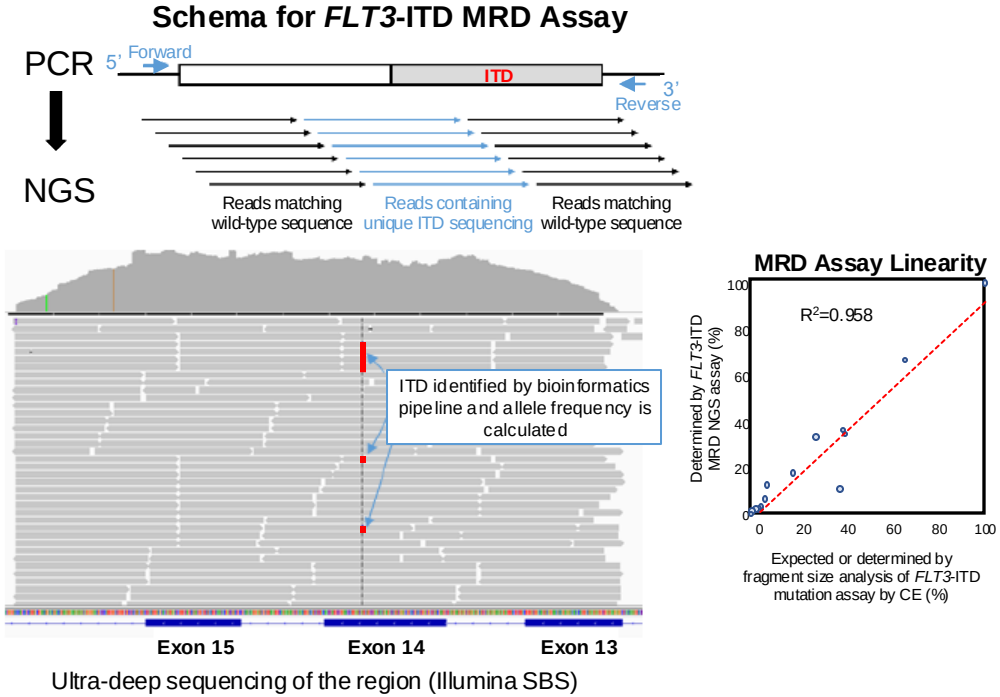
QuANTUM-First: <60 years old and all *FLT3*-ITD: 4-yr OS 60%





Measurable residual disease (MRD) and QuANTUM-First

- MRD
  - Key prognostic factor in AML[1-3]
  - Conventional PCR for *FLT3*-ITD less useful due to insensitivity (~1%)[2]
- PCR-NGS is sensitive and specific for *FLT3*-ITD MRD (targeting exons 14-15)[2,4]:
  - PCR amplification step[2]
  - Amplicons analyzed by NGS[2]
  - Developed specifically for this trial[2,4]
  - LLOQ = 10^{-4}
  - LLOD = 2×10^{-6}
  - Often identifies multiple ITD sequences

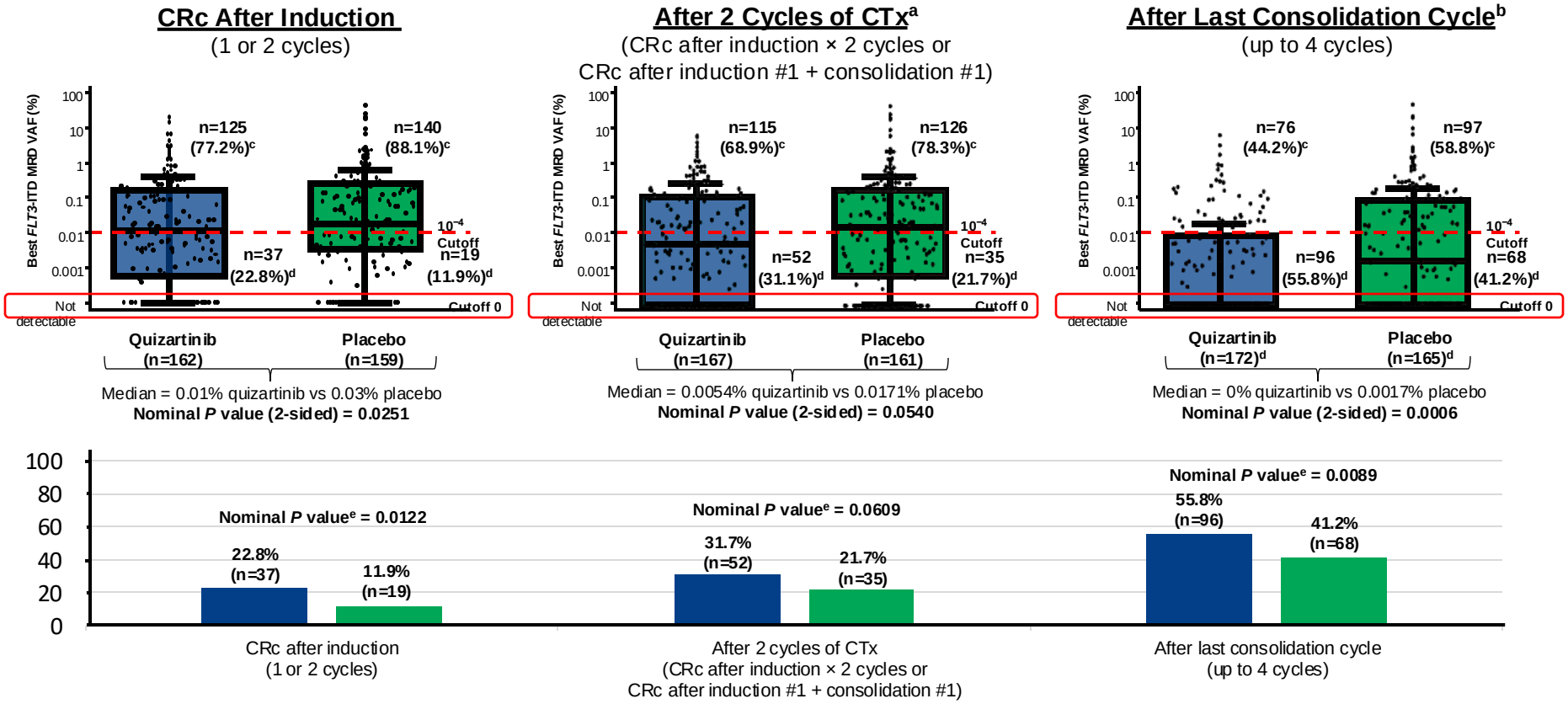


Ultra-deep sequencing of the region (Illumina SBS)

AML, acute myeloid leukemia; CE, capillary electrophoresis; CR, complete remission; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITD, internal tandem duplication; LLOD, lower limit of detection; LLOQ, lower limit of quantification; MRD, measurable residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction.

1. Jongen-Lavrencic M, et al. *N Engl J Med*. 2018;378(13):1189-1199. 2. Levis M, et al. *Blood Adv*. 2018;2(8):825-831. 3. Döhner H, et al. *Blood*. 2022;140(12):1345-1377. 4. Levis M, et al. *Blood*. 2020;135(1):75-78.

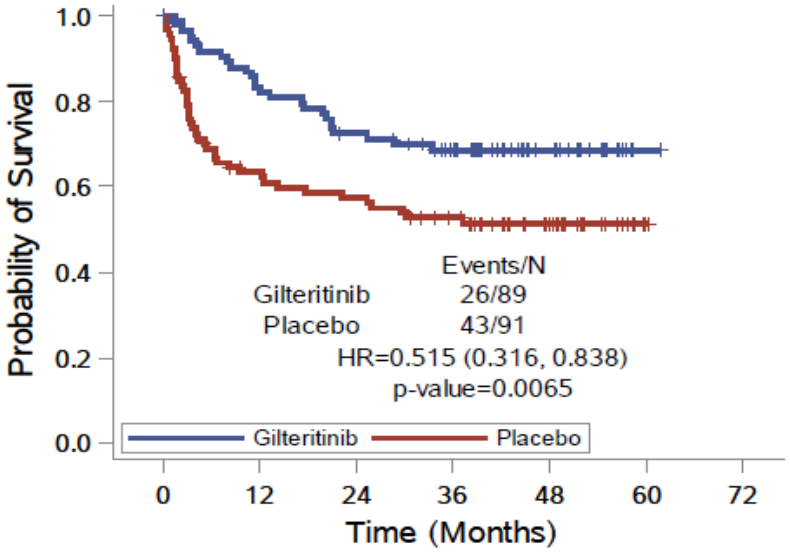
Across the treatment course, quizartinib leads to deeper responses and more frequently eliminates detectable MRD than placebo



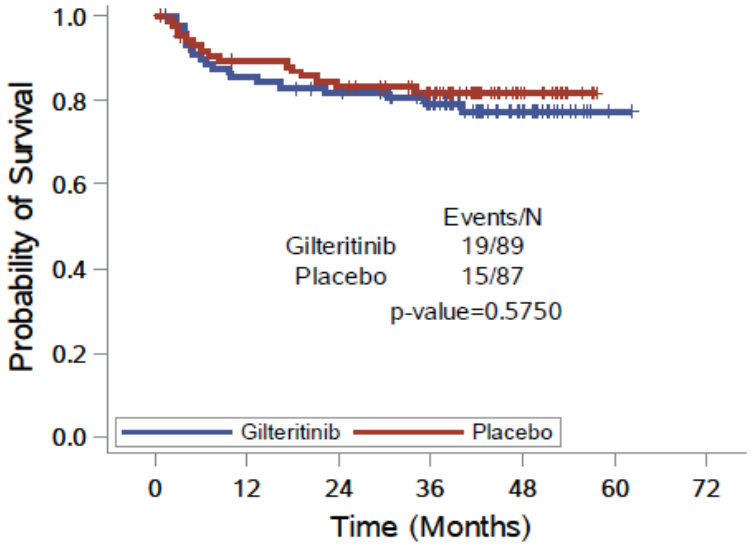
Post hoc analysis. [a]Defined as 2 cycles of induction CTx or 1 cycle of induction CTx + 1 cycle of consolidation CTx. [b]Include samples up to end of consolidation, including from induction. [c]Percentage of patients with *FLT3*-ITD MRD VAF>0 among CRc patients with MRD data. [d]Percentage of patients with *FLT3*-ITD MRD VAF=0 among CRc patients with MRD data. [e]Fisher's exact test. CRc, composite complete remission; CTx, chemotherapy; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; MRD, measurable residual disease; VAF, variant allele frequency.

Effect of detectable MRD on RFS by study arm (51% had peri-HSCT MRD detectable using 10e6 *FLT3* assay

RFS
MRD+



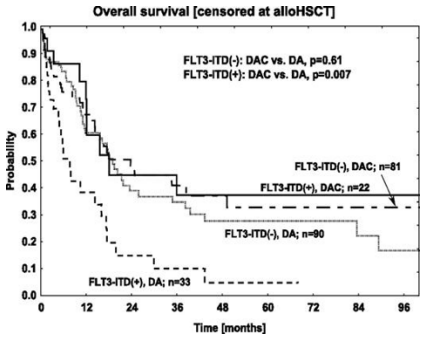
RFS
MRD-



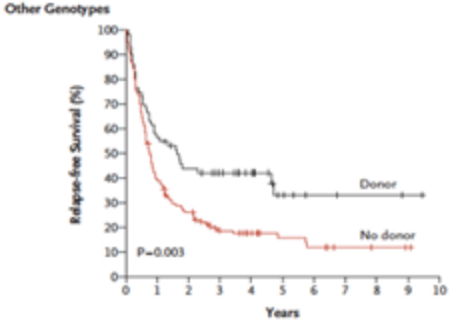
Levis M et al, LBA EHA 2023

Improving outcomes in frontline young/fit *FLT3*-ITD+ AML progress over last 15 years: 3- to 5-year OS now 65%–75% compared with 20%– 25%

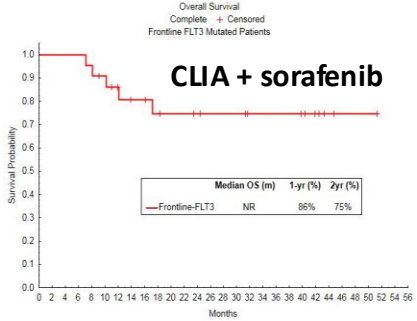
Adding purine analogue to DA (DAC)



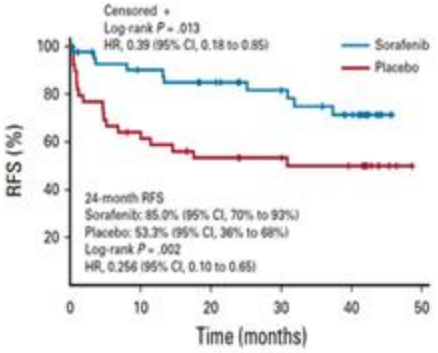
First remission AlloHSCT



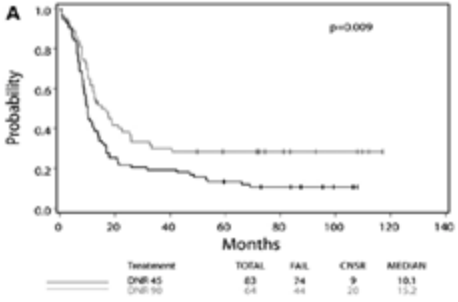
FLT3 inhibitors



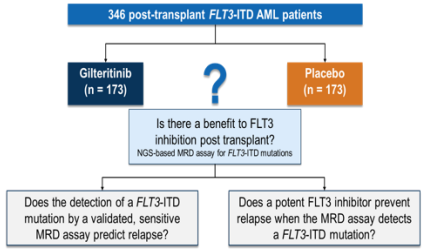
Post-AlloSCT sorafenib

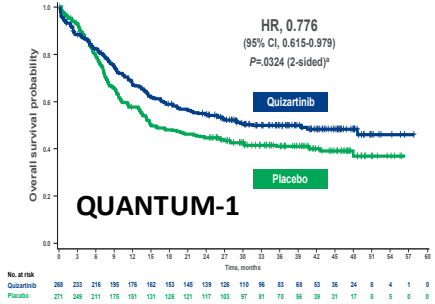


High-dose daunorubicin



GILT maintenance Ph III





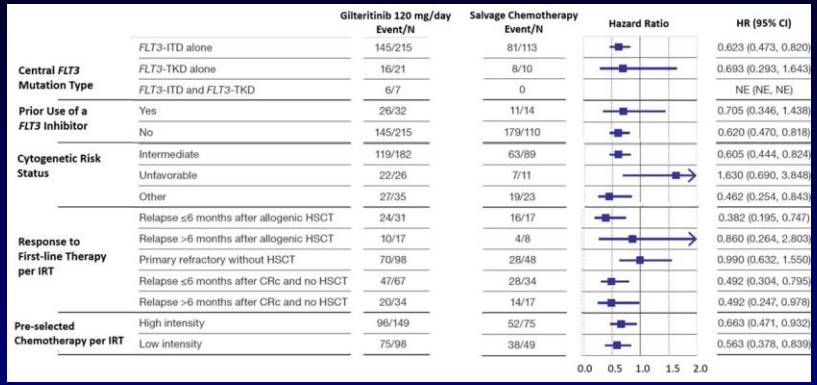
Would AZA+GILT be better?

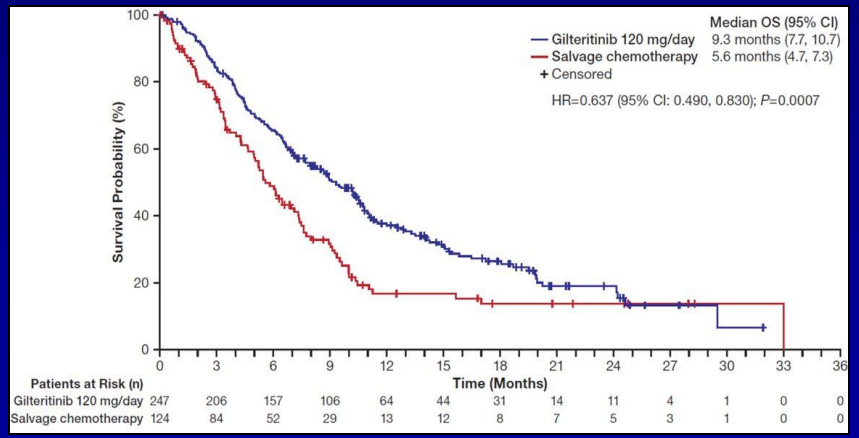
R/R AML

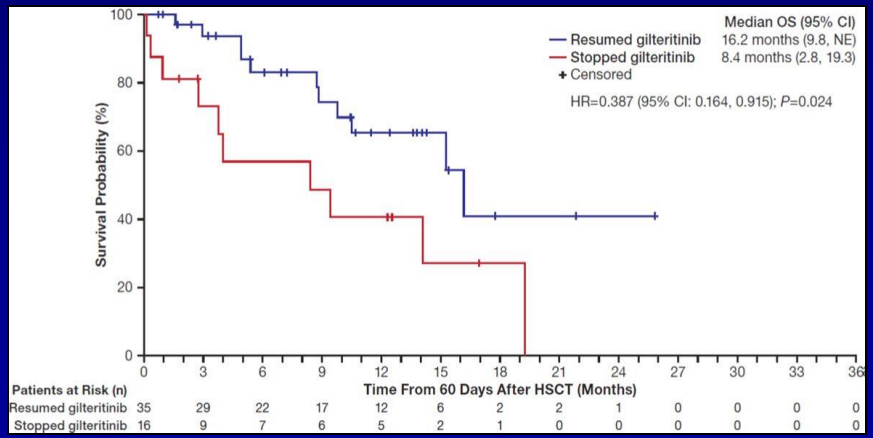
ADMIRAL trial: Gilteritinib vs salvage chemo in relapsed AML

- 371 patients with relapsed *FLT3*-mutated AML randomized to
  - Gilteritinib 120 mg/day (N = 247)
  - Salvage chemotherapy (N = 124)

Response	Gilteritinib	Salvage Chemotherapy
CR, n (%)	52 (21)	13 (11)
CRc [CR, CRi, CRp], n (%)	134 (**54**)	27 (**22**)
CR/CRh, n(%)	84 (**34**)	19 (**15**)







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

Gilteritinib outcomes following prior TKI therapy: ADMIRAL and CHRYSALIS trials

CLINICAL OUTCOMES IN PATIENTS WITH R/R *FLT3*+ AML BASED ON PRIOR TKI THERAPY: CHRYSALIS TRIAL

120-mg Gilteritinib		
Response Outcome, n (%)	With Prior TKI (n=15)	Without Prior TKI (n=41)
CR	1 (7)	6 (15)
CRp	1 (7)	1 (2)
CRi	6 (40)	11 (27)
PR	1 (7)	3 (7)
NR	5 (33)	18 (44)
NE	1 (7)	2 (5)
CRc[a]	8 (53)	18 (44)

200-mg Gilteritinib		
Response Outcome, n (%)	With Prior TKI (n=18)	Without Prior TKI (n=71)
CR	0	10 (14)
CRp	2 (11)	6 (8)
CRi	4 (22)	14 (20)
PR	1 (6)	6 (8)
NR	10 (56)	25 (35)
NE	1 (6)	10 (14)
CRc[a]	6 (33)	30 (42)

[a]Defined as the sum of the patients who achieved CR, Cri, and CRp

CLINICAL OUTCOMES IN PATIENTS WITH R/R FLT3+ AML BASED ON PRIOR TKI THERAPY: ADMIRAL TRIAL

Response Outcome, n (%)	With Prior TKI (n=45)		Without Prior TKI (n=326)	
	Gilteritinib (n=31)	Chemotherapy (n=14)	Gilteritinib (n=216)	Chemotherapy (n=110)
CR	6 (19)	0	46 (21)	13 (12)
CRp	4 (13)	0	15 (7)	0
CRi	5 (16)	3 (21)	58 (27)	11 (10)
PR	5 (16)	1 (7)	28 (13)	4 (4)
NR	9 (29)	4 (29)	57 (26)	39 (35)
NE	2 (6)	6 (43)	12 (6)	43 (39)
CRc[a]	15 (48)	3 (21)	119 (55)	24 (22)
Overall Survival, months				
Median	6.5	4.7	9.6	6.0
HR (95 % CI)	0.671 (0.328–1.376)		0.625 (0.474-0.824)	

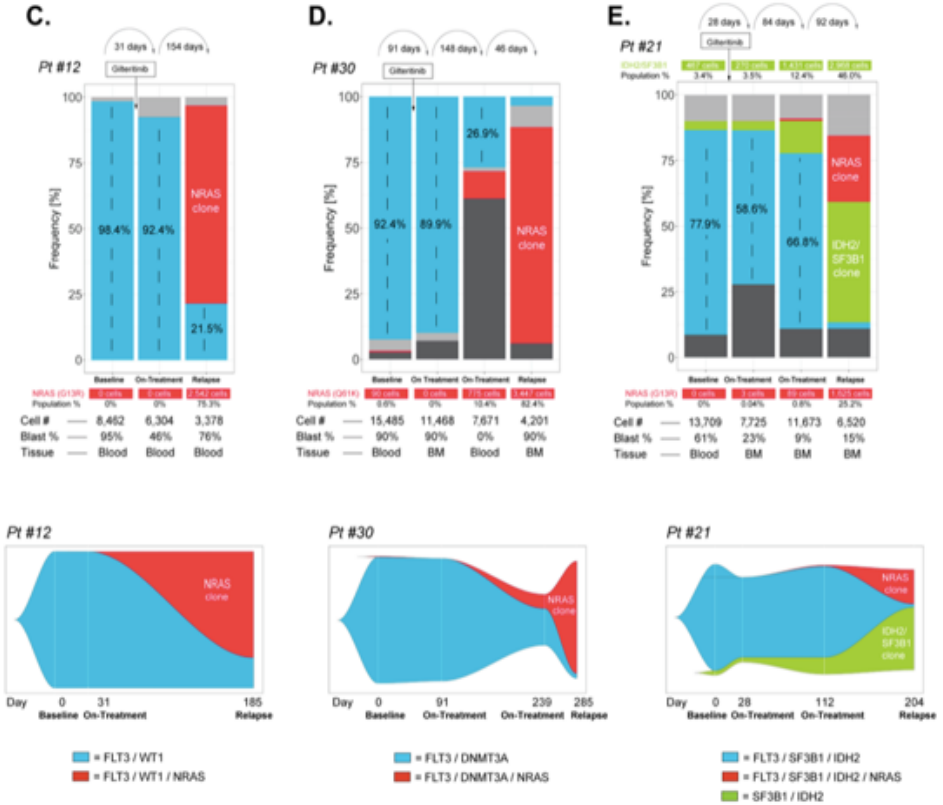
[a]Defined as the sum of the patients who achieved CR, Cri, and CRp

- Retrospective analysis of CHRYSALIS and ADMIRAL trials
- Analysis showed patients with prior TKI use were able to achieve remission with gilteritinib, but OS appeared to be numerically lower: 6.5 months

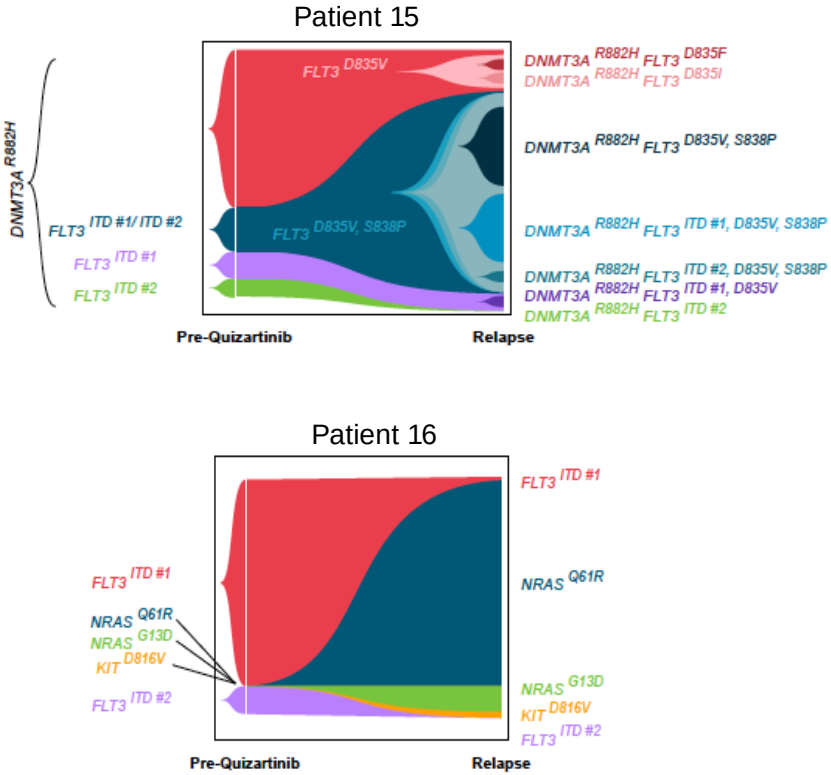
Perl A, et al. ASH 2020. Abstract 334.

Resistance to second-generation FLT3 TKIs is highly polyclonal: Single-agent FLT3is, no matter how potent, are unlikely to be curative

Gilteritinib (Type I): Activation of parallel prosurvival pathways *(RAS/MAPK), BCR-ABL*

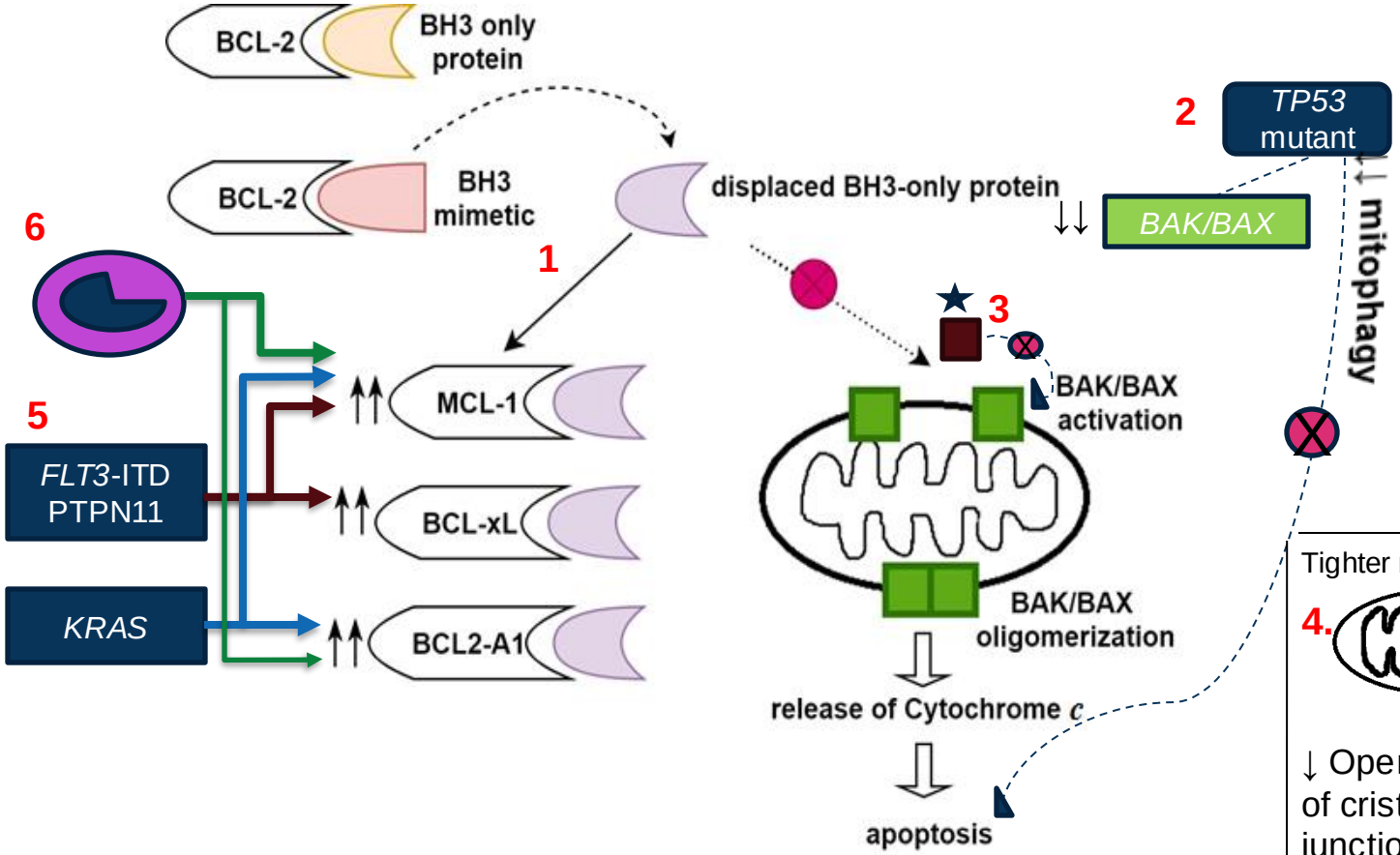


Quizartinib (Type II): On target resistance through acquisition of *FLT3*-TKD



McMahon CM, et al. Cancer Discov. 2019 Aug;9(8):1050-1063; Peretz C, Catherine Smith, et al. Blood Adv. 2021 Mar 9;5(5):1437-1441

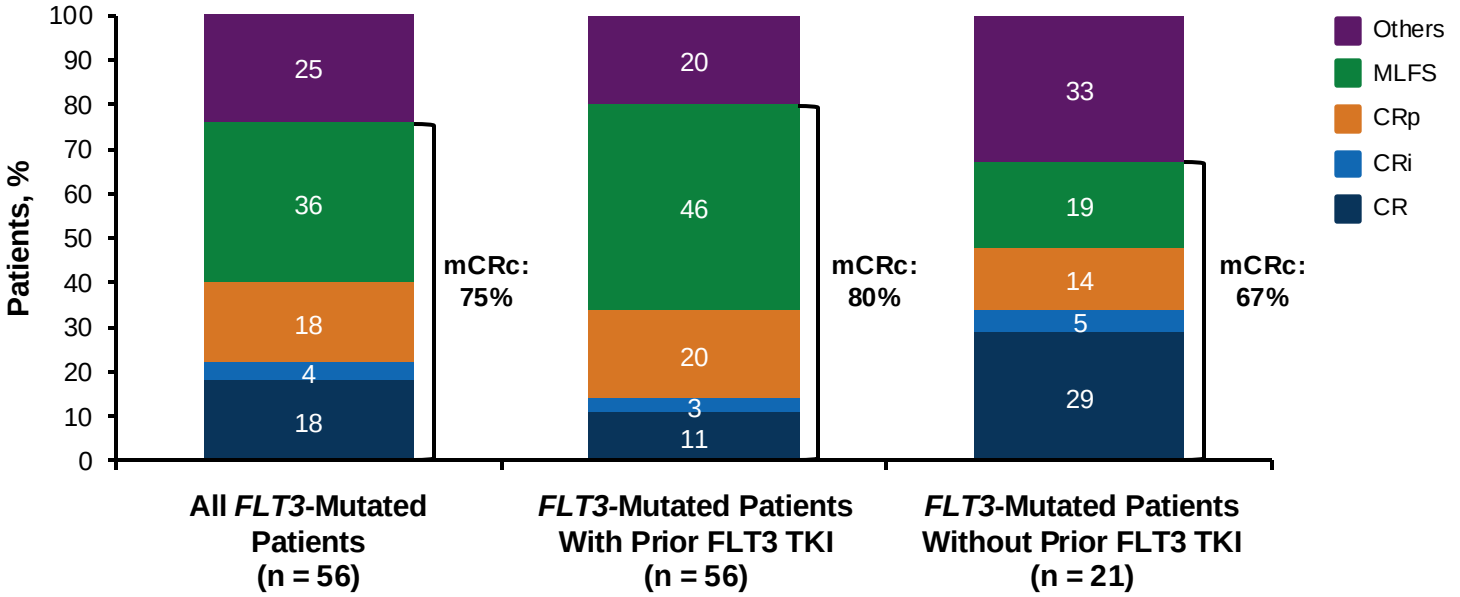
Venetoclax resistance: Road to “triplets”



1. Other anti-apoptotic BCL-2 family proteins
2. *TP53* mutation?
3. *BAX* mutation?
4. Mitochondrial aberration?
5. Mutations in activating kinases
6. Monocytic differentiation

Modified from Ong et al. Cancer Drug Resistance 2022

VEN + GILT: A backbone to build a frontline triplet[1,2]



Median salvage 2–3
Prior FLT3 TKI exposure: 60%
The mCRc rate in this study was **75**%, whereas the CRc rate in the ADMIRAL phase III study for single-agent GILT was **54.3%** (using the same response parameters)

1. Daver N et al. J Clin Oncol. 2022;40:4048-4059. 2. Perl AE et al. New Engl J Med. 2019;381:1728-1740.

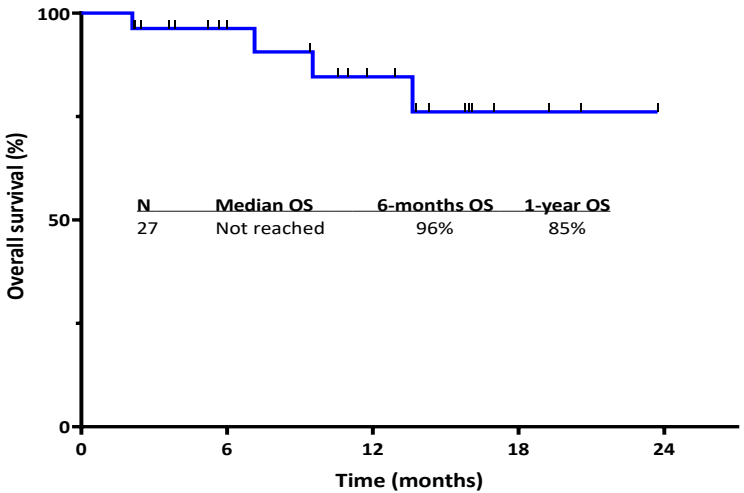
Aza + Ven + Gilteritinib in frontline *FLT3*-mutated AML: Healthier marrow, potentially more curative, and better tolerated

Induction

Azacitidine
75 mg/m² IV/SC on D1-7
Venetoclax R/U to goal 400 mg D1-14
Gilteritinib 80 mg on D1-14
(if blasts <5% on D14, hold both GV;
if blasts >5% on D14 continue GV and repeat BM in 1 week)

Consolidation (up to 24 cycles)

Azacitidine 75 mg/m² IV/SC on D1-5
Venetoclax 400 mg on D1-7
Gilteritinib 80 mg on D1-28

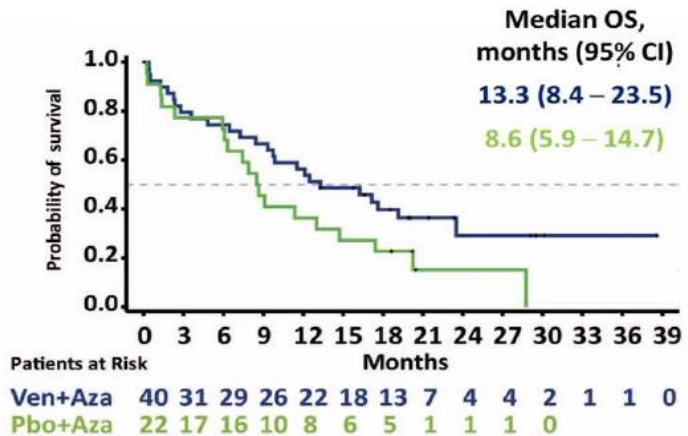


N=30

CR 92%
CRi 4%
CR+CRi: 96%

Recovery:
ANC ≥0.5 37d
Plt ≥50 25d

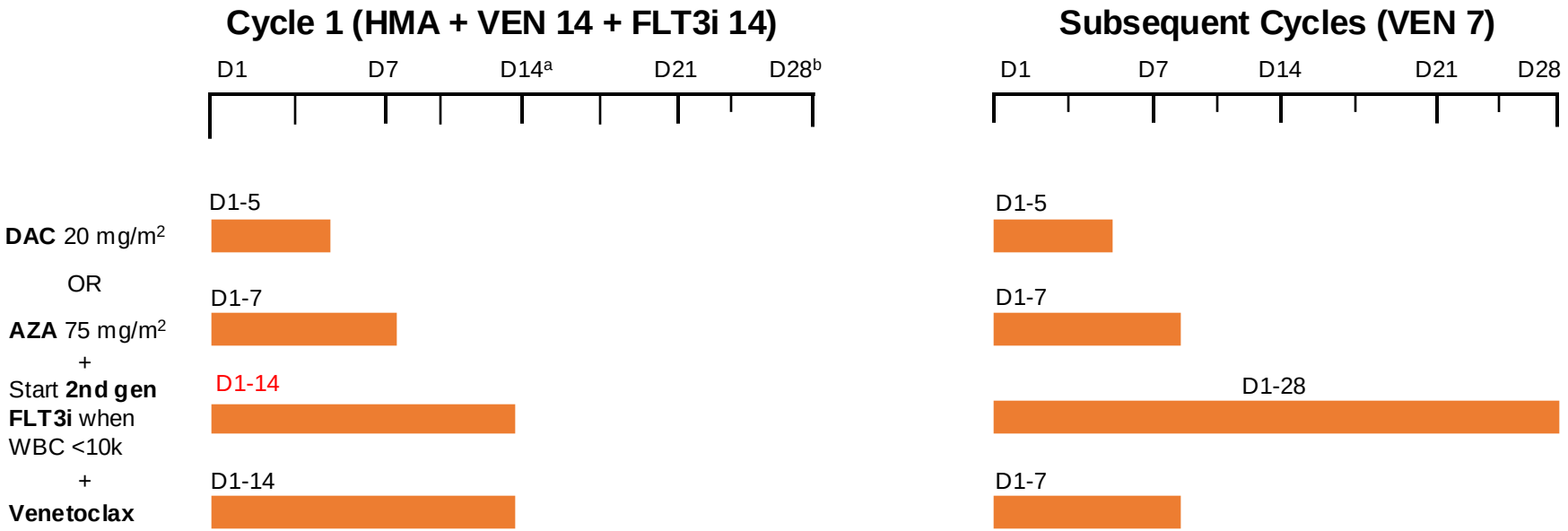
Historical perspective (Konopleva M et al CCR 2023)
AZA+VEN in FLT3m frontline AML (N=40)



Short N, Daver N, et al. JCO Jan 2024

Dosing, duration, and response evaluation timing with FLT3 triplets (dose optimization is critical)

Ongoing Prospective Trial Dosing: AZA + VEN + GILT; PI: Nick Short; DAC + VEN + Quiz; PI: Musa Yilmaz

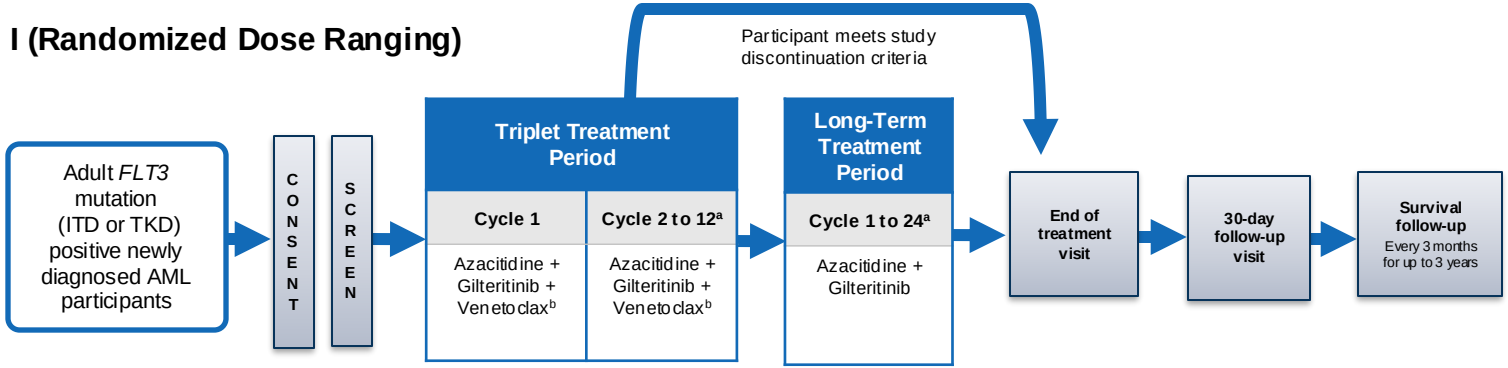


[a] C1 D14: Perform bone marrow biopsy; if bone marrow shows <5% blasts and/or <5% cellularity/insufficient sample → stop venetoclax on D14. [b] Repeat a C1 D28 bone marrow on all patients to confirm remission. If C1 D28 bone marrow confirms remission and ANC <0.5 and/or platelet <50K, consider interrupting FLT3i and using filgrastim to enhance count recovery.

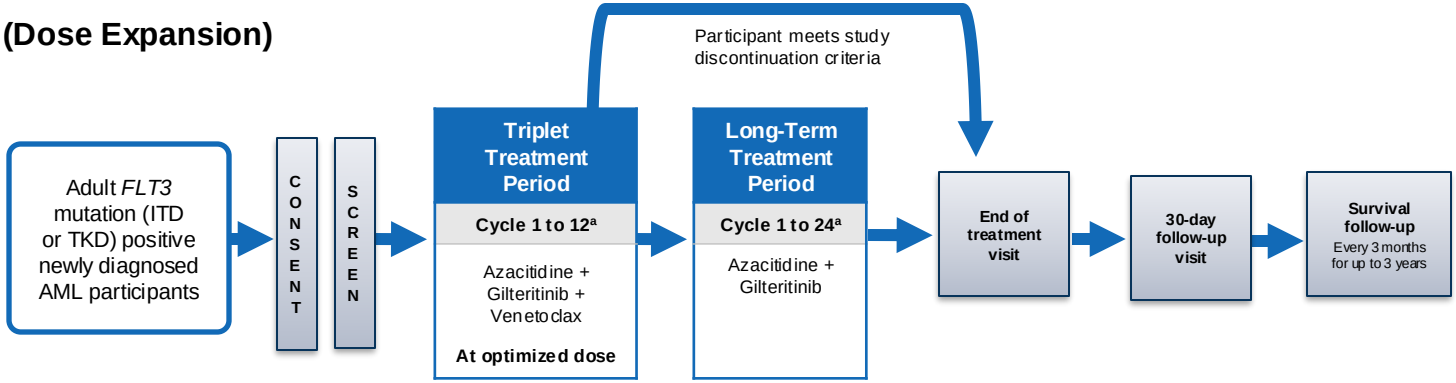
Daver N et al. Blood Cancer J. 2021;11:104.

VICEROY: Phase II multicenter frontline optimization trial of azacitidine, venetoclax, and gilteritinib (N = 80-100)

Phase I (Randomized Dose Ranging)



Phase II (Dose Expansion)



[a] Participants enrolled in phase I or phase II and receiving clinical benefit can continue treatment under the triplet treatment period beyond 12 cycles and under long-term treatment beyond 24 cycles. [b] The dose/duration of gilteritinib and venetoclax administration will depend on the dose level evaluated during phase I. The venetoclax dose will be either 200 mg or 400 mg.

PIs : J Altman and N Daver

Preliminary results of QUIWI: A double blinded, randomized clinical trial comparing standard chemotherapy plus quizartinib versus placebo in adult patients with newly diagnosed *FLT3*-ITD negative AML

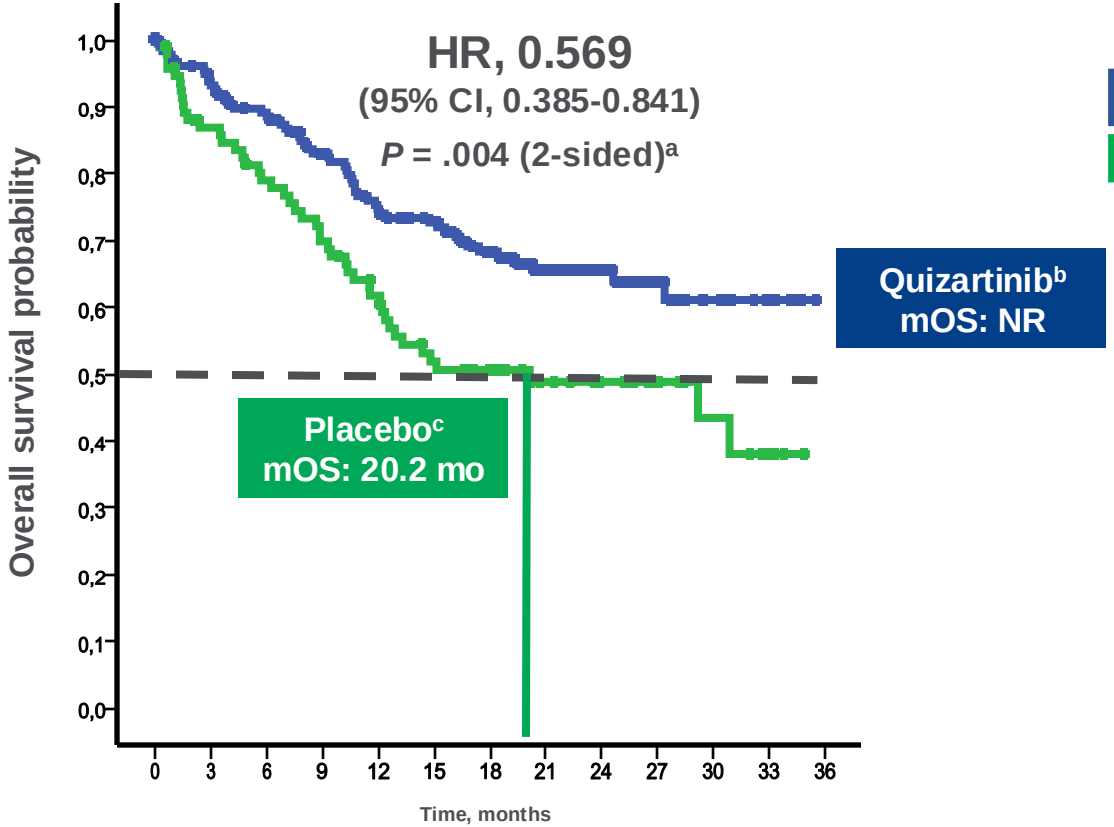
Montesinos P[1], Rodríguez-Veiga R[1], Bergua JM[2], Algarra Algarra JL[3], Botella C[4], Pérez-Simón JA[5], Bernal T[6], Tormo M[7], Calbacho M[8], Salamero O[9], Serrano J[10], Noriega V[11], López-López JA[12], Vives S[13], Colorado M[14], López-Lorenzo JL[15], Vidriales MB[16], García-Boyero R[17], Olave MT[18], Herrera P[19], Arce O[20], Barrios M[21], Sayas MJ[22], Polo M[23] Gómez-Roncero MI[24], Barragan E[1], Ayala R[8], Chillon MC[16], Calasanz MJ[25], Boluda B[1], Martínez-Cuadrón D[1], Labrador J[26].

[1]Hospital Universitari I Politécnic La Fe, Valencia, Spain; [2]Hospital San Pedro de Alcántara, Cáceres, Spain; [3]Hospital General Universitario de Albacete, Albacete, Spain; [4]Hospital General Universitario de Alicante, Alicante, Spain; [5]Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS) / CISC, Universidad de Sevilla, Sevilla, Spain; [6]Hospital Universitario Central de Asturias, Oviedo, Spain; [7]Hospital Clínico Universitario de Valencia, Valencia, Spain; [8]Hospital Universitario 12 de Octubre, Madrid, Spain; [9]Hospital Universitari Vall d'Hebron, Barcelon, Spain; [10]Hospital Universitario Reina Sofía, Córdoba, Spain; [11]Hospital Universitario de A Coruña, La Coruña, Spain; [12]Hospital Universitario de Jaen, Jaén, Spain; [13]Hospital Germans Trias i Pujol-ICO, Badalona, Spain; [14]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [15]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [16]Hospital Universitario de Salamanca, IBSAL, Salamanca, Spain; [17]Hospital General Universitario de Castellón, Castellón de la Plana, Spain; [18]Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; [19]Hospital Universitario Ramón y Cajal, Madrid, Spain; [20]Hospital Universitario Basurto, Bilbao, Spain; [21]Hospital Universitario Regional de Málaga, Málaga, Spain; [22]Hospital Universitario Doctor Peset, Valencia, Spain; [23]Hospital Clínico San Carlos, Madrid, Spain; [24]Hospital Virgen de la Salud de Toledo, Toledo, Spain; [25]CIMA LAB Diagnostics, Universidad de Navarra, Pamplona, Spain; [26]Hospital Universitario de Burgos, Burgos, Spain.

PETHEMA

AML, acute myeloid leukemia; FLT3, fms related receptor tyrosine kinase 3; ITD, internal tandem duplication.

Secondary endpoint (interim analysis): Overall survival



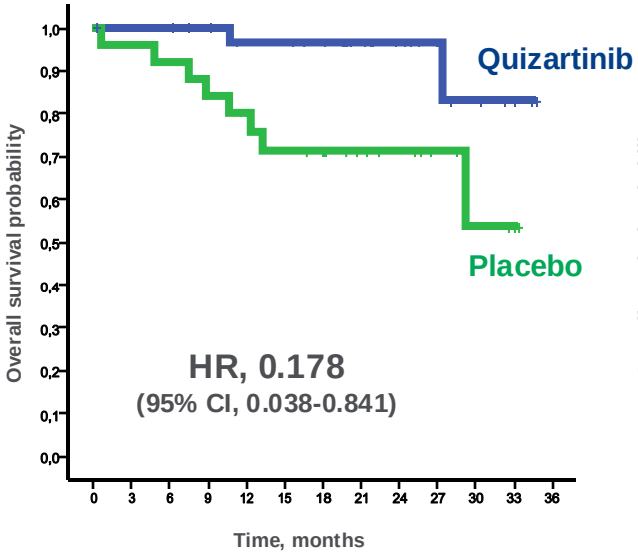
Number of Events

Quizartinib	56/180
Placebo	46/93

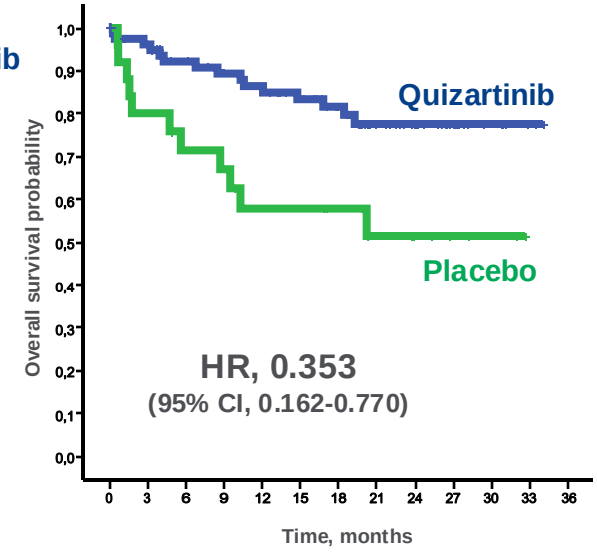
HR, hazard ratio; mOS, median overall survival; NR, not reached.
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 21.5 months. [c] Median follow-up time for placebo arm, 20.3 months.

Sensitivity analysis: Overall survival according to ELN2017 risk

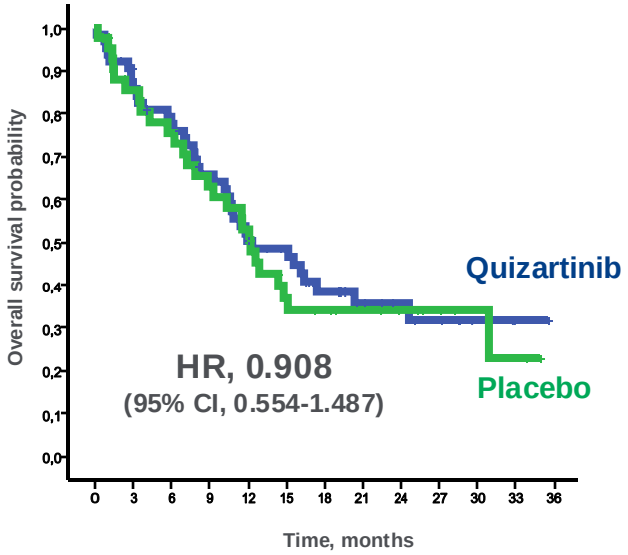
OS – ELN2017 Favorable



OS – ELN2017 Intermediate



OS – ELN2017 Adverse



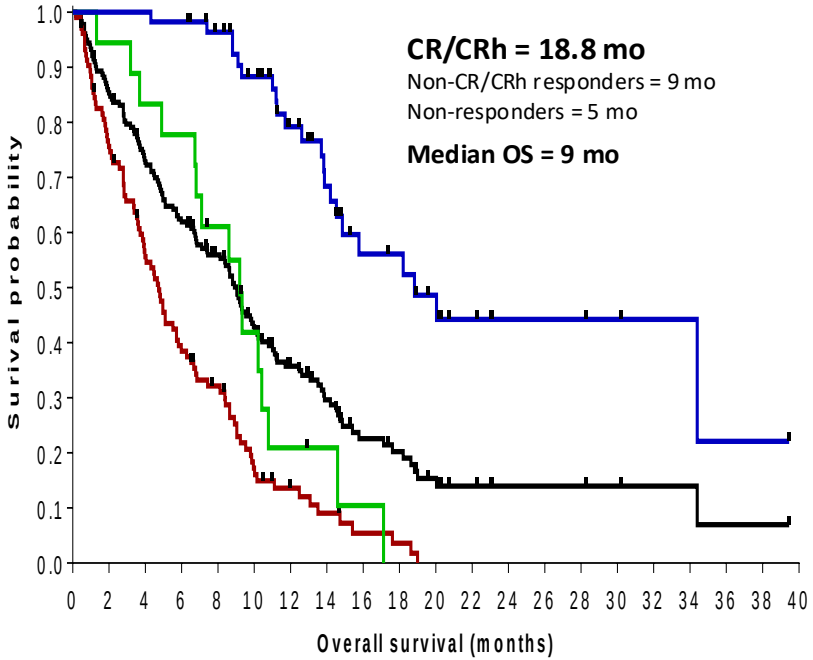
ELN, European LeukemiaNet; HR, hazard ratio

2. Targeting *IDH1* and *IDH2*

IDH inhibitor monotherapy in R/R AML: F1H phase I study outcomes

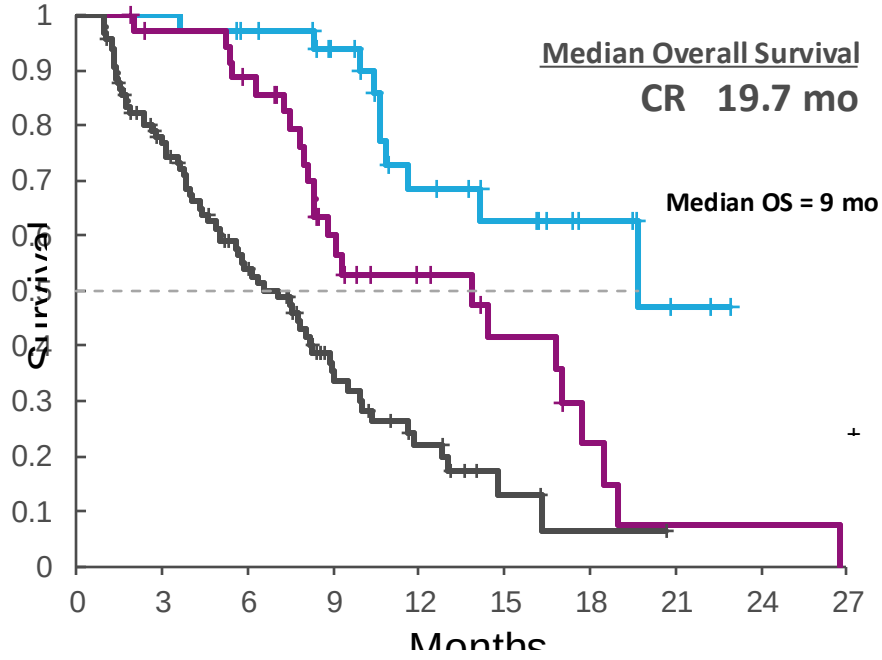
CR rate ~20%
CR/CRh rate ~30%
ORR ~40%

Ivosidenib (IDH1 inhibitor)



DiNardo CD et al, NEJM 2018

Enasidenib (IDH2 inhibitor)



Stein EM et al, Blood 2017

OLUTA R/R monotherapy response rates

Response rates	Efficacy evaluable population (N = 147)
CR* or CRh	
n (%) [95% CI]	51 (35) [27.0-43.0]
Median time to CR/CRh, months (range)	1.90 (0.9-5.6)
CR*	
n (%) [95% CI]	47 (32) [24.5-40.2]
Median time to CR, months (range)	2.80 (0.9-7.4)
Overall response	
n (%) [95% CI]	71 (48) [40.0-56.7]
Median time to first overall response, months (range)	1.90 (0.9-10.2)
Best overall response, n (%)	
CR*	47 (32)
CRh	4 (3)
CRi	15 (10)
PR	3 (2)
MLFS	2 (1)
SD**	42 (29)
Progressive disease	10 (7)
Not evaluable / not done	6 (4) / 18 (12)

CR/CRh rate of 35%
(compared to ~30% with IVO)

ORR rate of 48%
(compared to 42% with IVO)

Median Duration of CR/CRh ~26 mo
(compared to ~8 mo w/ IVO)

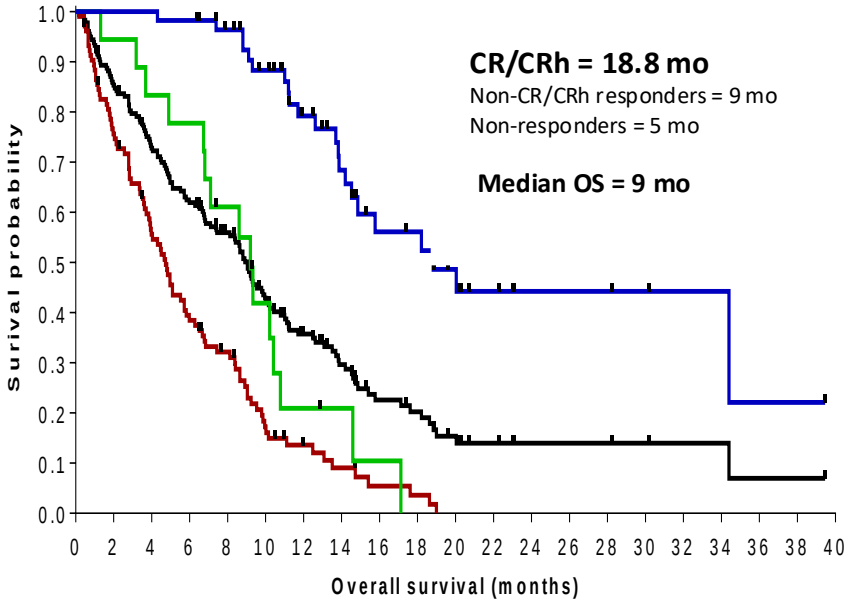
Median Duration of Response ~12 mo
(compared to ~6.5 mo w/ IVO)

***17 patients had received prior VEN:**
CR/CRh rate 30%, CR rate 24%, and DOR 18.5 mo.

De Botton S et al, Blood Adv 2023

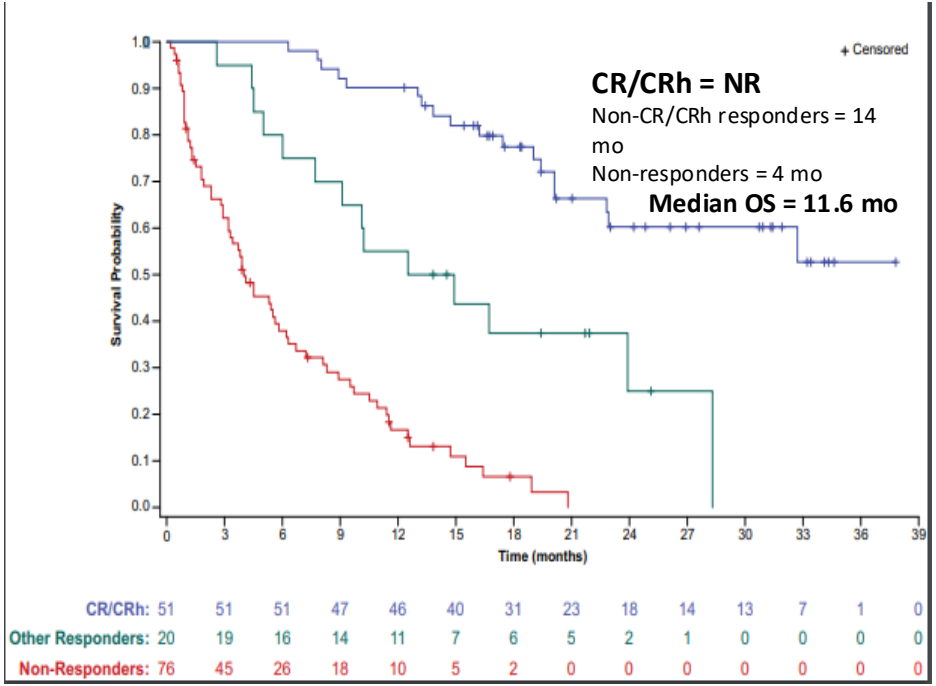
IDH1 OS with IVO and OLUTA from phase I study approval populations

Ivosidenib (IDH1 inhibitor)



DiNardo CD et al, NEJM 2018

Olutasidenib (IDH1 inhibitor)



De Botton S et al, Blood Adv 2023

Safety/anticipated IDH inhibitor adverse effects

Grade 3/4 TEAEs in ≥2% of pts, n (%)	Enasidenib 100 mg/day (n = 153)	Ivosidenib 500 mg/day (n = 179)	Olutasidenib 150 mg BID (n = 147)
Hyperbilirubinemia	**13 (8)**	NR	NR
Prolonged QT interval	---	**14 (8)**	1 (<1)
IDH differentiation syndrome	**11 (7)**	**7 (4)**	**12 (7)**
Anemia	10 (7)	4 (2)	7 (5)
Thrombocytopenia	8 (5)	3 (2)	6 (4)
Tumor lysis syndrome	5 (3)	---	3 (2)
Decreased appetite	3 (2)	---	---
Leukocytosis	---	3 (2)	7 (5)
Hepatic AESI (transaminitis)	---	----	**23 (15)**

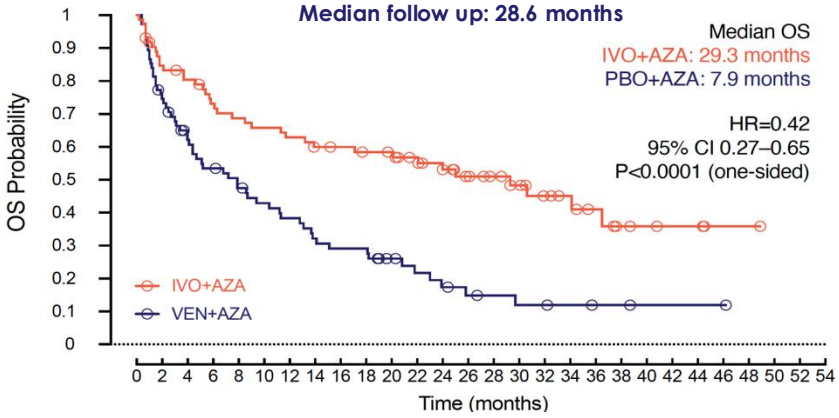
DS manifestations typically include

- Fever
- Dyspnea
- Pulmonary infiltrates
- Hypoxia
- Rash
- Edema

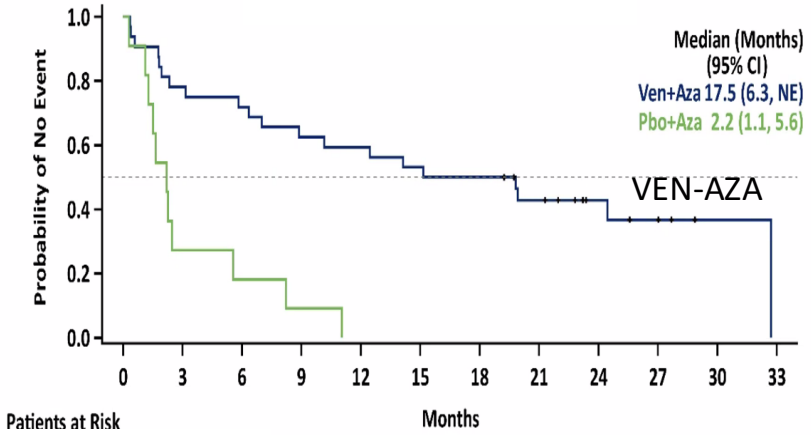
Stein EM, et al. *Blood*. 2017;130:722-731.
DiNardo CD, et al. *N Engl J Med*. 2018;378:2386-2398.
De Botton S et al, *Blood Adv*. 2023

IVO-AZA or VEN-AZA for *IDH1*m AML?

*IDH1*m	IVO + AZA	AZA	VEN-AZA	AZA
N	72	74	32	11
Median age	76	76	76	76
ORR (CR/CRi)	54%	16%	66%	9%
CR	47%	15%	28%	0%
Median time to CR/CRi	4.3 m	3.8 m	1.1 m	3.4 m
Median OS	29.3 m	7.9 m	17.5 m (in *IDH1:* 15m)	2.2 m



Montesinos et al, NEJM 2022, 386; 1519-31
De Botton et al. P142 , ASCO 2023

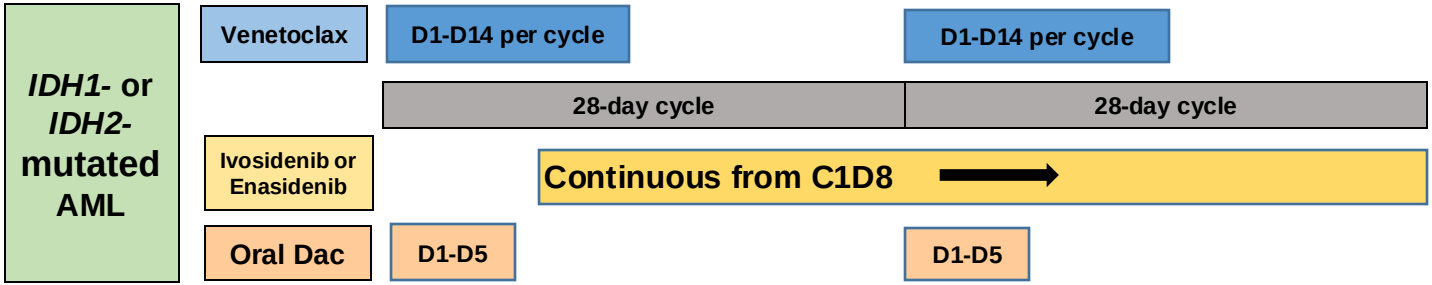


Pollyea, et al, *Clin Cancer Res 2022;28:2753–61*

New all-oral triplet study for *IDH1*- or *IDH2*-Mutated AML

Phase Ib: To determine the safety and tolerability, maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of the combination of oral decitabine/cedazuridine, venetoclax, and ivosidenib or enasidenib

Phase II: To confirm efficacy based on composite remission rate (CR, CRh, CRi)



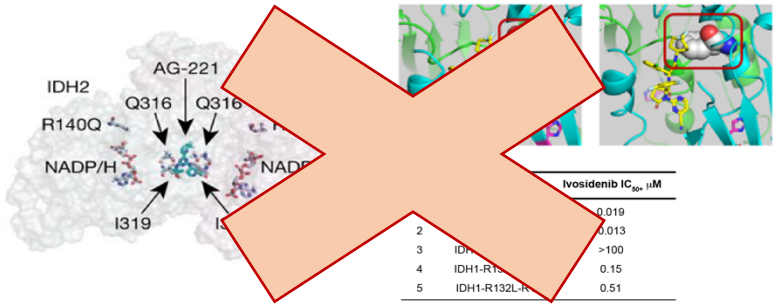
Response, %	Newly Dx *IDH1* (n = 10)	Newly Dx *IDH2* (n = 14)	R/R (n = 26) *IDH1*	R/R (n = 26) *IDH2*
CRc	90	100	50	44
MRD neg	80	93	50	19

***Most pts in R/R setting received prior VEN and/or IDH inhibitor exposure, different from most studies that exclude prior VEN or IDHi therapy.**

Atluri H…..DiNardo C et al, ASH 2022.

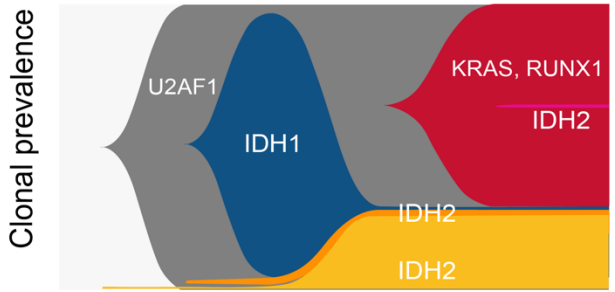
How does this compare with IDH inhibitor monotx resistance?

2HG Related



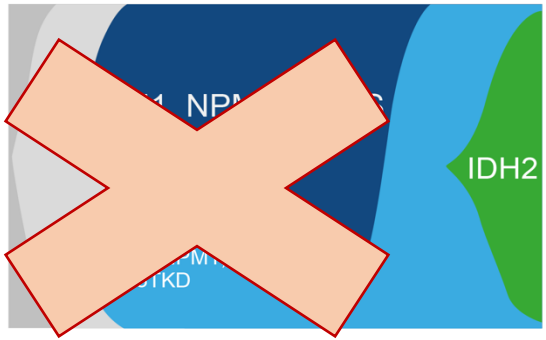
"Second Site Mutations"

Non-2HG Related

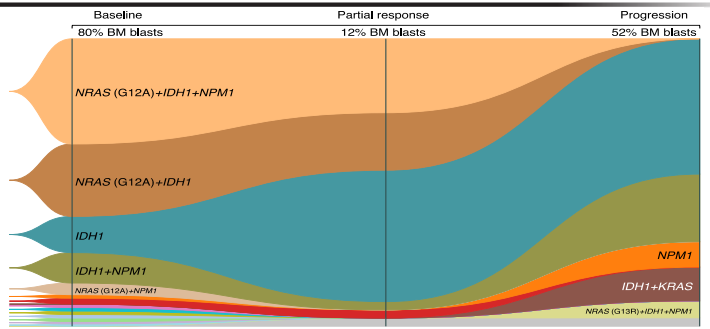


Reinstitution of Differentiation Block
(CEBPα, RUNX1, GATA2)

***IDH2* mutation acquired in *IDH1*-mutant clone with elevation of 2-HG at relapse (single-cell DNA-seq, individual patient)**



"Isoform Switching"

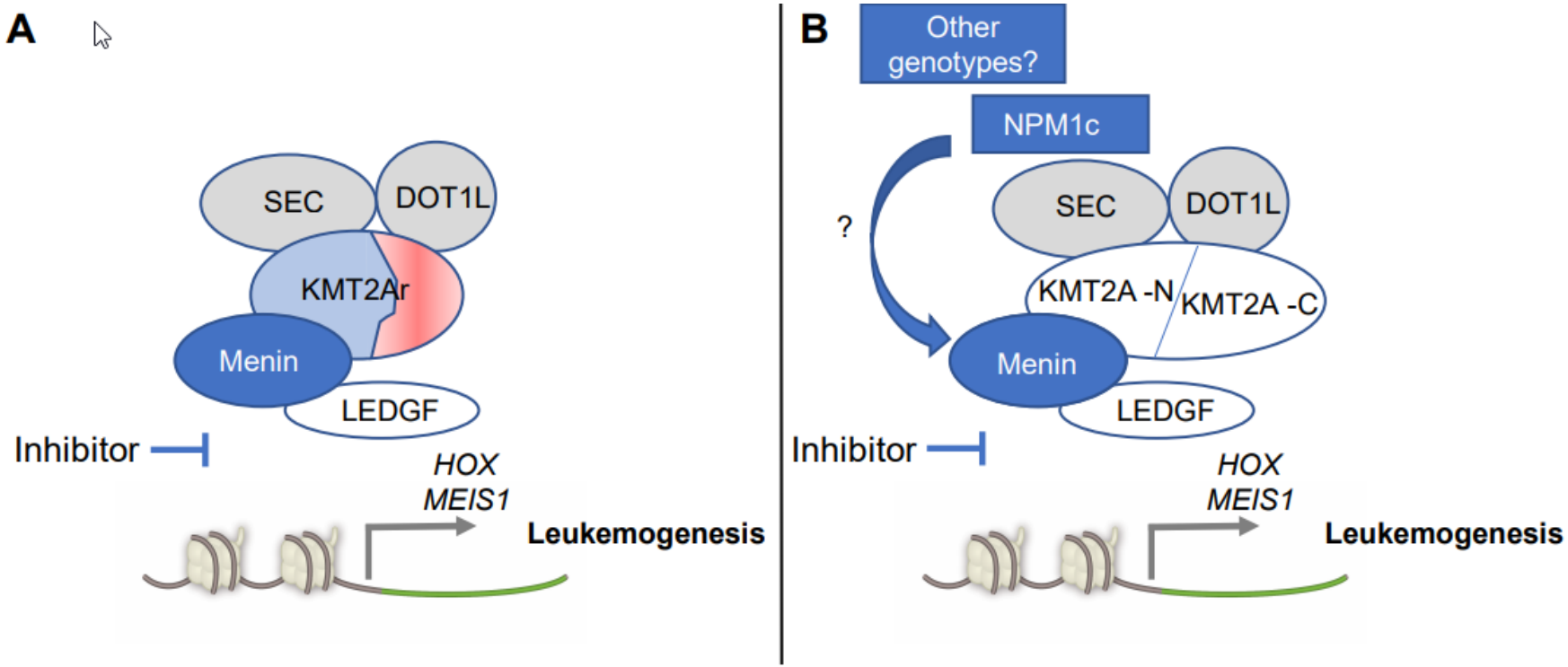


Activated Signaling / Proliferation Pathways
(FLT3-ITD, K/NRAS, PTPN11)

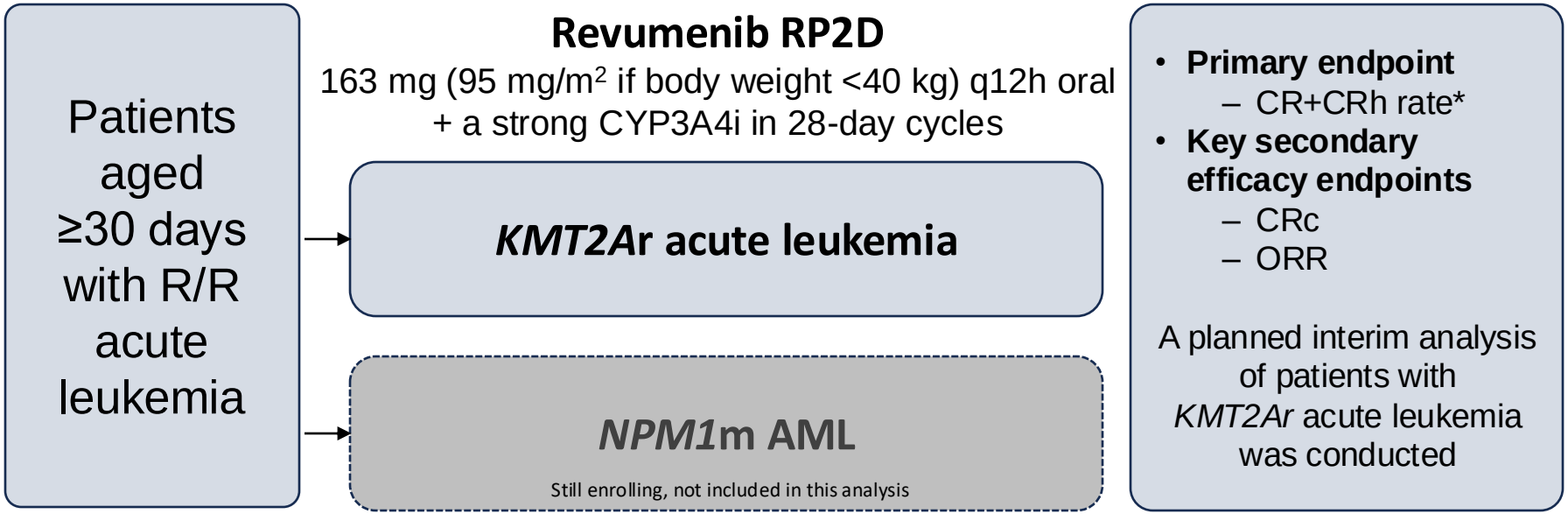
Quek L et al, Nature Med 2018, Intlekofer AM et al, Nature 2018, Harding JJ et al, Cancer Discov 2018, Choe S et al, Blood Adv 2020

3. Targeting *KMT2A*r and *NPM1*m AML with HMA + VEN with menin inhibitor

Menin inhibition – MOA in leukemia



AUGMENT-101 phase II study design



*CR+CRh rate >10% in adult evaluable population considered lower efficacy bound.

AML, acute myeloid leukemia; CR, complete remission; CRc, CR composite (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, nucleophosmin 1–mutated; ORR, overall response rate; q12h, every 12 hours; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Response

Parameter	Efficacy Population (n = 57)
ORR, n (%)	**36 (63)**
CR+CRh rate, n (%)	13 (23)
95% CI	12.7–35.8
P value, 1-sided	0.0036
CRc	25 (44)
95% CI	30.7–57.6
Negative MRD status[a]	
CR+CRh	7/10 (70)
CRc	15/22 (68)

Data cutoff: July 24, 2023. [a]MRD done locally; not all patients had MRD status reported. [b]Includes patients without postbaseline disease assessment.

Parameter	Efficacy Population (n = 57)
Best response, n (%)	
CR	10 (18)
CRh	3 (5)
CRi	1 (1.8)
CRp	11 (19)
MLFS	10 (18)
PR	1 (1.8)
PD	4 (7)
No response	14 (25)
Other[b]	3 (5)

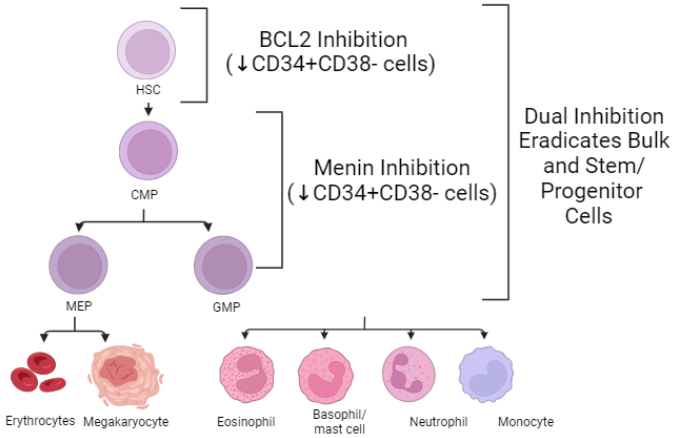
CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR); PD, progressive disease; PR, partial remission.

Rationale for SAVE combination

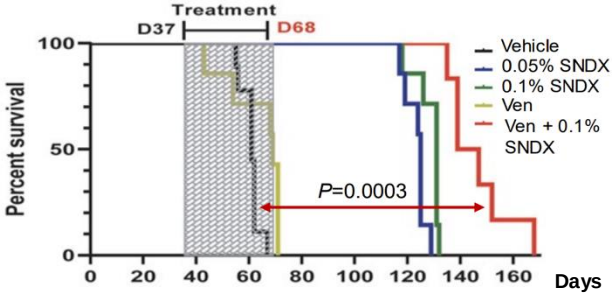
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Abstract #58 SAVE

- HMA + **venetoclax** is standard for older/unfit AML
- **Oral decitabine-cedazuridine (ASTX727)** is approved, has equivalent efficacy as IV decitabine[1]
- *KMT2A*r or *NPM1*m leukemias are susceptible to apoptosis through BCL2 inhibition[2-5]
- **BCL2 + menin inhibition** → eradication of bulk and stem/progenitor cells and improved survival in preclinical models[6,7]
- All-oral combination of **S**NDX-5613 + **A**STX727 + **VE**netoclax (**SAVE**)



PDX: *NPM1*, *FLT3* ITD/TKD[6]



1. Garcia-Manero G et al. Blood 2020;136:674-83. 2. Benito JM et al. Cell Reports 2015;13:2715-27. 3. Tiong IS et al. Br J Haematol. 2021;192(6):1026-1030.
4. Lachowiez CA et al. Blood Adv. 2020;4(7):1311-1320. 5. Issa GC et al. Blood Adv. 2023;7(6):933-942. 6. Carter BZ et al. Blood. 2021;138(17):1637-1641.
7. Fiskus W et al . Blood cancer journal 2022;12:5

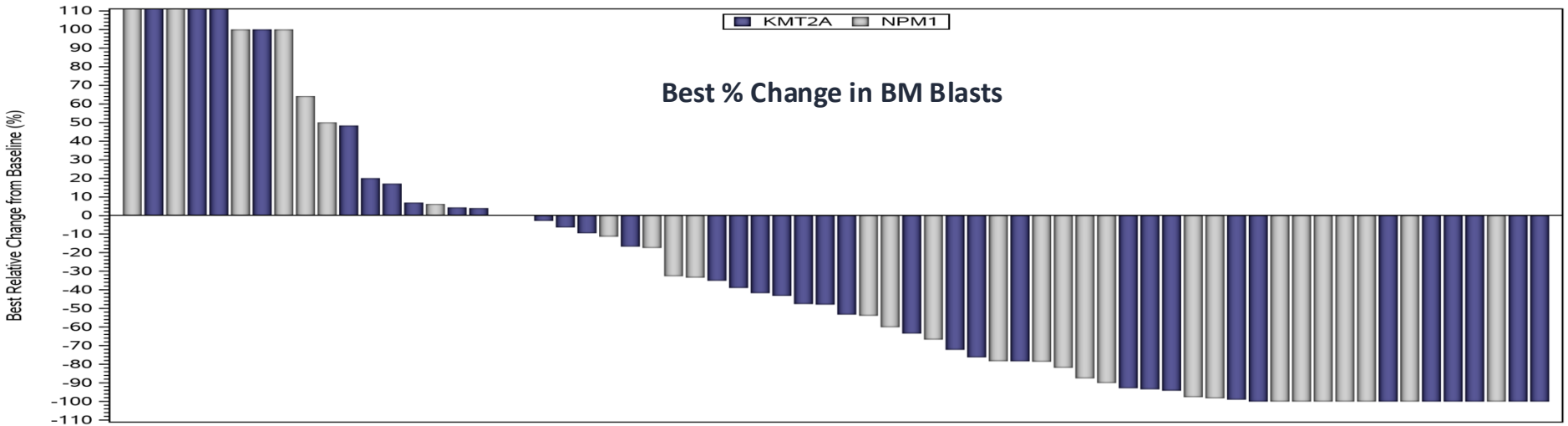
SAVE (SNDX-5613+ASTX727 +Ven) in R/R AML

- All oral combination: Oral DAC D1-5, VEN D1-14, revumenib) 113–163 mg Q12h D1–28
- 9 pts Rx: 5 *KMT2A*r, 3 *NUP98*r, 1 *NPM1*m
- Median 3 prior lines (range 1–6)
- DLT: prolonged ↓ plts
- ORR 100%. CRc 78%. 3 CR, 1 CRh, 3 CRp, 1 PR, 1 MLFS. MRD– 6/9; 4/4 MRD- CR/CRh
- Most clearance by D14 BM
- Plan: explore intermittent revumenib (hold if BM blast <5%)

Issa. Blood 142: abst 58; 2023

JNJ-75276617 (menin inhibitor) in R/R *KMT2A* AML/ALL

- 86 pts Rx with JNJ-6617 orally daily; 78 AML – *KMT2A* 58%, *NPM1* 42%
- DS 12%; QTc 1%
- CR-CRh-CRi 27%; ORR 53% (33 pts Rx 45–130 mg BID)
- *KMT2A* (n = 19) – ORR 42%
- *NPM1* (n = 14) – ORR 50%
- 8 (53%) ongoing response; Median DOR 6.5+ mo

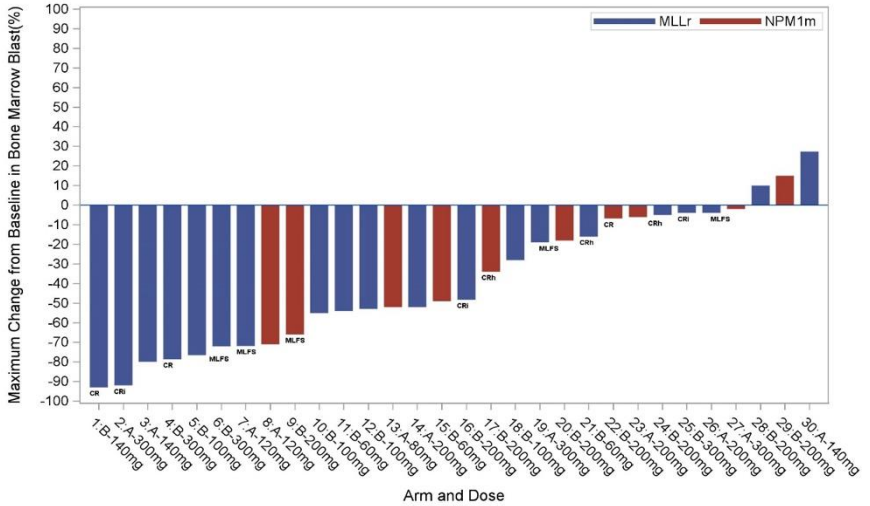


Jabbour. Blood 142: abst 57; 2023

Sumitomo DSP-5336 (menin inhibitor) in R/R *KMT2A* AML/ALL

Robust clinical responses have been consistently observed at therapeutic doses

Intent to treat population ≥140 mg BID			
Responses by ELN 2017 in AML patients w/*KMT2A*r or *NPM1*m at doses ≥140 mg BID*	***KMT2A*r** ≥140 mg BID *n = 12*	***NPM1*m** ≥140 BID mg *n = 9*	***KMT2A*r + *NPM1*m** ≥140 mg BID *n = 21*
ORR	8 (67%)	4 (44%)	**12 (57%)**
Composite CR	5 (42%)	3 (33%)	**7 (33%)**
CR + CRh	2 (17%)	3 (33%)	**5 (24%)**



- In patients treated at lower doses, 1 CRh at 60 mg BID Arm B and 1 MLFS at 120 mg BID Arm A were observed
- 4 patients who achieved an objective response then underwent allogeneic stem cell transplantation
- Median time to CR or CRh of 1.4 months (range: 1 to 4 months)

*Included patients with no prior menin inhibitor treatment. Gene alteration status (eg, *KMT2A*r or *NPM1*m) as determined based upon local laboratory documented results.

Composite CR: CR + CRh + CRi (If CRh was achieved, it was counted as this and not as CRi)

Objective Response Rate: CR + CRh + CRi + MLFS (If CRh was achieved, it was counted as this and not as CRi or MLFS)

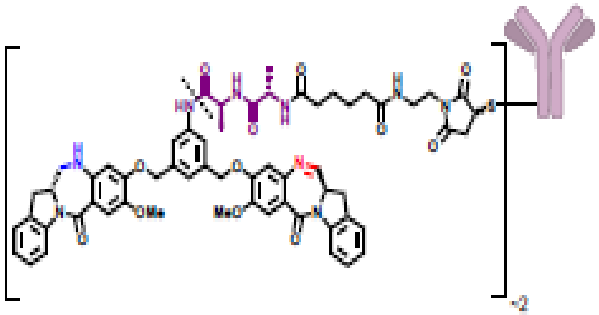
Daver N. EHA 2024 Abst S411

4. Adding a targeted or immunotherapy to prevent resistance/relapse: mutation agnostic

Genotype-agnostic: ***Immunotherapy Venetoclax and anti-CD123 ADC***

Beyond single pathway inhibition in AML: Blockade of apoptosis/targeting CD123

- CD123 (α subunit of IL-3 receptor) is highly expressed on leukemic blast and stem cells compared with normal HSC
- **IMGN632** - CD123 targeting ADC (**pivekimab sunirine, PVEK**)
  - Conjugate of a unique anti-CD123 antibody and a novel IGN payload
  - Antibody is humanized IgG1 and binds to CD123
  - Payload works by **alkylating DNA without cross-linking**
  - **Well tolerated: no CLS, CRS, VOD in AML at RP2D**
  - **Single-agent CR/CRi 20%–22%**

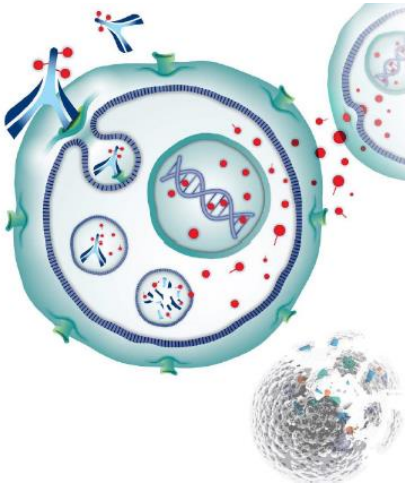


Red: imine (site of DNA alkylation)

Blue: amine (non-covalently binds DNA)

Purple: peptide linker

Dashed line: Site of catabolism

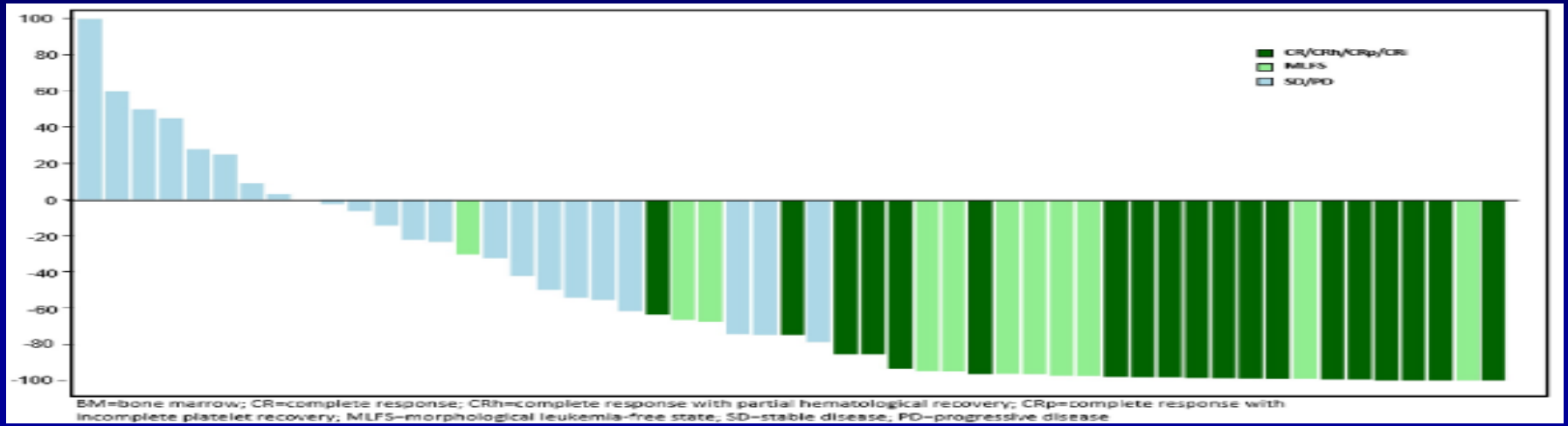


Daver N et al Lancet Oncology March 2024

Triplet pivekimab (IMGN632), azacitidine and venetoclax in HR R/R AML

- 71 pts with R/R AML. Median age 68 yr (25–82). 52% 2+ Rxs

Group	No	ORR, %	CR, %
Total	61	51	31
VEN-naive	34	62	47
Prior VEN	27	37	11
Prior HMA-VEN	22	32	11
FLT3-ITD	11	82	64



Daver. Blood 140: abst 62; 2022

Conclusions

- Rational combinations of targeted therapy with venetoclax or with HMA + venetoclax appear to enhance efficacy (response, molecular clearance, early survival) and overcome resistance
- Dose optimization (overcoming urge to overdose VEN!), early assessment with bone marrow, and use of growth factors to safely deliver combination regimens need to be very carefully evaluated and implemented
- Use of molecular clearance may be a useful early surrogate of efficacy in certain combinations such as with *FLT3, NPM1, KMT2A* clearance, but maybe not all mutations
- Careful assessment and long-term follow-up of ongoing single-arm studies, backed up by rapidly performed focused confirmatory clinical trials, are needed to fully confirm benefit

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Q&A

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Therapeutic approaches in high-risk and frail patients with AML

Charles Craddock

APTITUDE HEALTH®

Therapeutic Approaches in High-Risk and Frail Patients With AML

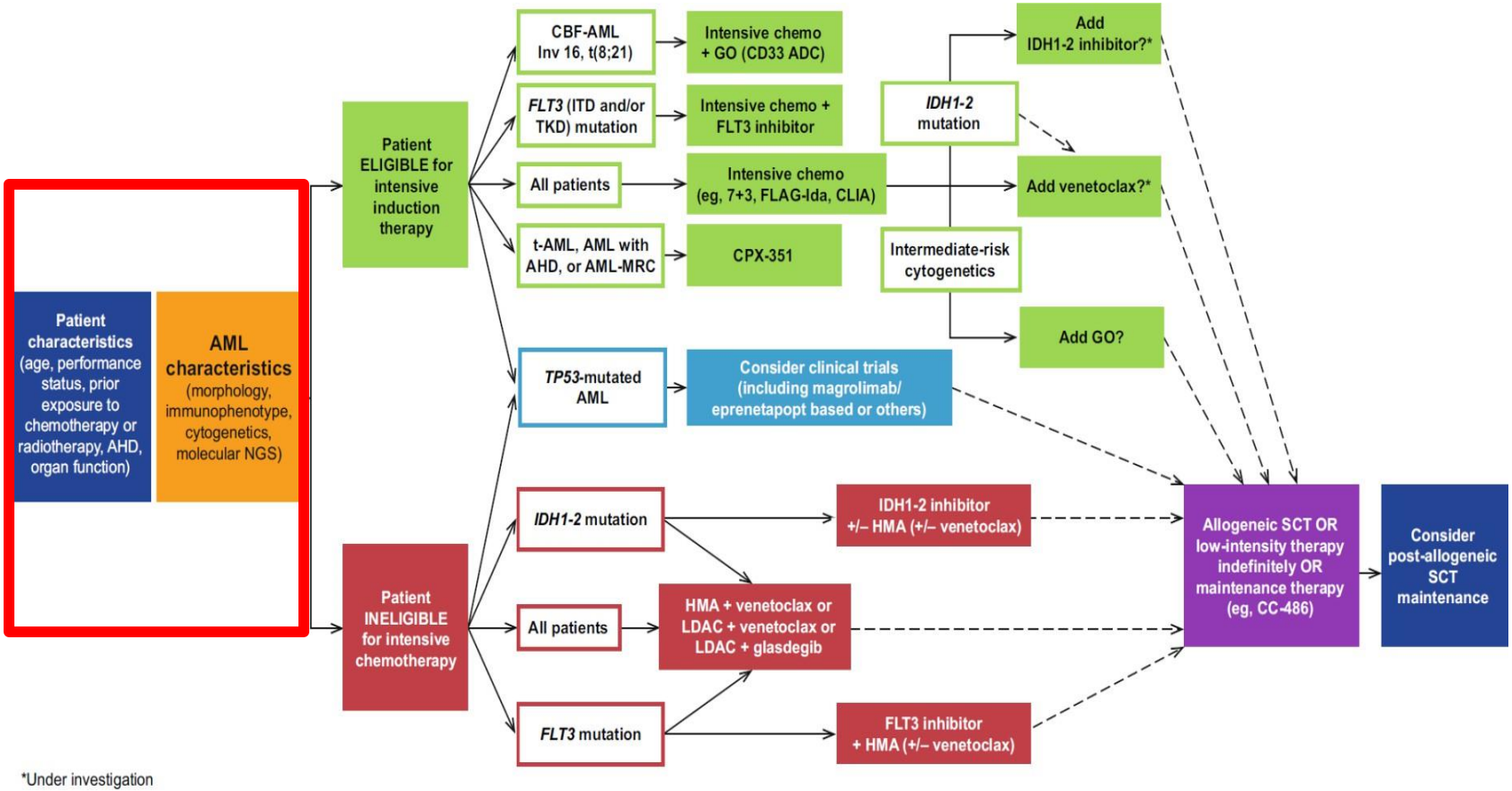
Charles Craddock, CBE, FRCP, FRCPath, FMedSci

Centre for Clinical Haematology,
Queen Elizabeth Hospital Birmingham
University of Birmingham

Disclosures: Prof C. Craddock

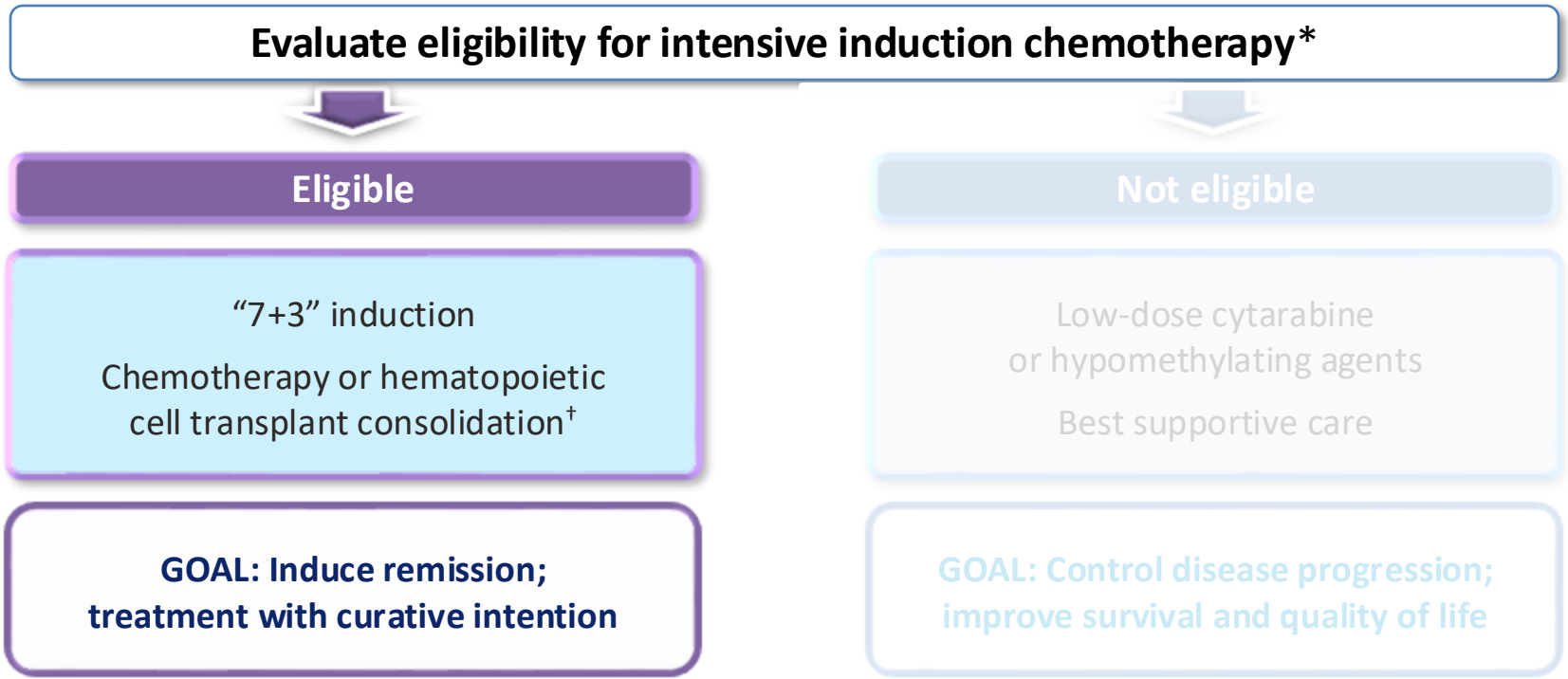
Company Name	Research Support	Employee	Consultant	Stockholder	Speaker Bureau	Advisory Capacity	Other
Abbvie	No	No	Yes	No	Yes	Yes	No
Janssen	No	No	Yes	No	Yes	Yes	No
KITE	Yes	No	Yes	No	No	No	No
Novartis	No	No	Yes	No	Yes	Yes	No
Roche	No	No	Yes	No	Yes	No	No
Jazz	Yes	No	Yes	No	No	No	No
BMS	No	No	Yes	No	Yes	Yes	No
Pfizer	No	No	Yes	No	Yes	Yes	No
Astellas	No	No	Yes	No	Yes	Yes	No
Daiichi Sankyo	No	No	Yes	No	Yes	Yes	No
Eurocept	No	No	Yes	No	Yes	Yes	No

Evolving Diagnostic and Treatment Paradigm for Newly Diagnosed AML



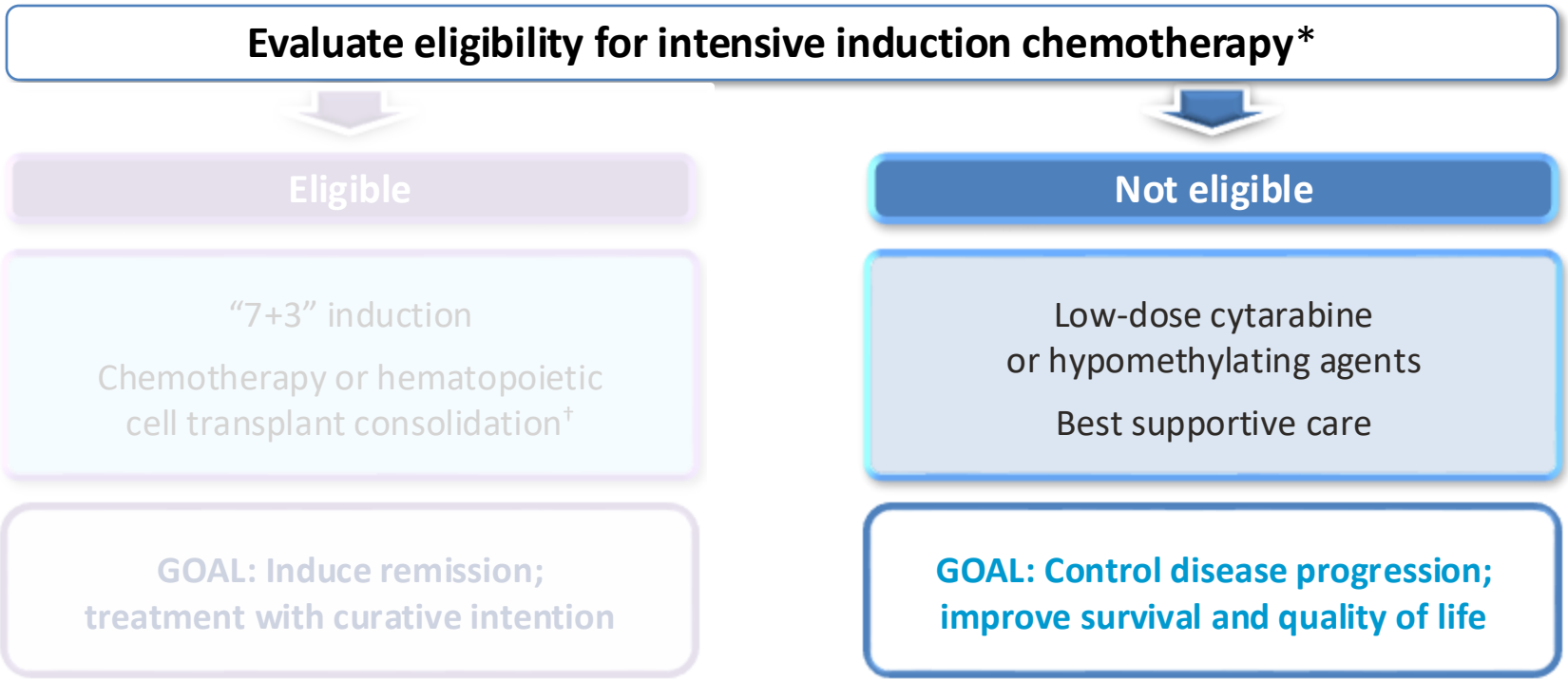
Daver N, et al. *Blood Cancer J.* 2020;10:107.

2022 ELN Guidelines: Therapeutic Approaches and Treatment Goals



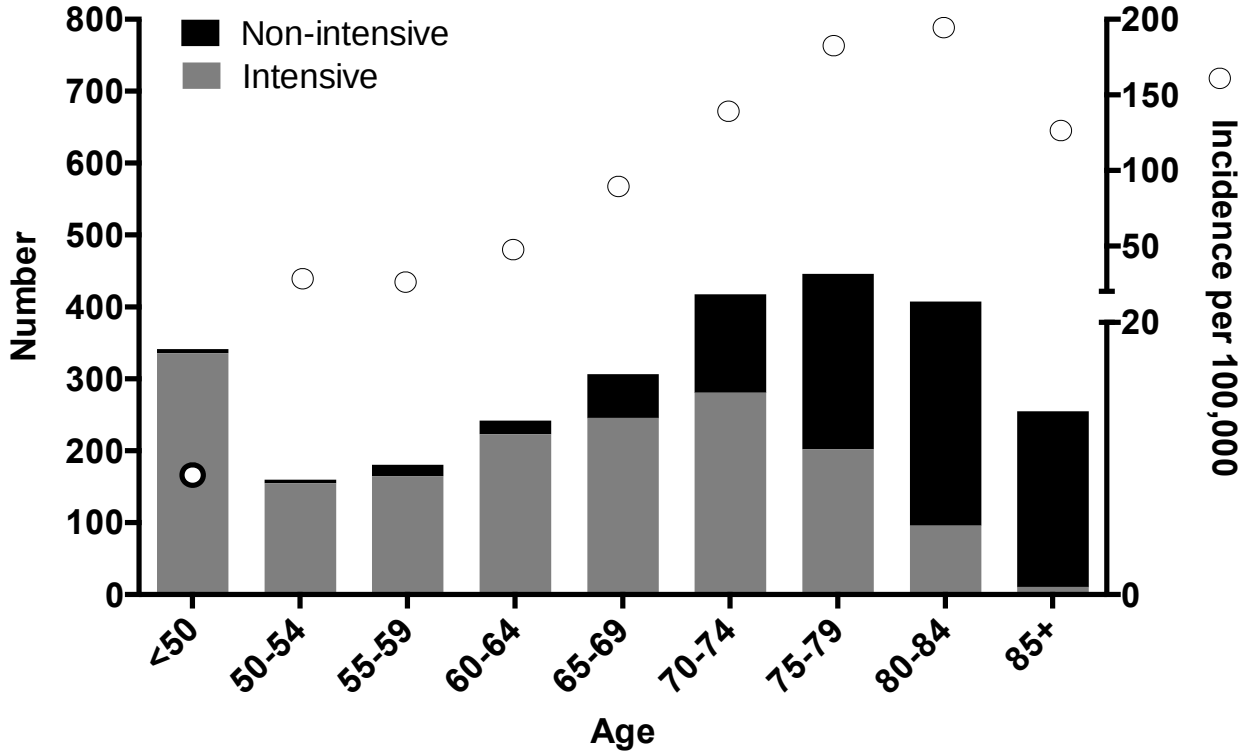
Döhner H, et al. *Blood*. 2022;140:1345-1377.

2022 ELN Guidelines: Therapeutic Approaches and Treatment Goals



Döhner H, et al. *Blood*. 2022;140:1345-1377.

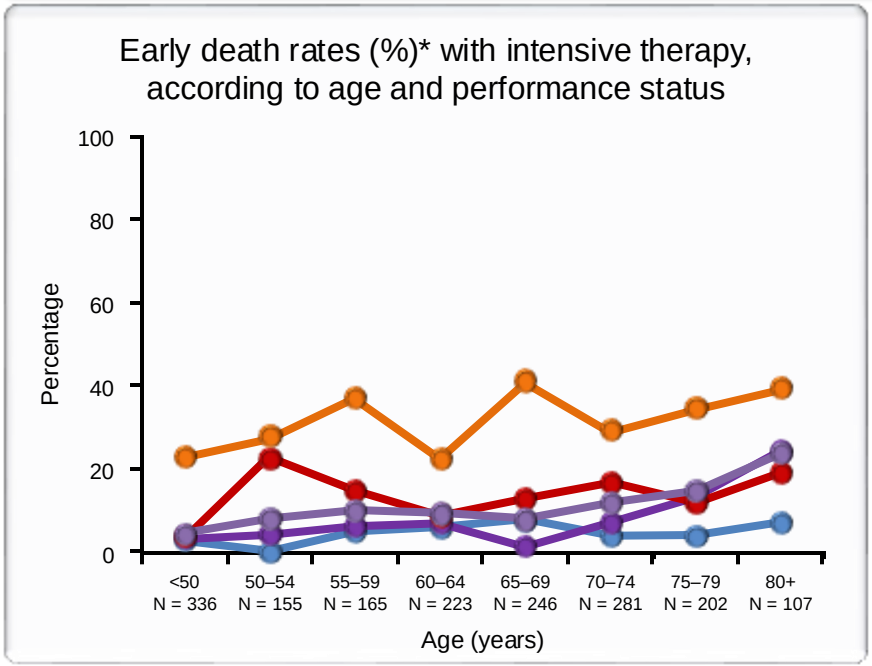
The Majority of Adults With Newly Diagnosed AML Are Not Eligible for Intensive Chemotherapy

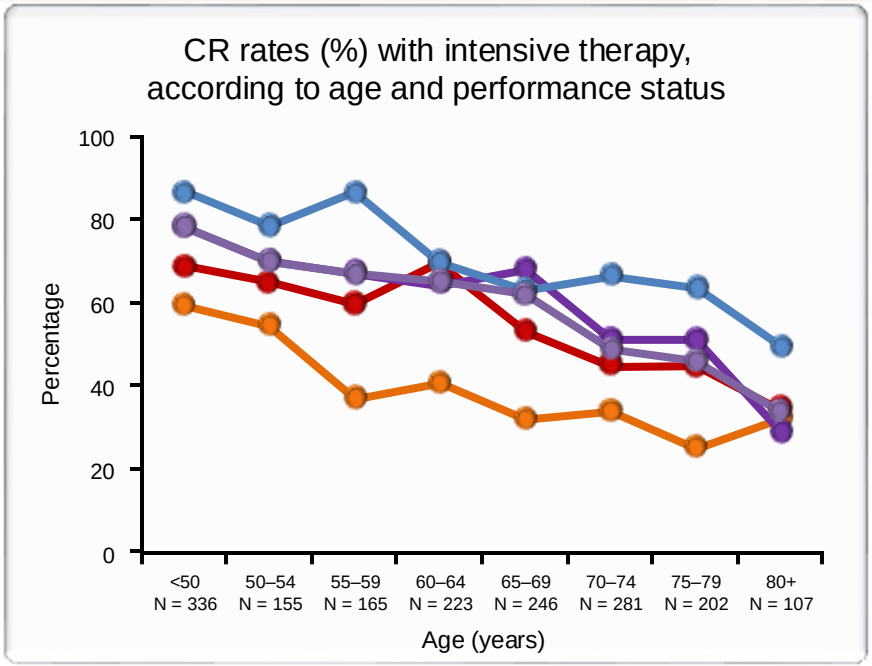


Adapted from Juliusson G, et al. *Blood*. 2009;113:4179-4187.

Outcomes After Induction Chemotherapy Vary According to Patient Age and Performance Status

Real-world data from 2,767 patients with AML from the Swedish Acute Leukemia Registry



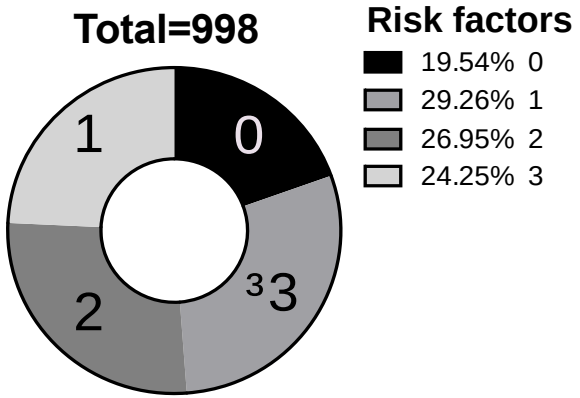


*Within 30 days from diagnosis. AML, acute myeloid leukemia; CR, complete response; PS, performance status; WHO, World Health Organization

Juliusson G, et al. *Blood*. 2009;113:4179-4187.

Mortality Risk From Intensive Chemotherapy ≥65 Years

Risk factors for 8-week mortality
Age ≥75 yr
ECOG ≥2
Complex karyotype
Treatment outside LAFR
Antecedent MDS/MPN ≥12 mo
Creatinine >1.3 mg/dL (115 µmol/L)



Risk Factors	8-wk Mortality (%)	CR (%)	Median OS (months)
0	10	69	16
1	19	57	9
2	36	40	4
≥3	65	19	1

CR, complete remission; ECOG, Eastern Cooperative Oncology Group; LAFR, laminar airflow room; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; OS, overall survival.
Kantarjian H, et al. *Cancer*. 2006;106:1090-1098.

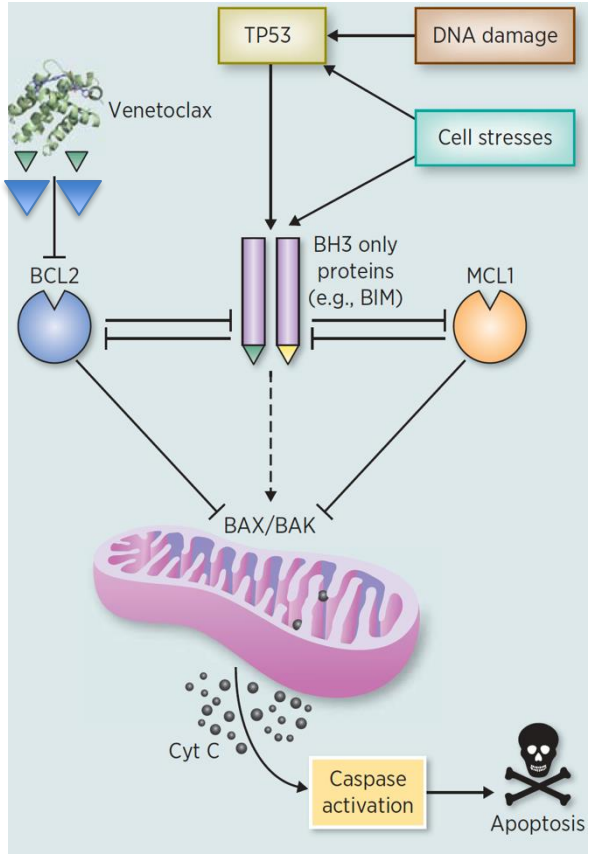
Criteria to Select Patient Suitability for Intensive Chemotherapy

- Age ≥75 years (however, this cannot be an absolute criterion; for instance, patients with more-favorable disease and without relevant comorbidities may derive benefit from intensive chemotherapy)
- ECOG performance status >2 and/or age-related comorbidities, such as
  - Severe cardiac disorder (eg, congestive heart failure requiring treatment, ejection fraction ≤50%, or chronic stable angina)
  - Severe pulmonary disorder (eg, DLCO ≤65% or FEV1 ≤65%)
  - Creatinine clearance <45 mL/min
  - Hepatic disorder with total bilirubin >1.5 times the upper limit of normal
  - Any other comorbidity that the physician assesses to be incompatible with intensive chemotherapy

2022 ELN AML recommendations. Döhner H, et al. *Blood*. 2022;140:1345-1377.

The Emerging Role of Venetoclax in Adult AML

Venetoclax



Pro-survival function of BCL-2
(Vaux, Nature 1988)

BCL-X_L structure
(Murchmore, Science 1996)

First BH3-mimetic (ABT-737)
(Oltersdorf, Nature 2005)

BCL-2 selective inhibitor
(Souers, Nature 2013)

Phase I venetoclax in AML
(Konopleva, Cancer Discov 2016)

Phase Ib/II venetoclax + HMA in AML
(Di Nardo, Lancet Oncol 2018)

Phase Ib/II venetoclax + LDAC in AML
(Wei, J Clin Oncol 2019)

FDA approval in AML >75 or unfit
November 21, 2018

Roberts A, et al. *Clin Cancer Res.* 2017;23:4527-4533.

International Consensus Classification: Impact on Initial Genetic Workup in AML

Cytogenetics*	Additional Information
Screening for gene mutations (for diagnosis) • *FLT3*,† *IDH1, IDH2* (actionable targets) • *NPM1* • *CEBPA*,‡ *DDX41, TP53, ASXL1, BOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*	Results within 3–5 days Results within first treatment cycle
Screening for gene rearrangements§ • *PML::RARA, CBFB::MYH11, RUNX1::RUNX1T1, KMT2A::R, BCR::ABL1,* other fusion genes (if available)	Results within 3–5 days
Other recommended genes to test at diagnosis • *ANKRD26, BCORL1, BRAF, CBL, CSF3R, DNMT3A, ETV6, GATA2, JAK2, KIT, KRAS, NRAS, NF1, PHF6, PPM1D, PTPN11, RAD21, SETBP1, TET2, WT1*	Information can be used to monitor disease by NGS-based MRD analyses (except mutations consistent with premalignant clonal hematopoiesis)

*In case of no analyzable metaphases, FISH is an alternative method to detect genetic abnormalities like *RUNX1::RUNX1T1, CBFB::MYH11, KMT2A::R*, and *MECOM::R*, or myelodysplasia-related chromosome abnormalities, eg, del(5q), del(7q), or del(17p). †*FLT3* mutational screening should include the analysis of internal tandem duplications (ITD) and of tyrosine kinase domain (TKD) mutations. ‡Report should specify type of mutation: only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, regardless of whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome. §Performed if rapid information is needed for recommendation of suitable therapy, if chromosome morphology is of poor quality, or if there is typical morphology but the suspected cytogenetic abnormality is not present.

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

VIALE-A[1]: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Venetoclax + Azacitidine

KEY INCLUSION CRITERIA

- Ineligible for induction therapy defined as either
  - ≥75 years of age
  - 18–74 years of age with at least 1 of the comorbidities
    - CHF requiring treatment or ejection fraction
    - ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV1 ≤65%
    - ECOG 2 or 3

KEY EXCLUSION CRITERIA

- Prior receipt of any HMA, venetoclax, or chemotherapy for MDS

Venetoclax + Azacitidine

VEN: 400 mg PO, daily, days 1–28
+ AZA: 75 mg/m^2 SC/IV days 1–7

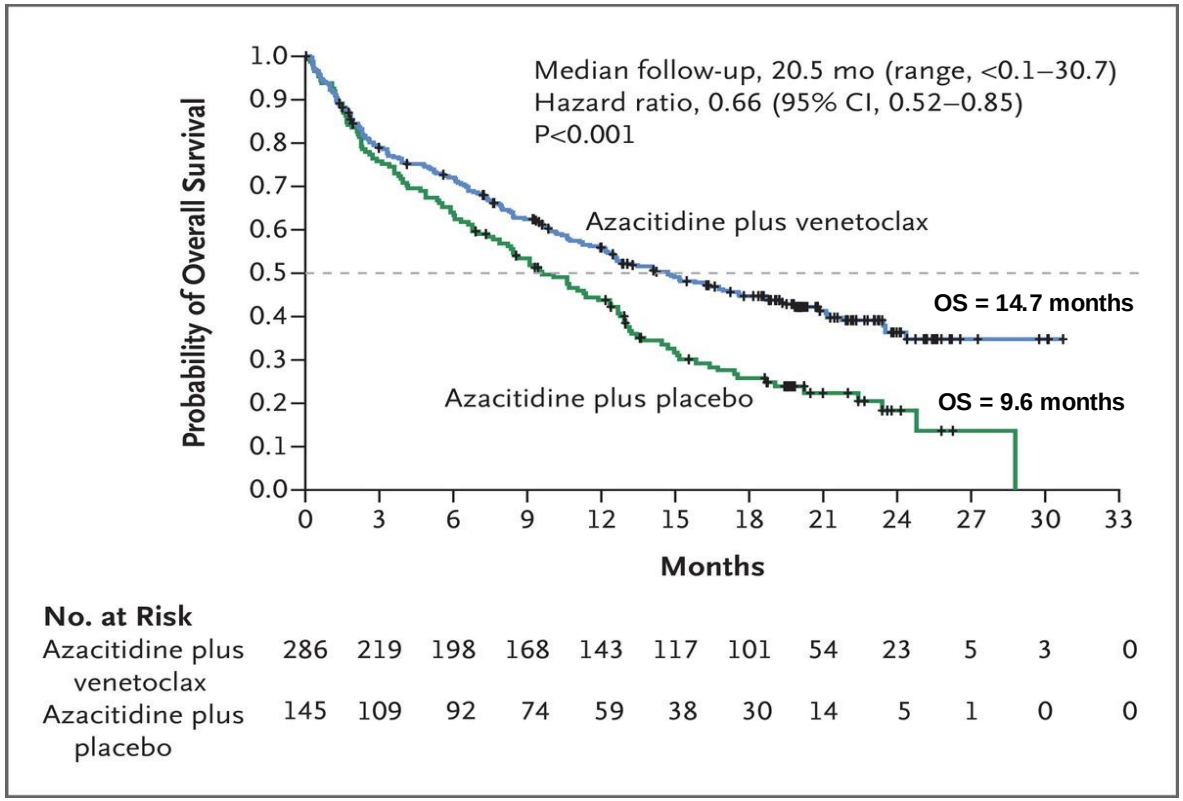
Placebo + Azacitidine

PBO daily, days 1–28 +
AZA 75 mg/m^2 SC /IVdays 1–7

VEN, venetoclax; AZA, azacitidine; PBO, placebo; OS, overall survival.

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

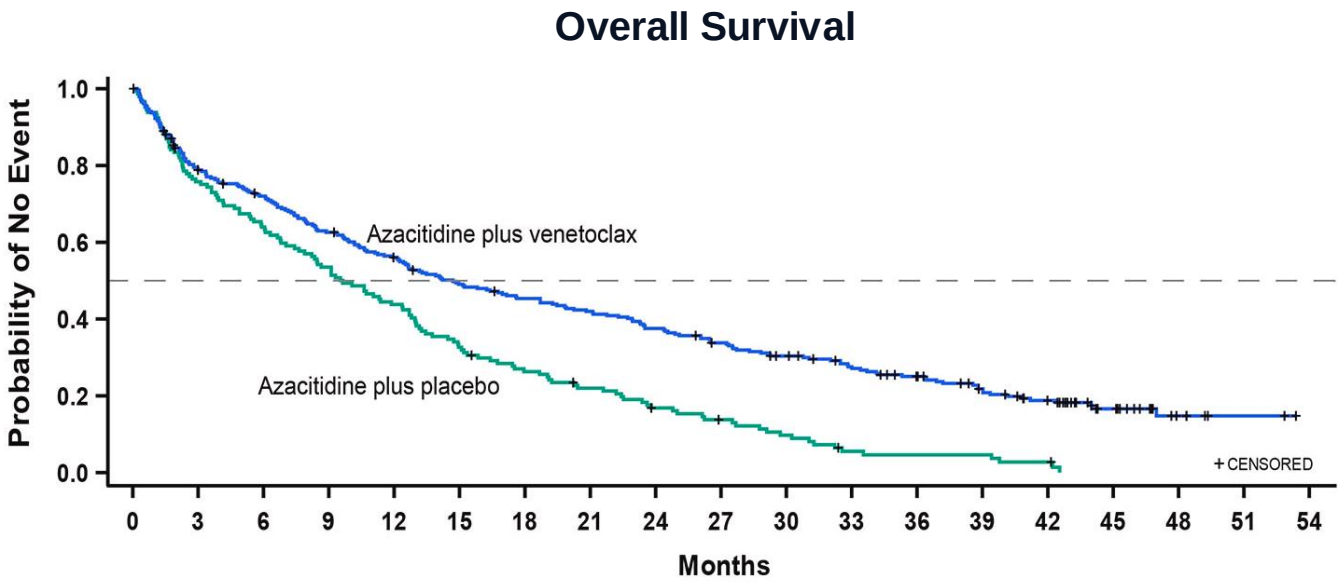
Results of Phase III VIALE-A trial (n = 431):
Azacitidine + Venetoclax Confers a Survival Advantage



- Febrile neutropenia
  - 30% vs 10%
- 30-day mortality
  - 7% vs 6%
- CRc
  - 66% vs 28%
- MRD $<10^{-3}$
  - 41% of those achieving CRc
- US FDA approval
  - Adults ≥75 years old or with comorbidities that preclude intensive chemotherapy

DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629; Pratz KW, et al. *J Clin Oncol.* 2022;40:855-865.

Long-Term Follow-Up of VIALE-A: OS[1]



Median follow-up: 43.2 mo

mOS

- 14.7 mo (95% CI, 12.1–18.7) in the Ven + Aza group
- 9.6 mo (95% CI, 7.4–12.7) in the Pbo + Aza group

(HR 0.58; 95% CI, 0.47–0.72; nominal *P* <.001)

Survival benefit since the interim analysis in the overall population maintained

OS, overall survival; HR, hazard ratio; PBO, placebo.

1. Pratz KW, et al. *Blood*. 2022;140:529-531.

Cytopenia Management in Patients With Treatment-Naive AML Treated With Ven + Aza in the VIALE-A Study

Cytopenia and Dose Adjustments in Responders Who Had CR/CRh	Ven + Aza (n = 186)	Pbo + Aza (n = 33)
Post-remission grade 4 cytopenia lasting ≥1 wk, %	**87**	**45**
• 1 episode	19	24
• ≥2 episodes	68	21
In-cycle dose interruptions for any reason, %	26	24
Median duration per cycle, days (range)	2.0 (1-20)	1.0 (1-13)
Post-remission cycle delays due to cytopenia, %	77	30
Median duration per cycle delay (range), days	14.0 (1-129)	11.0 (3-63)
Post-remission reduction of Ven/Pbo dosing days and/or cycle delay totaling ≥7 days due to neutropenia, %	75	27
Median number of cycles (range)	2.0 (0-15)	0 (0-7)
Post-remission Ven/Pbo dosing ≤21-day cycles, %	69	30
Median time from remission to first ≤21-day cycle, days (range)	92.0 (1-480)	74.0 (6-405)

- CR/CRh rate: 68% (Ven + Aza) vs 23% (Pbo + Aza)

Pratz KW, et al. ASH 2020. Abstract 1944.

TLS Prophylaxis and Monitoring for AML

Patients treated with venetoclax may develop TLS[1]

Prior to venetoclax initiation[1,2]

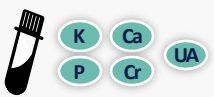
WBC count <25 × 10^9/L
(cytoreduction may be required)

Adequately hydrate*

Anti-hyperuricemics

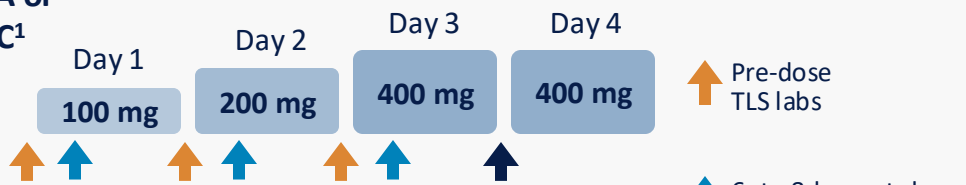
Hydration

Assess blood chemistries and correct abnormalities

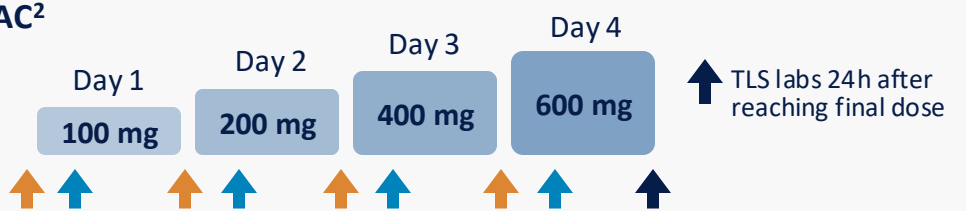


During venetoclax ramp-up†

VEN + AZA or VEN + DEC[1]



VEN + LDAC[2]



AML, acute myeloid leukemia; AZA, azacitidine; BM, bone marrow; Ca, calcium; Cr, creatinine; DEC, decitabine; K, potassium; LDAC, low-dose cytarabine; LDH, lactate dehydrogenase; P, phosphorous; TLS, tumor lysis syndrome; UA, uric acid; VEN, venetoclax; WBC, white blood cell.
*Prior to initiation of first dose of venetoclax and during dose-titration phase; †For patients with risk factors for TLS (eg, circulating blasts, high burden of leukemia involvement in BM, elevated pretreatment LDH levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing VEN starting dose.

1. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics, Jun 2021; 2. Wei AH, et al. *Blood*. 2020;135:2137-2145.

Incidence of TLS in VIALE-A and VIALE-C

VIALE-A[1]

TLS was reported during dose titration in

- **3/283 patients (1.1%) in the VEN + AZA arm**
  - 1 clinical TLS

VIALE-C[2]

TLS was reported during dose titration in

- **8/142 patients (6%) in the VEN + LDAC arm**
  - 2 were reported as serious AEs related to TLS; both patients received TLS prophylaxis as per protocol

M14-358[1] 0 patients with TLS with VEN + DEC

In VIALE-A, TLS was reported in 3 patients receiving VEN + AZA.[1]
In VIALE-C, TLS was reported in 8 patients receiving VEN + LDAC; 2 were reported as serious AEs related to TLS.[2]

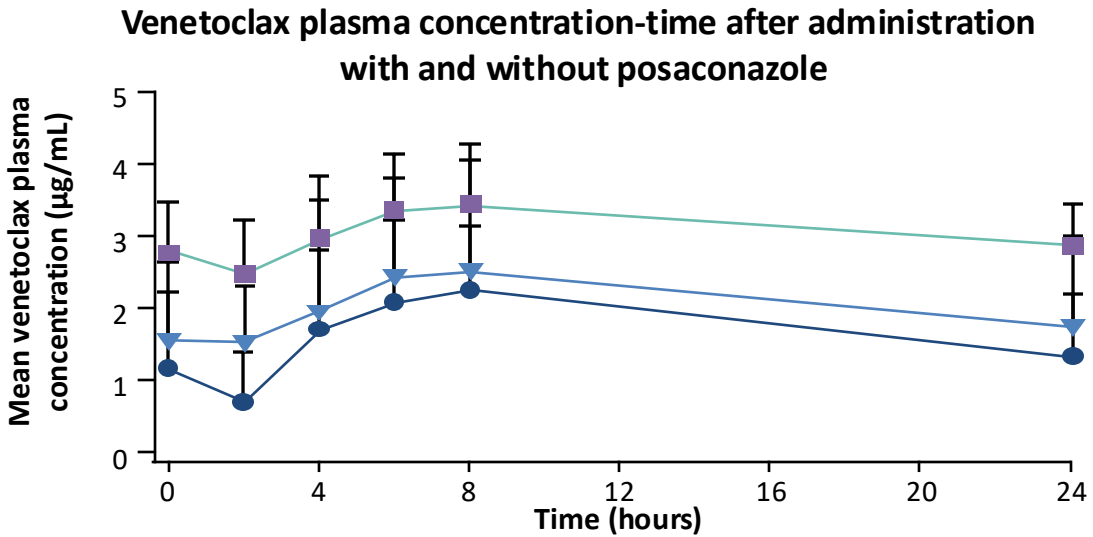
AE, adverse event; AZA, azacitidine; LDAC, low-dose cytarabine; PBO, placebo; TLS, tumor lysis syndrome; VEN, venetoclax.

1. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics, Jun 2021; 2. Wei AH, et al. *Blood*. 2020;135:2137-2145.

Venetoclax Exposure Increases in the Presence of CYP3A Inhibitors

As venetoclax is predominantly metabolized by CYP3A, co-administration with antifungal agents that are strong or moderate CYP3A inhibitors will increase venetoclax exposure.

Based on a posaconazole DDI substudy from M14-358, posaconazole increases venetoclax dose-normalized C_{max} 7.1-fold and $AUC_{0–24}$ 8.8-fold



Treatment schedule

- Day 1–5: 20–200 mg oral VEN (ramp-up) + 20 mg/m^2 IV DEC
- Day 6–20: 400 mg oral VEN
- Day 21–28: 300 mg posaconazole + 50 or 100 mg VEN

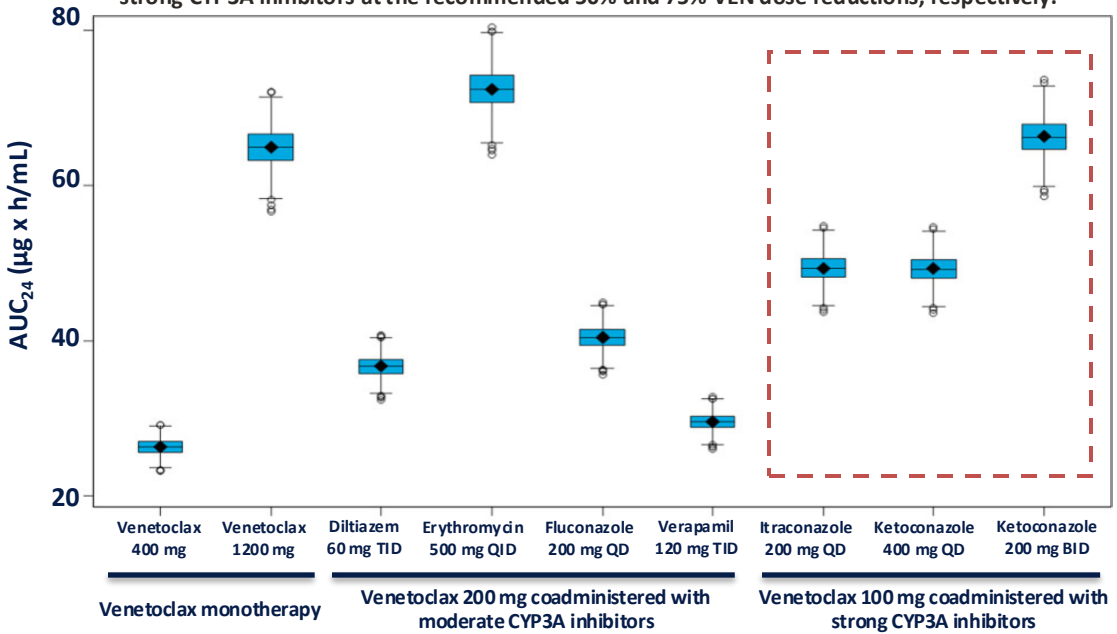
AUC0–24, area under curve over 24 hours; Cmax, maximum serum concentration; CYP3A, cytochrome P450 3A; DEC, decitabine; DDI, drug-drug interaction; VEN, venetoclax.

Agarwal SK, et al. *Clin Ther.* 2017;39:359-367.

Dose Reduction in the Presence of Strong CYP3Ai Maintains Ven Exposure

When coadministered with strong CYP3A inhibitors a 75% dose reduction of venetoclax (100 mg) maintains venetoclax exposures between therapeutic and maximally administered safe doses.

Box plot of VEN exposure when administered alone and when coadministered with moderate and strong CYP3A inhibitors at the recommended 50% and 75% VEN dose reductions, respectively.



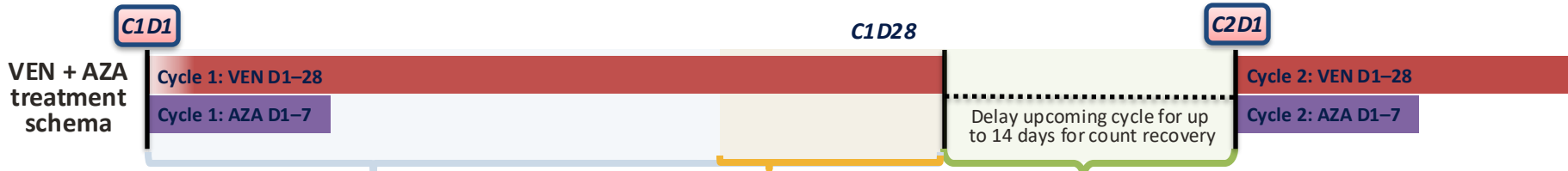
Physiologically based PK (PBPK) model results support the recommended venetoclax dose reductions of at least 50% and 75% when it is coadministered with moderate and strong CYP3A inhibitors, respectively, maintaining venetoclax exposures between those at the therapeutic dose of 400 mg once daily and the established safe maximal administered dose of 1200 mg once daily.

AUC24, area under the concentration time curve over the 24-hour dosing interval; BID, twice daily; QD, once daily; QID, 4 times daily; TID, 3 times daily; VEN, venetoclax.

1. Freise KJ, et al. *J Clin Pharmacol.* 2017;57:796-804.

With Venetoclax Treatment, Guidelines Recommend BM Assessment at the End of Cycle 1 Since Treatment Interruptions for Cytopenias Are Based on Remission Status

Neutropenia is the dominant treatment-related toxicity associated with venetoclax + HMAs and is addressed in the NCCN Guidelines with dose management strategies based on disease assessment.



Treatment should not be interrupted

Continue treatment regardless of cytopenias until a response assessment is made, with aggressive transfusion support and supportive care as needed.

Withhold growth factors until the first-cycle response assessment.

A BM biopsy is necessary for response assessment on days 21–28

If no morphologic remission, proceed to second cycle

Treatment should be held

If blasts are <5% during the first cycle, in the setting of cytopenias all treatment should be held.

G-CSF should be considered for patients with neutropenia who are in morphologic remission but whose counts have not recovered.

AZA, azacitidine; BM, bone marrow; C, cycle; D, day; G-CSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent; NCCN, National Comprehensive Cancer Network; VEN, venetoclax.

Pollyea DA, et al. *J Natl Compr Canc Netw*. 2021;19:16-27.

Consider BM Evaluation After Cycle 1 or as Clinically Indicated to Assess for Remission

If the patient is not in remission and experiencing grade 4 cytopenia, continue therapy

Has patient demonstrated remission* and is experiencing grade 4 cytopenia†?

No

Prior to remission[2,3]

In most instances, do not interrupt VEN‡ due to cytopenias prior to demonstrating remission

In VIALE-A/C, for patients with resistant disease at the end of cycle 1, a bone marrow assessment was performed after cycle 2 or 3, and as clinically indicated

Response definition[1]	RD
BM blasts, %	5-25% and >50% from pretreatment
Neutrophils, µL	<1000
	AND/OR
Platelets, µL	<100,000

ANC, absolute neutrophil count; BM, bone marrow; HMA, hypomethylating agent; LDAC, low-dose cytarabine; RD, resistant disease; VEN, venetoclax.
*Consider BM evaluation. Remission defined as <5% blasts with grade 4 cytopenia following cycle 1; †ANC <500/µL; platelet count <25,000/µL; ‡In combination with HMA or LDAC.
1. Döhner H, et al. *Blood*. 2017;129:424-447; 2. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics, Jun 2021; 3. Wei AH, et al. *J Clin Oncol*. 2019;37:1277-1284.

Consider BM Evaluation After Cycle 1 or as Clinically Indicated to Assess for Remission

If patient is in remission and experiencing grade 4 cytopenia, delay subsequent cycle and monitor blood counts

After demonstrating remission[2,3]

Has patient demonstrated remission* and is experiencing grade 4 cytopenia†?

No

In most instances, do not interrupt VEN‡ due to cytopenias prior to demonstrating remission

Yes

Delay subsequent cycle of VEN‡ and monitor blood counts

Administer G-CSF if clinically indicated for neutropenia

In VIALE-A/C, for patients with resistant disease at the end of cycle 1, a bone marrow assessment was performed after cycle 2 or 3, and as clinically indicated

Response definition[1]	RD	PR	Blast clearance: MLFS	Blast clearance: CRi	CR
BM blasts, %	5-25% and >50% from pretreatment	5-25% and >50% from pretreatment	<5%	<5%	<5%
Neutrophils, µL	<1000	>1000	<1000	>1000	>1000
	AND/OR			OR	
Platelets, µL	<100,000	>100,000	<100,000	>100,000	>100,000

ANC, absolute neutrophil count; BM, bone marrow; CR, complete remission. CRi, CR with incomplete count recovery; G-CSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent; LDAC, low-dose cytarabine; MLFS, morphologic leukemia-free state; PR, partial remission; RD, resistant disease; VEN, venetoclax. *Consider BM evaluation. Remission defined as <5% blasts with grade 4 cytopenia following cycle 1; †ANC <500/µL; platelet count <25,000/µL. ‡In combination with HMA or LDAC.

1. Döhner H, et al. *Blood*. 2017;129:424-447; 2. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics, Jun 2021; 3. Wei AH, et al. *J Clin Oncol*. 2019;37:1277-1284.

Consider BM Evaluation After Cycle 1 or as Clinically Indicated to Assess for Remission

In VIALE-A, 74% of patients who had remission delayed subsequent cycle after blast clearance to allow ANC >500

After demonstrating remission[2,3]

Has patient demonstrated remission* and is experiencing grade 4 cytopenia†?

No

In most instances, do not interrupt VEN‡ due to cytopenias prior to demonstrating remission

In VIALE-A/C, for patients with resistant disease at the end of cycle 1, a bone marrow assessment was performed after cycle 2 or 3 and as clinically indicated

Yes

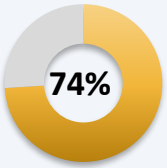
Delay subsequent cycle of VEN‡ and monitor blood counts

Administer G-CSF if clinically indicated for neutropenia

VIALE-A[3]

Cumulative demonstration of BM blast clearance
(in 185 patients with best response of CR/CRh):

76.2%	87.0%	91.4%	96.8%	100%
by end of cycle 1	by end of cycle 2	by end of cycle 3	by end of cycle 4	by end of cycle 7+



of patients who had CR/CRh delayed subsequent cycle after blast clearance to allow ANC >500

Median duration of cycle delay: **10 DAYS**

43% **of patients# received concomitant G-CSF[4]**

ANC, absolute neutrophil count; BM, bone marrow; CR, complete remission. CRi, CR with incomplete count recovery; G-CSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent; LDAC, low-dose cytarabine; MLFS, morphologic leukemia-free state; PBO, placebo; PR, partial remission; RD, resistant disease; VEN, venetoclax. *Consider BM evaluation. Remission defined as <5% blasts with grade 4 cytopenia following cycle 1. †ANC <500/µL; Platelet count <25,000/µL; ‡In combination with HMA or LDAC. #Of all 286 patients regardless of response. 1. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics, Jun 2021; 2. Wei AH, et al. *J Clin Oncol*. 2019;37:1277-1284; 3. Pratz K, et al. 62nd ASH Annual Meeting; Dec 5-8, 2020. Poster 1944; 4. DOF, AbbVie Inc. ABVRRTI71211.

2024 ELN Risk Classification for Patients Receiving Less-Intensive Therapies[a]

Risk category	Genetic abnormality
Favorable	• Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH1*[b] (*TP53*^{wt}) • Mutated *DDX41*[c] • Other cytogenetic and/or molecular abnormalities[d] (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	• Other cytogenetic and molecular abnormalities[d] (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	• Mutated *TP53*

[a]This classification does not apply to patients who have received prior treatment with a hypomethylating agent; [b]Favorable risk applies specifically to patients treated with **azacitidine + ivosidenib**, irrespective of the presence of activating signaling gene mutations; [c]Identification of a *DDX41* mutation at near-heterozygous frequency should prompt consideration of germline *DDX41* mutation; [d]For many cytogenetic and molecular abnormalities, single or as co-aberrations, no data are currently available; they are tentatively categorized as favorable and intermediate-risk depending on the absence or presence of activating signaling gene mutations.

2024 ELN recommendations. Döhner H, et al. *Blood*. 2024. Epub ahead of print.

Advances in the Treatment of Older and Unfit Adults With Acute Myeloid Leukemia

Potential Targeted Molecular Therapies in AML

***FLT3*-ITD mutations:** gilteritinib, quizartinib, sorafenib

***IDH1/2* mutations:** enasidenib (IDH2) or ivosidenib (IDH1)

***NPM1* mutation:** menin inhibitors

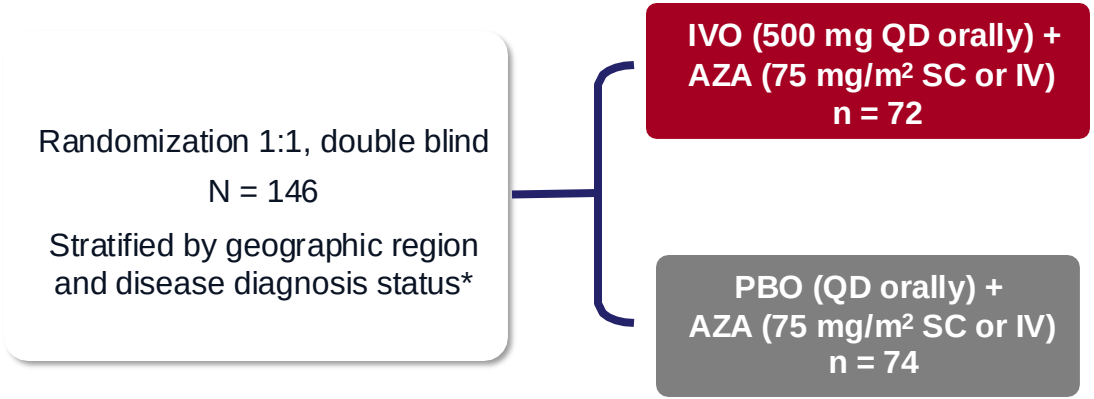
***MLL*-rearranged AML; t(11q23;---):** menin inhibitors

***TP53* mutation:** venetoclax, (magrolimab), (APR-246), allogeneic stem cell transplantation

AGILE[1]: Global Phase III Study Designed for Elderly Unfit Patients With AML and *IDH1* Mutations

ENROLLMENT CRITERIA

- ≥18 years old
- **Centrally confirmed diagnosis of previously untreated AML with m*IDH1***
- No previous treatment with IDH1 inhibitors or hypomethylating agents for MDS
- ECOG PS 0–2
- Adequate liver and kidney function
- Meeting ≥1 of the following criteria to define ineligibility for intensive chemotherapy
  - ≥75 years old
  - ECOG PS of 2
  - Congestive heart failure requiring treatment
  - Ejection fraction ≤50% or chronic stable angina
  - Diffusing capacity of the lungs for CO ≤65% or forced expiratory volume in 1 second ≤65%



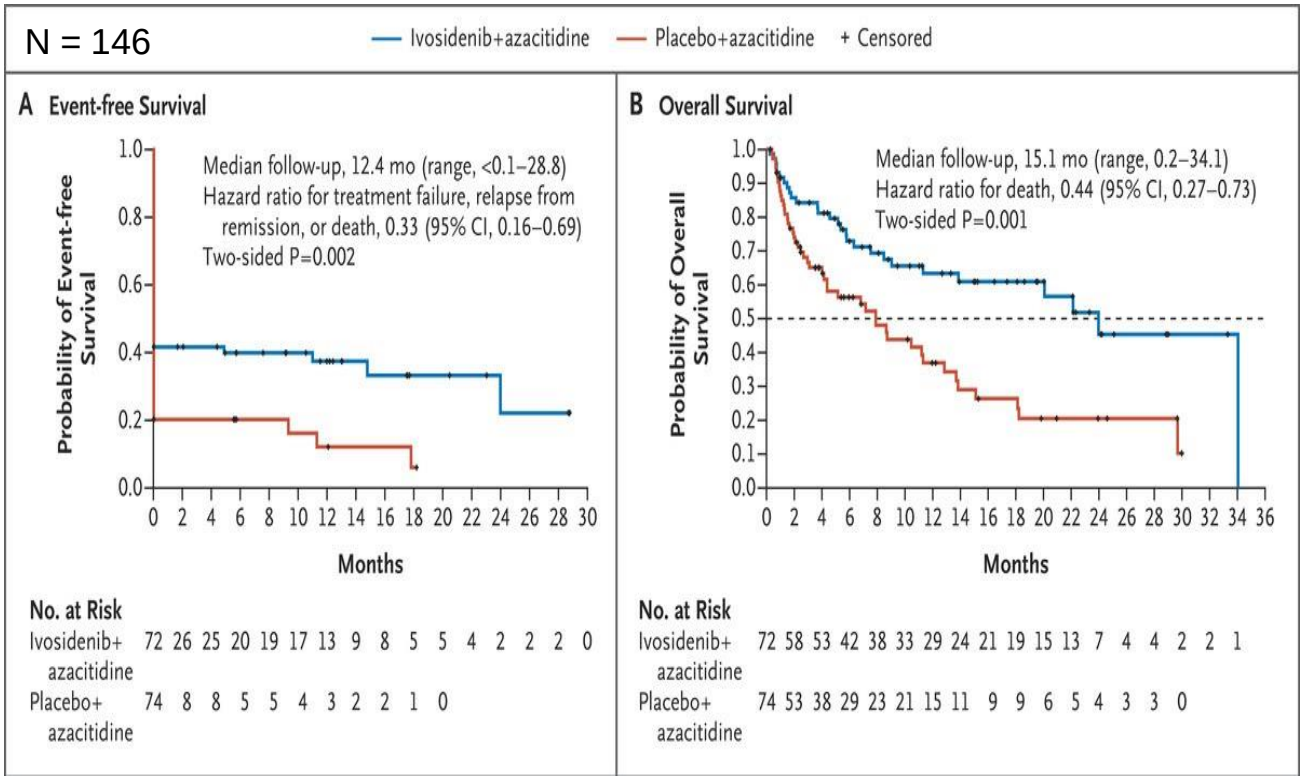
Primary endpoint: event-free survival

Key secondary endpoints: overall survival, CR rate, CR + CRh rate, ORR

CR, complete response; CRh, complete response with incomplete hematologic recovery; ORR, objective response rate; IVO, ivosidenib; VEN, venetoclax; AZA, azacitidine, PBO, placebo.

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

AGILE: Ivosidenib + Azacitidine in Treatment-Naive Adults With AML Unfit for Intensive Chemotherapy



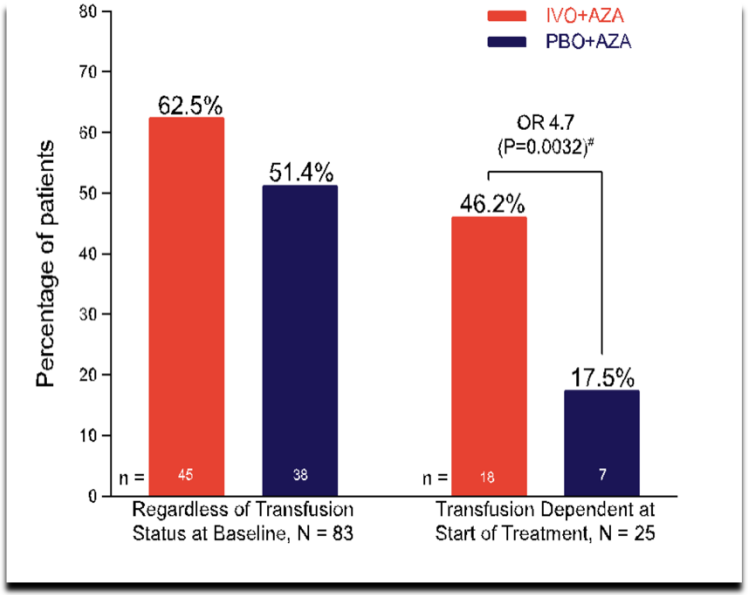
Results (Ivo + Aza vs Placebo + Aza)

- Overall survival: 24 months vs 7.9 months
- CR rate: 47% vs 11%
- CR/CRi/CRp: 54% vs 12%
- Differentiation syndrome: 14% vs 8%
- Febrile neutropenia: 10% vs 8%

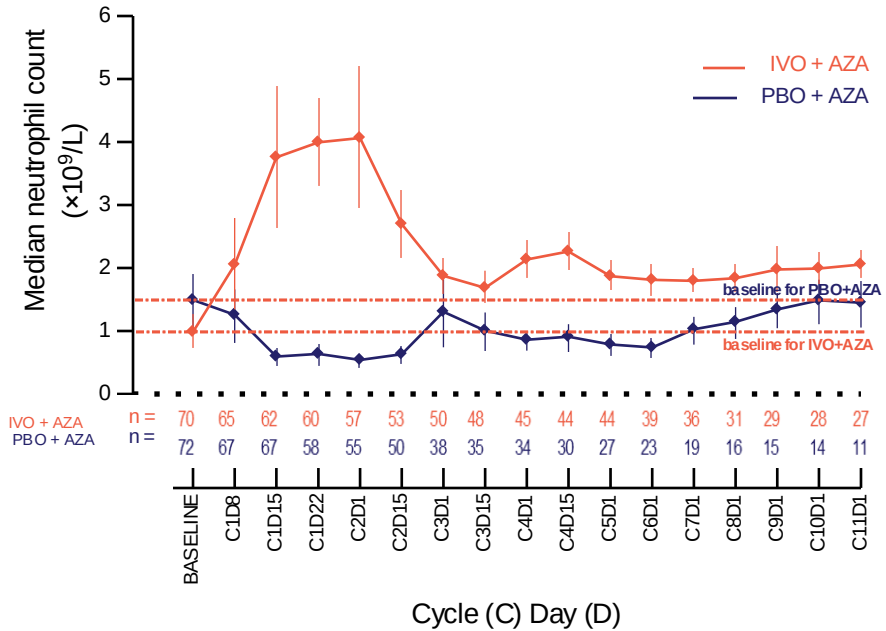
Montesinos P, et al. *N Engl J Med.* 2022;386:1519-1531.

Transfusion Independence, Neutrophil Recovery: IVO-AZA[1]

Transfusion independence rates IVO + AZA vs AZA[1]



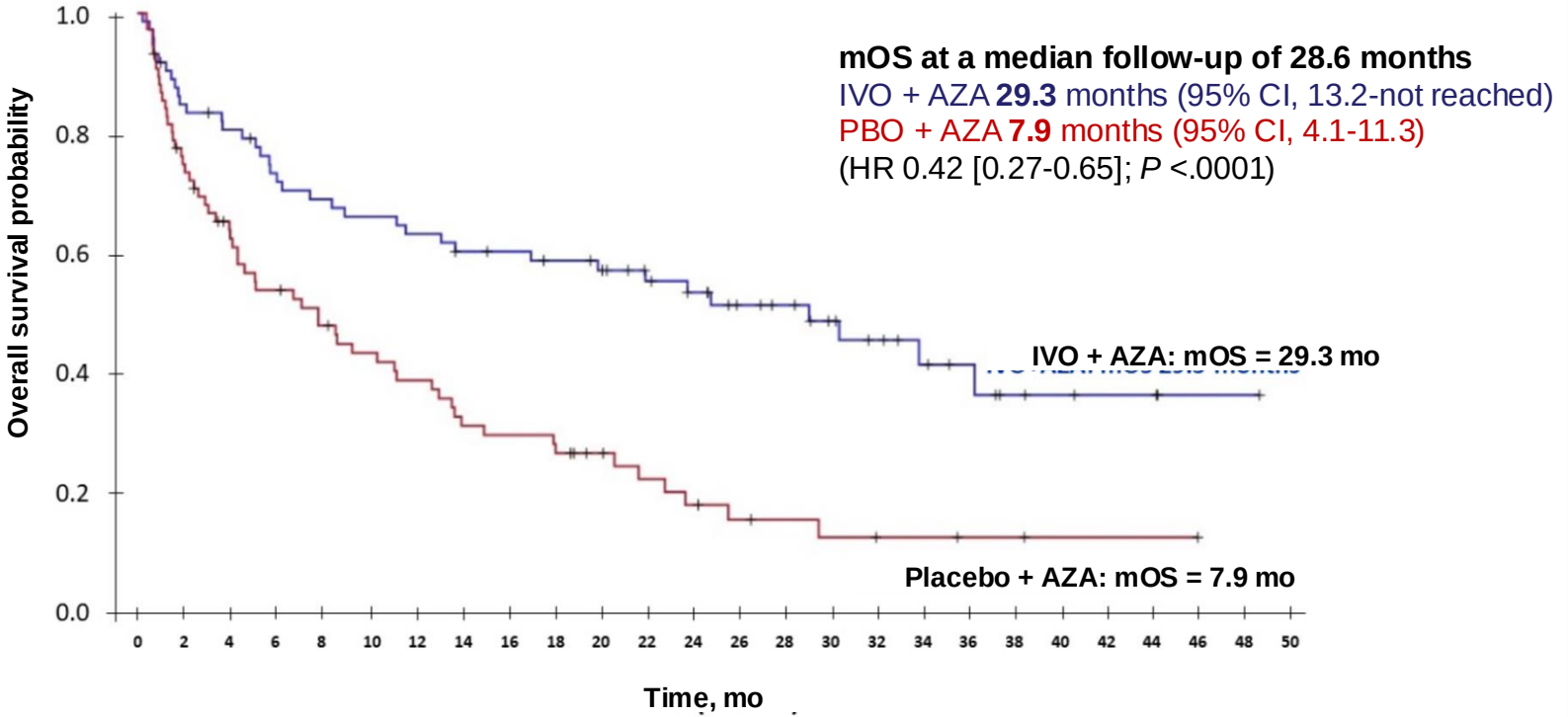
Change in absolute neutrophil count from baseline with IVO + AZA vs PBO + AZA



IVO, ivosidenib; AZA, azacitidine; PBO, placebo; TEAEs, treatment-emergent adverse events.

1. Montesinos P, et al. *N Engl J Med.* 2022;386:1519-1531; 2. DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629.

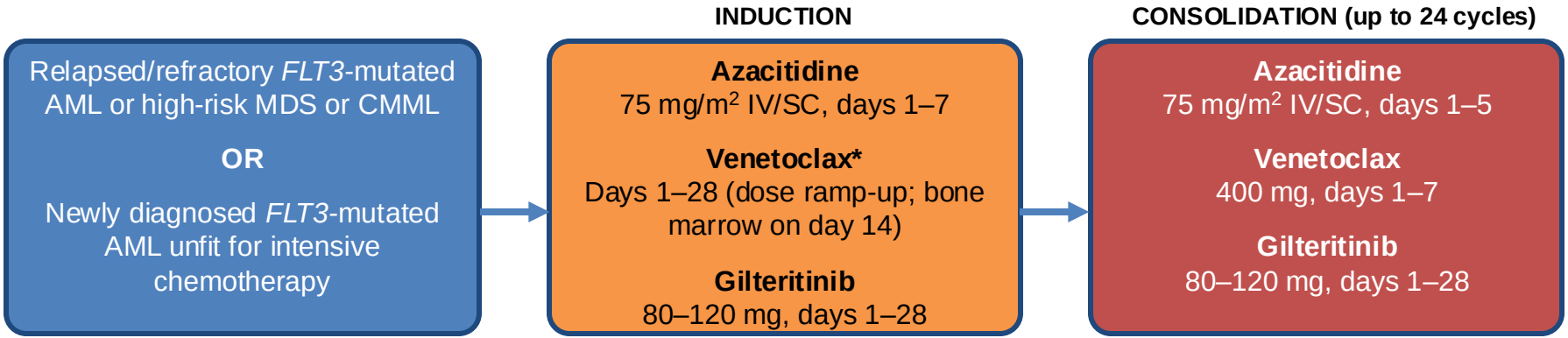
AGILE Update: Continued Overall Survival Benefit With Ivosidenib + Azacitidine



Döhner H, et al. EHA 2023. Abstract P490.

Phase I/II Study of the Triplet Combination of Azacitidine, Venetoclax, and Gilteritinib for Patients With *FLT3*-Mutated AML

- Gilteritinib is a FLT3 inhibitor that improves response rate and OS in relapsed/refractory *FLT3*-mutated AML,[1] and has potential synergy with venetoclax[2,3]



- **Primary endpoints**
  - MTD of gilteritinib in combination (phase I)
  - CR/CRi rate (phase II)

- The phase I data have previously been reported
- Myelosuppression was greater with gilteritinib 120 mg, and **gilteritinib 80 mg was selected as the phase II dose**

- **Secondary endpoints:** CR rate, MRD negativity rate, duration of response, OS, safety

*Venetoclax ramp-up during cycle 1: 100 mg on day 1, 200 mg on day 2, 400 mg on day 3+. If <5% blasts or insufficient on cycle 1 day 14, venetoclax was held (both cohorts) and gilteritinib held (frontline only). AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete count recovery; IV, intravenous; MDS, myelodysplastic syndrome; MRD, minimal residual disease; MTD, maximum tolerated dose; OS, overall survival; SC, subcutaneous.

1. Perl AE, et al. *New Engl J Med.* 2019;381:1728-1740; 2. Mali RS, et al. *Haematologica*. 2021;106:1034-1046; 3. Daver N, et al. *J Clin Oncol.* 2022 (in press). Short N, et al. ASH 2022. Abstract 831 (oral presentation).

Phase I/II Study of the Triplet Combination of Azacitidine, Venetoclax, and Gilteritinib: Patients and Response

Baseline Characteristics	Category	Frontline (N = 27)	R/R (N = 20)*
Median age, years (range)		70 (18–86)	69 (19–90)
Diagnosis, n (%)	AML MDS/CMML	27 (100) 0	19 (95) 1 (5)
***FLT3* mutation type**, n (%)	ITD TKD ITD + TKD	19 (70) 8 (30) 0	9 (45) 7 (35) 4 (20)

Response	Frontline (N = 27)	R/R (N = 20)*
mCRc, n (%) CR CRi MLFS PR No response	**27 (100)** 25 (92) 1 (4) 1 (4) 0 0	**14 (70)** 4 (20) 3 (15) 7 (35) 1 (5) 5 (25)
MRD negativity Flow cytometry (10^{-4}) PCR (10^{-2})	 **82%** 89%	 **43%** 57%

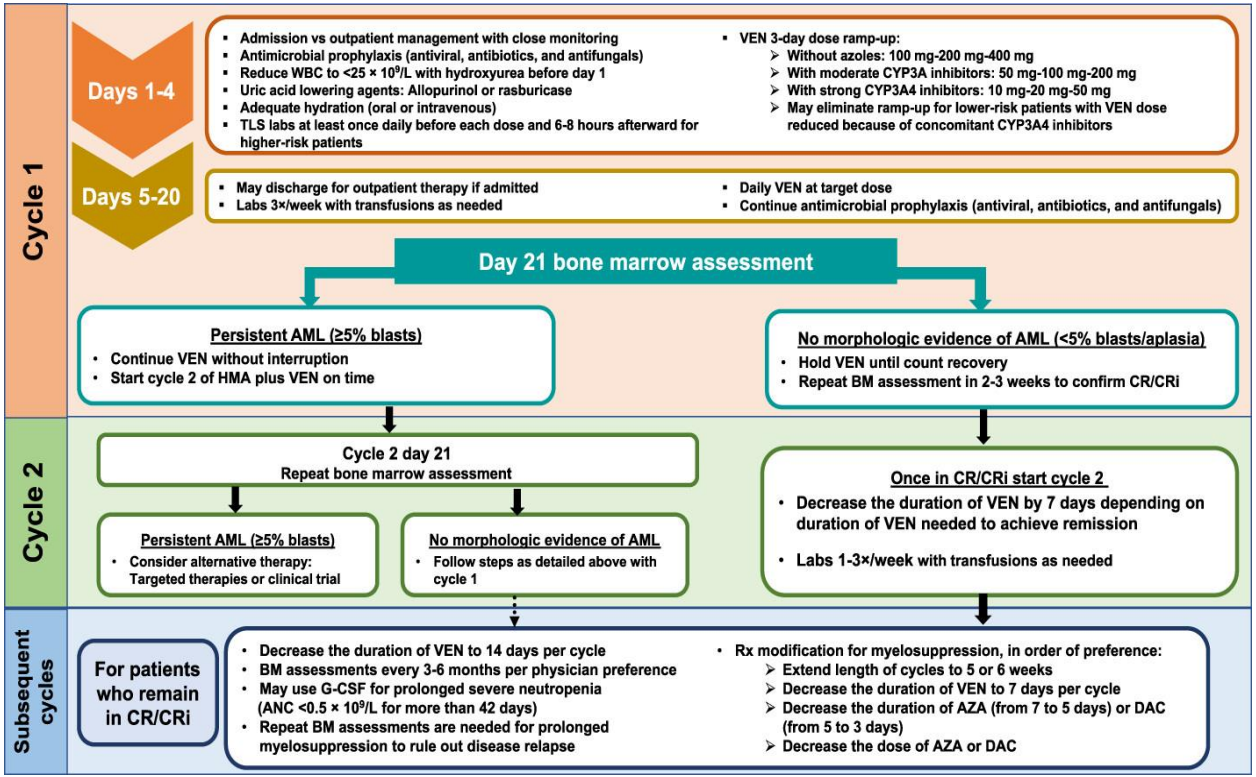
*Prior treatments: FLT3 inhibitor, n = 6; gilteritinib, n = 2; hypomethylating agent + venetoclax, n = 8; HSCT, n = 5.
AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete count recovery; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication; mCRc, modified composite complete response; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; PCR, polymerase chain reaction; PR, partial remission; R/R, relapsed/refractory; TKD, tyrosine kinase domain.
Short N, et al. ASH 2022. Abstract 831 (oral presentation).

Selected Treatment Options for Patients With AML Not Suitable for Intensive Chemotherapy

Regimen	Recommended dosing
Azacitidine or decitabine + venetoclax†,‡	Azacitidine 75 mg/m^2 SC/IV d1-7 (alternatively d1-5 + d8-9) or decitabine 20 mg/m^2 IV d1-5; venetoclax dose ramp up: 100 mg d1, 200 mg d2, 400 mg PO QD d3-28 • Adjust venetoclax dose if concurrent strong CYP3A4 inhibitors: 10 mg on d1, 20 mg on d2, 50 mg on d3, 100 mg (or less‡) PO QD from d4 • For venetoclax dose modifications and management of myelosuppression see Table 12
Low-dose cytarabine + venetoclax†,‡	Cytarabine 20 mg/m^2 SC daily, d1-10; venetoclax dose ramp up: 100 mg d1, 200 mg d2, 400 mg d3, 600 mg d4-28 PO • Adjust venetoclax dose if concurrent strong CYP3A4 inhibitors: 10 mg d1, 20 mg d2, 50 mg d3, 100 mg (or less‡) PO QD d4-28 • For venetoclax dose modifications and management of myelosuppression see Table 12
Azacitidine + ivosidenib (AML with *IDH1* mutation)	Azacitidine 75 mg/m^2 SC/IV d1-7 (alternatively d1-5 + d8-9); ivosidenib 500 mg PO QD d1-28; both q4 wk, until progression
Ivosidenib (AML with *IDH1* mutation)	For very frail patients, ivosidenib 500 mg PO QD d1-28 as monotherapy, until progression may be considered
Best supportive care	Including hydroxyurea; for patients who cannot tolerate any anti-leukemic therapy, or who do not wish any therapy

2022 ELN AML recommendations. Döhner H, et al. *Blood*. 2022;140:1345-1377.

Optimizing Outcomes in Patients Treated With VEN-HMA Combinations



Abaza Y, et al. *ASCO Educ Book.* 2024. DOI: 10.1200/EDBK_4386.

Global Leukemia Academy

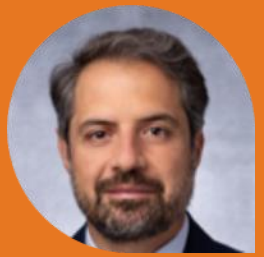
Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Panel discussion: Open questions in ALL and AML – regional challenges

Elias Jabbour and all faculty



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Panel discussion

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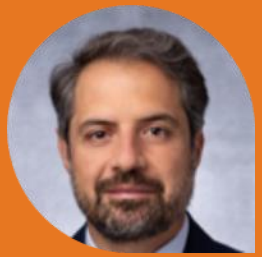
Session close

Elias Jabbour



APTITUDE HEALTH

Question 3 [REPEATED]

At what time points is MRD quantification prognostic for survival in ALL?

A. After induction/consolidation
B. Prior to allogeneic hematopoietic cell transplant
C. After transplant
D. All of the above

Question 4 [REPEATED]

Which of the following is NOT true for treating ALL?

A. Inotuzumab and blinatumomab plus chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients

B. Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL

C. MRD– CR does not correlate strongly with outcome

D. Since 1999, median survival for patients with ALL older than 60 has been increasing with each successive decade

Agenda: Day 2

Time UTC+2	Title	Speaker
18.30 – 18.40	Welcome to Day 2	Naval Daver
18.40 – 19.00	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
19.00 – 19.20	Long-term safety considerations for leukemias (focus on ALL)	Nicola Gökbuget
19.20 – 19.40	Current and future role of transplantation in acute leukemias in Europe	Josep-Maria Ribera
19.40 – 19.50	Break	
19.50 – 20.10	Current treatment options for relapsed AML in adult and elderly patients	Charles Craddock
20.10 – 20.40	AML case-based panel discussion • Case 1 AML: Vitor Botafogo (Spain) • Case 2 AML: Samantha Drummond (UK)	Naval Daver Patient case presenters Panelists: All faculty
20.40 – 21.20	Panel discussion: How treatment in first line influences further therapy approaches in ALL and AML • Will CAR T and bispecifics change the treatment landscape? • Role of HSCT – is it still necessary? • What does the future look like? Adoption of therapies and evolving standards of care in Europe	Naval Daver and all faculty
21.20 – 21.30	Session close	Naval Daver

Global Leukemia Academy

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October 16–17

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