Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

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

June 19–20, 2023 – Latin America

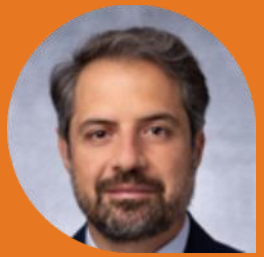
Meeting sponsors AMGEN rigel

APTITUDE HEALTH®

Global Leukemia Academy

Welcome and meeting overview

Elias Jabbour



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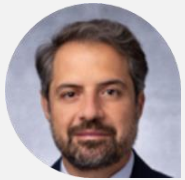
Meet the Faculty

CO-CHAIR



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

CO-CHAIR

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

FACULTY

Roberta Demichelis, MD
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Jae Park, MD
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Phillip Scheinberg, MD, PhD
Hospital A Beneficência Portuguesa, São Paulo, Brazil

Fabio Santos, MD, PhD
Hospital Israelita Albert Einstein, São Paulo, Brazil

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 LATAM

Day 1: Virtual Plenary Sessions

Wednesday, June 19, 2024
5.00 PM – 8.00 PM UTC -5 (Houston)
7.00 PM – 10.00 PM UTC -3 (Brasilia/Buenos Aires)

Time (UTC -3)	Title	Speaker
7.00 PM – 7.10 PM	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
7.10 PM – 7.25 PM	Latest achievements and developments in ALL and AML	Elias Jabbour
7.25 PM – 7.40 PM	Review of prognostic value of MRD in ALL and AML	Jae Park
7.40 PM – 7.50 PM	Best practices for first-line treatment in ALL	Elias Jabbour
7.50 PM – 8.05 PM	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	Roberta Demichelis
8.05 PM – 8.35 PM	ALL case-based panel discussion • Case ALL: elderly/frail (8 min + 5-min discussion) • Case ALL: AYA (8 min + 5-min discussion)	Roberta Demichelis (moderator) • Fausto A. Rios-Olais, MD • Jessica Zalapa, MD Panelists: all faculty
8.35 PM – 8.45 PM	Break	
8.45 PM – 9.10 PM	Genetic characterization and risk stratification of AML; role of *FLT3* and *IDH* in AML and special considerations for young and fit patients	Naval Daver
9.10 PM – 9.25 PM	Therapeutic approaches in high-risk and frail patients with AML	Philip Scheinberg
9.25 PM – 9.50 PM	Panel discussion: Open questions in ALL and AML – regional challenges (transplant, CAR T, studies, and other)	Elias Jabbour and all faculty
9.50 PM – 10.00 PM	Session close	Elias Jabbour

Day 2: Virtual Plenary Sessions

Thursday, June 20, 2024
5.00 PM – 8.00 PM UTC -5 (Houston)
7.00 PM – 10.00 PM UTC -3 (Brasilia/Buenos Aires)

Time (UTC -3)	Title	Speaker
7.00 PM – 7.10 PM	Welcome to Day 2	Naval Daver
7.10 PM – 7.30 PM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
7.30 PM – 7.50 PM	Long-term safety considerations for leukemias (focus on ALL)	Jae Park
7.50 PM – 8.10 PM	Current and future role of transplantation in acute leukemias in LATAM	Phillip Scheinberg
8.10 PM – 8.20 PM	Break	
8.20 PM – 8.40 PM	Current treatment options for relapsed AML in adult and elderly patients	Fabio Santos
8.40 PM – 9.10 PM	AML case-based panel discussion • Case AML: young high-risk (8 min + 5-min discussion) • Case AML: elderly (10 min) (8 min + 5-min discussion)	Fabio Santos and TBD (case presenters) All faculty
9.10 PM – 9.50 PM	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 LATAM	Naval Daver and all faculty
9.50 PM – 10.00 PM	Session close	Naval Daver

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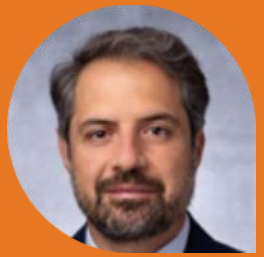
Introduction to the voting system

Elias Jabbour



APTITUDE HEALTH®

Question 1

In which country do you currently practice?

A. Argentina
B. Bolivia
C. Brazil
D. Chile
E. Colombia
F. Mexico
G. Peru
H. Venezuela
I. Other country in Latin America
J. Other country outside Latin America

Question 2

Which leukemias do you primarily treat?

A. AML

B. ALL

C. Both

Question 3

If an elderly patient with Ph-negative ALL tests positive for MRD after dose-adjusted Hyper-CVAD induction chemotherapy, what would you advise?

Please assume that you have access to all of these options.

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

Question 4

Which of the following factors are important in assessing patients with AML at diagnosis?

Select all that apply.

A. Adverse genetic alterations
B. Age
C. Comorbidities
D. Performance status
E. Prior cytotoxic therapy
F. Prior myelodysplasia

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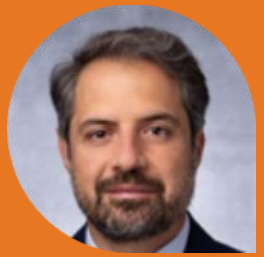
Latest achievements and developments in ALL and AML

Elias Jabbour



APTITUDE HEALTH®

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 8: S131: 2024

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 8: S134: 2024

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 8: S132: 2024

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 8: S133: 2024

SAR 443579 (CD 123-NK Engager) in R-R AML

- 59 pts with RR AML; median age 67 yrs; median prior Rx 2 (1-10)
- SAR 0.75 mg-6 mg/kg Q wk or 2x/wk
- Target dose 1 mg/kg/wk—CR-CRi 5/15 (33%; 4 CR, 1 CRi)

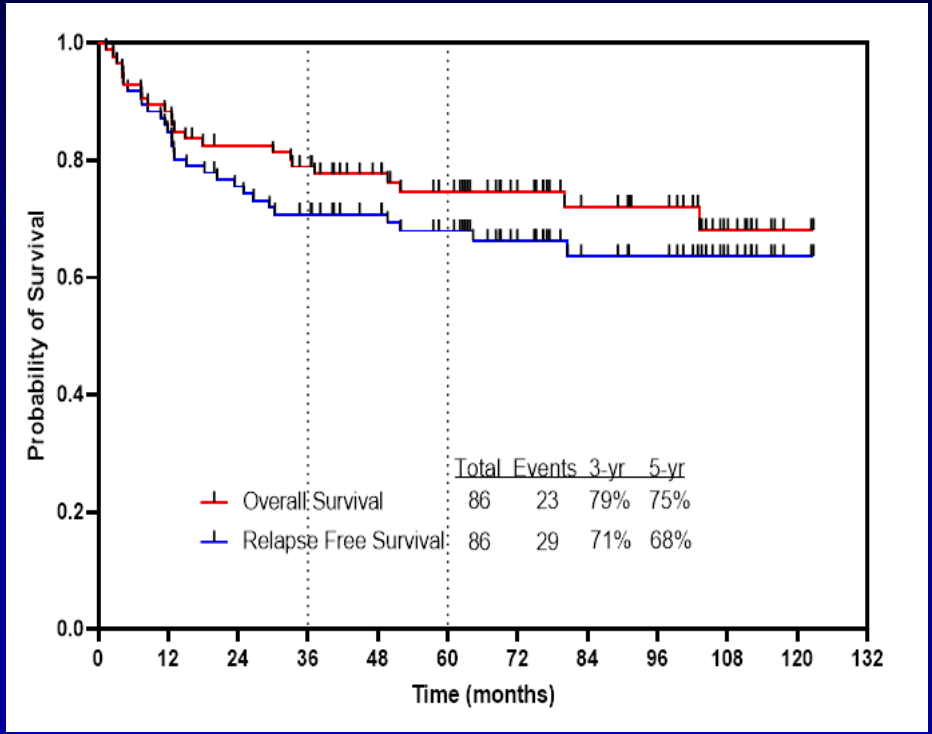
Garciaz. HemaSphere 8: S146; 2024

What Is New in ALL

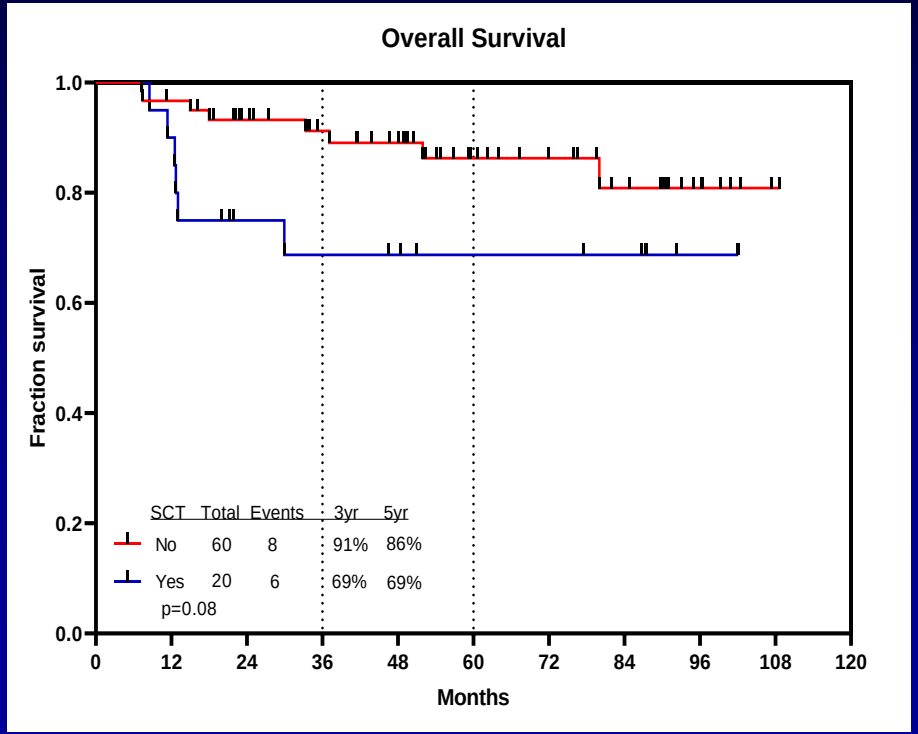
HyperCVAD + Ponatinib in Ph+ ALL

- 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



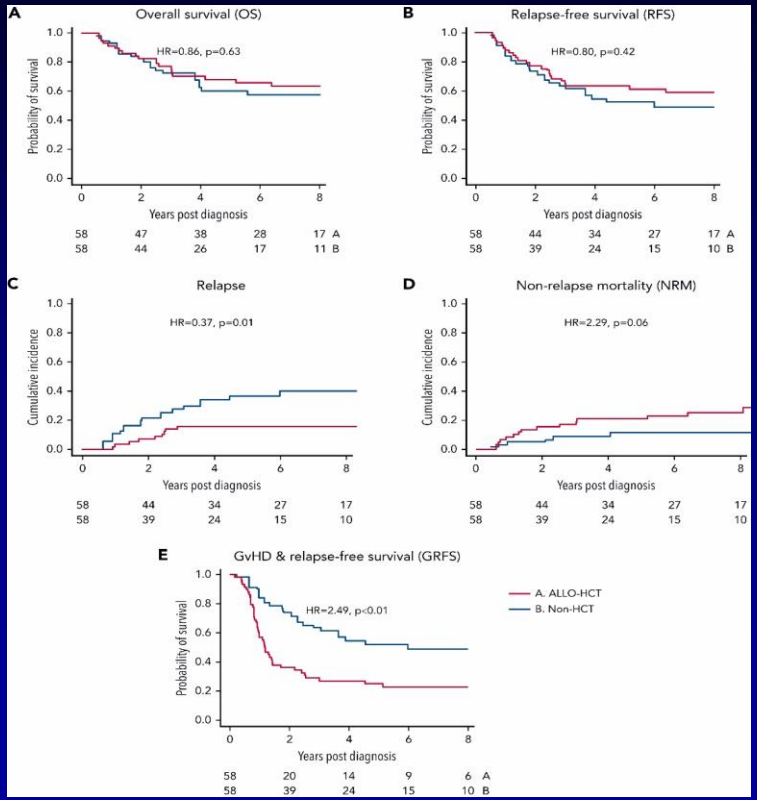
6-month Landmark



Kantarjian. Am J Haematol 98:493-501;2023

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

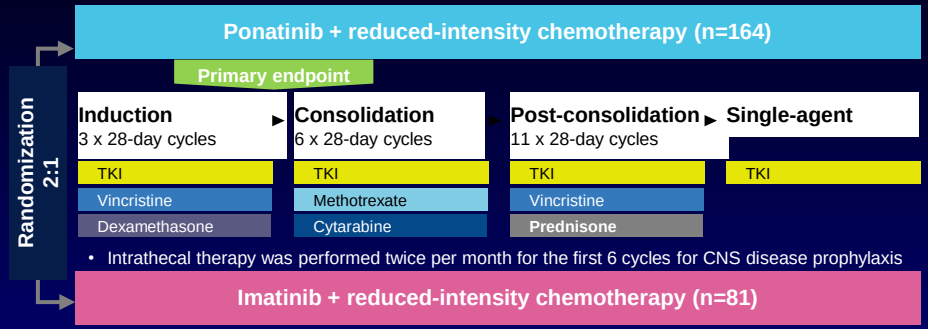
- Propensity score analysis of patients who achieved CMR within 3 months
- Allogeneic SCT → lower risk of relapse but higher NRM
- No impact of SCT on OS or RFS



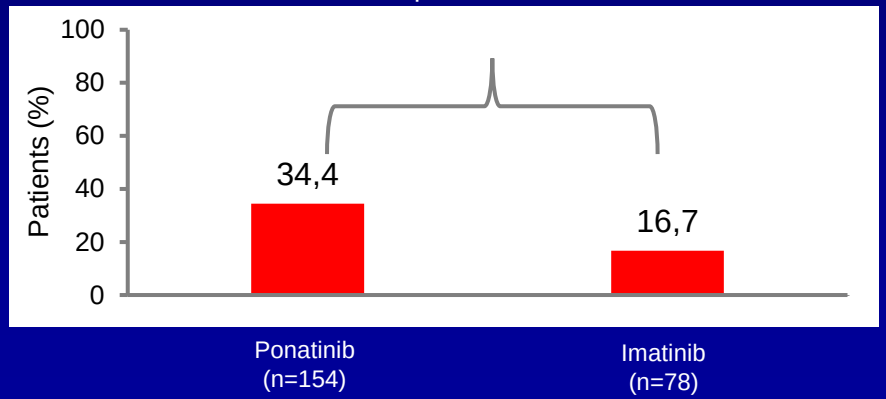
Ghobadi A et al. *Blood* 2022;140(20):2101-12

Ponatinib vs Imatinib With Rx in Ph+ ALL: PhALLCON

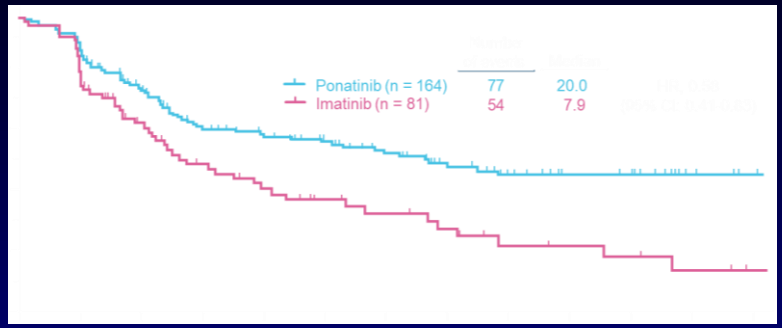
Study design



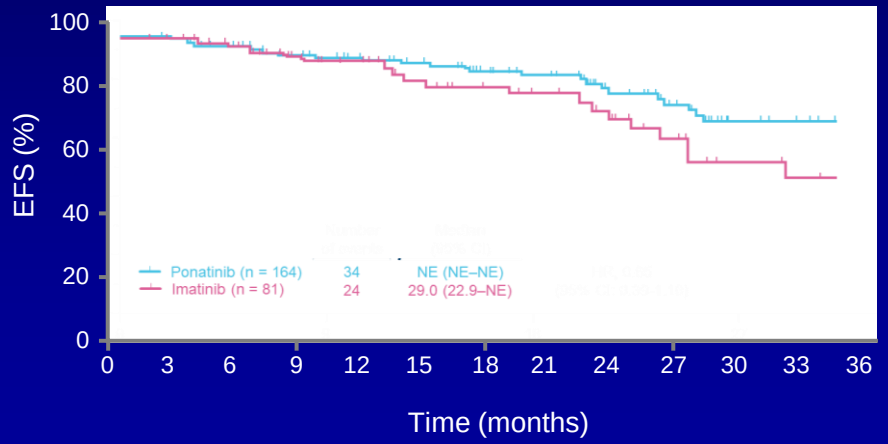
Primary endpoint:
MRD– (MR4) CR at end of induction
RR: 2.06 (95% CI=1.19–3.56)
p=0.0021



PFS



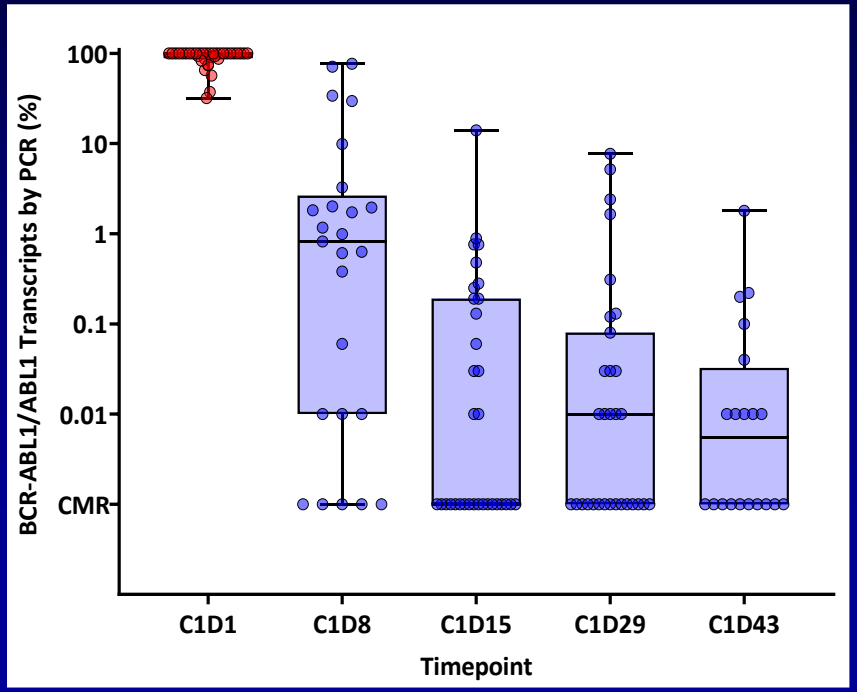
EFS

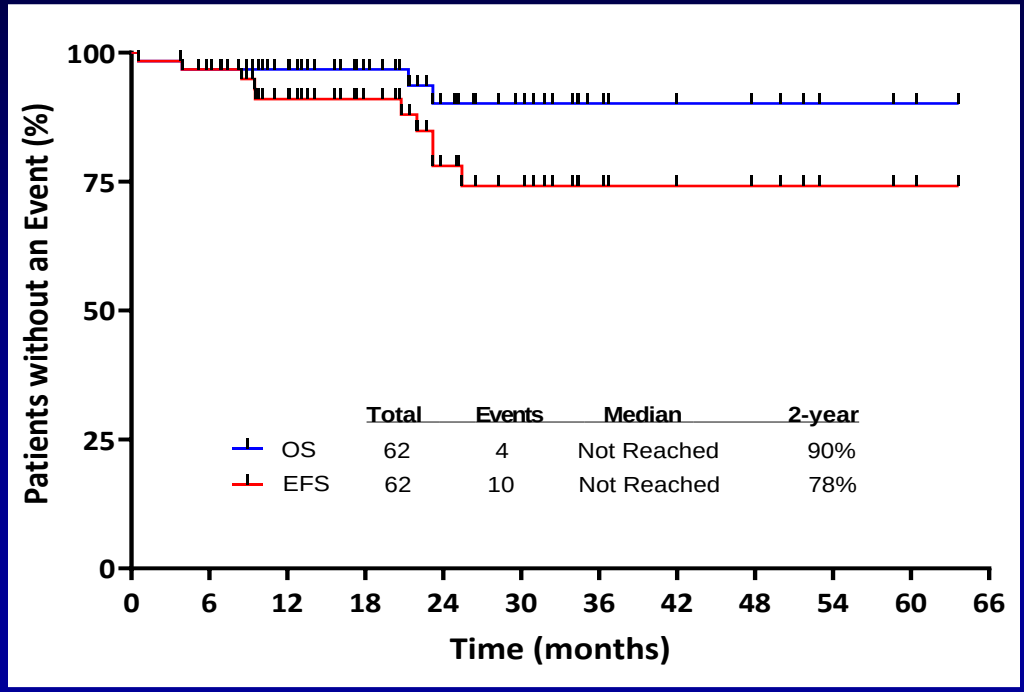


Jabbour. JAMA. 2024 May 9:e244783.

Ponatinib and Blinatumomab in Newly Dx Ph+ ALL

- 62 pts Rx with simultaneous ponatinib 30-15 mg/D and blinatumomab x 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. Lancet Haematol. 2023;10(1):e24-e34.

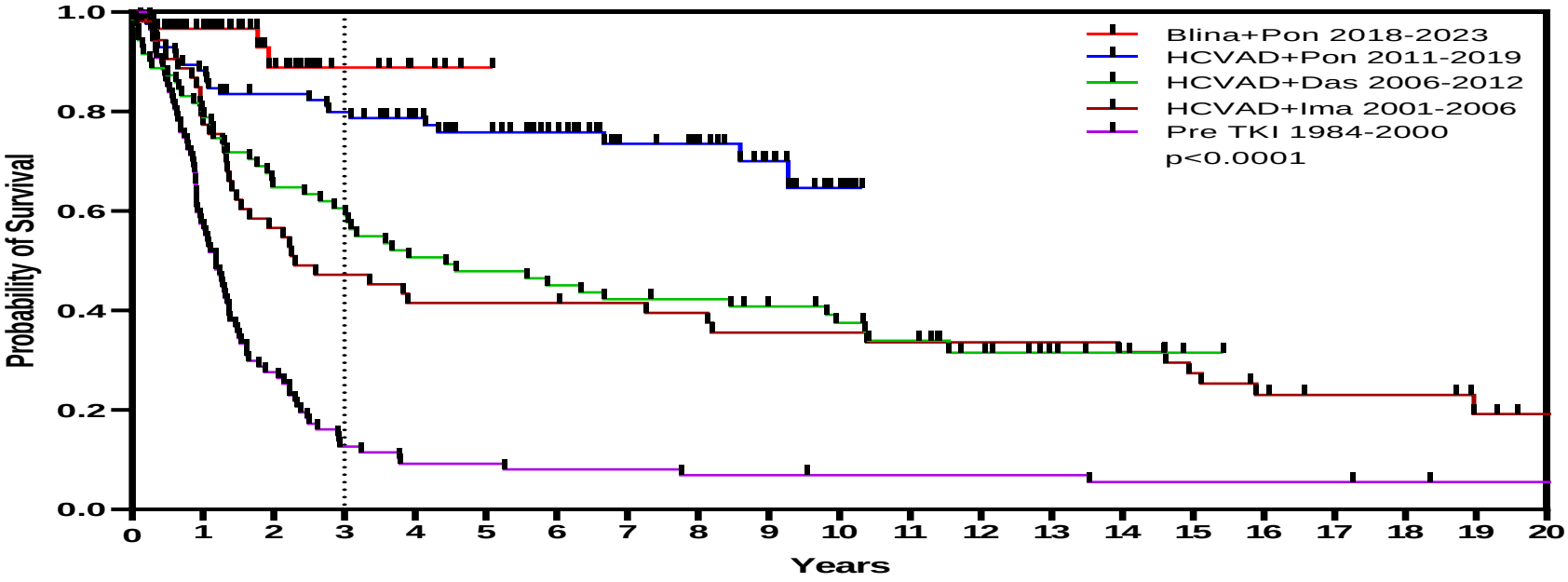
Haddad. Blood 142: abstr 2827;2023

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. Lancet Haematol. 2023;10(1):e24-e34. Foa. JCO online, December 23; 2023. Advani. Blood 142: Abst 1499; 2023

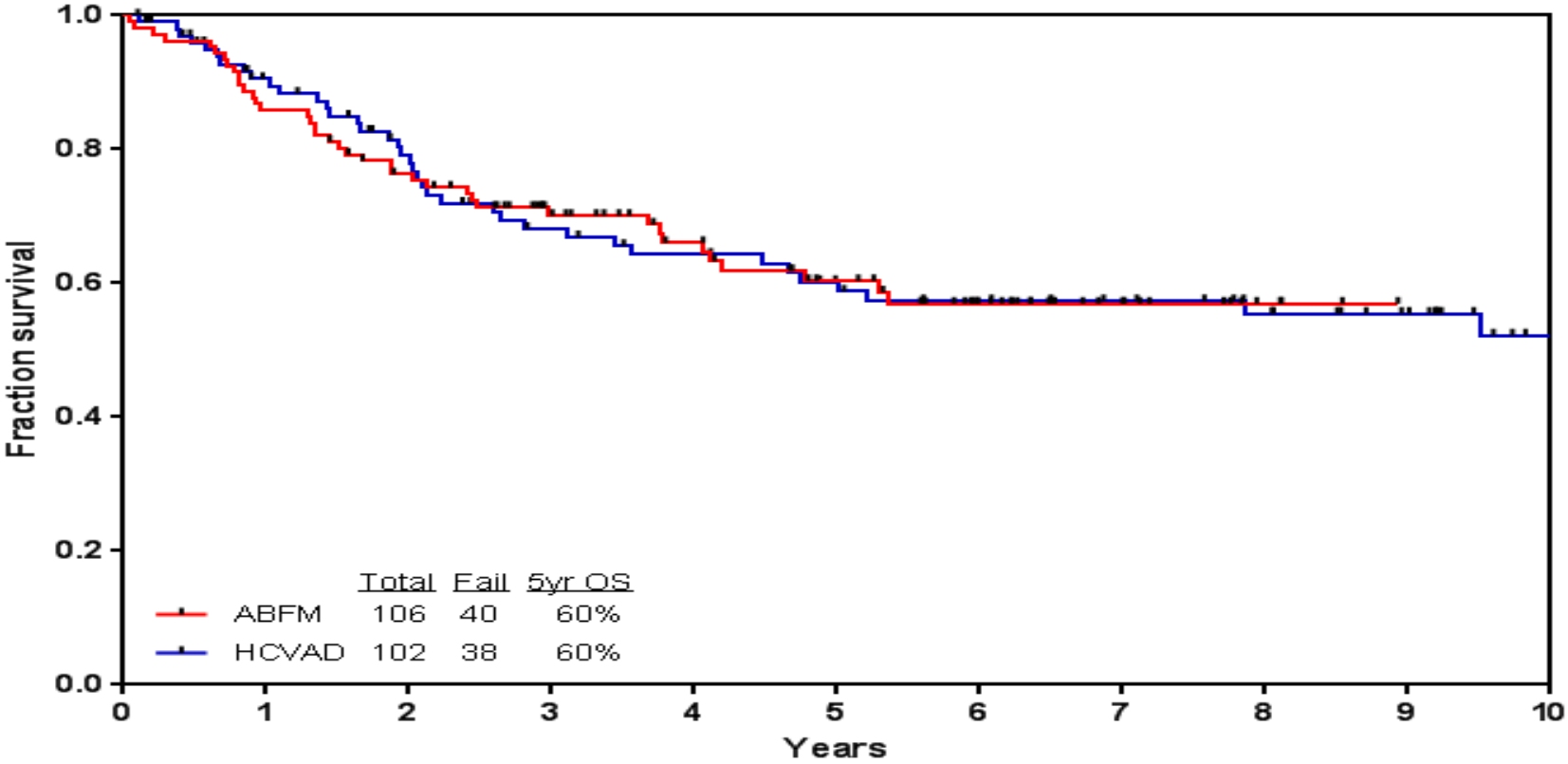
Ph+ ALL: Survival by Decade (MDACC 1984-2023)



	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

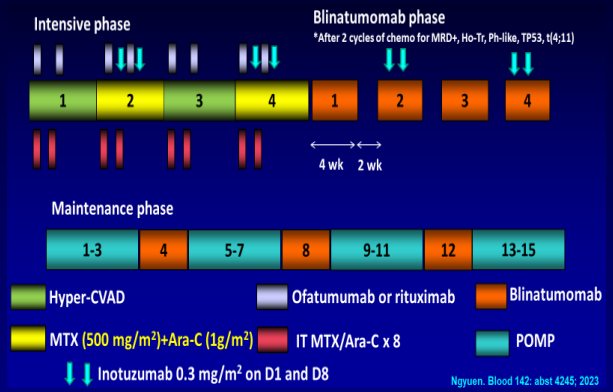
Hyper-CVAD vs ABFM: Overall Survival

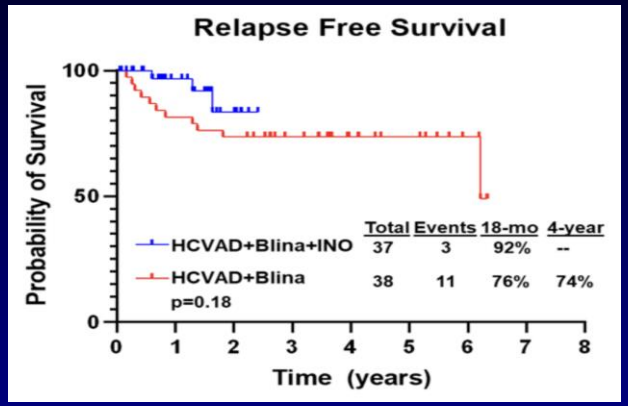


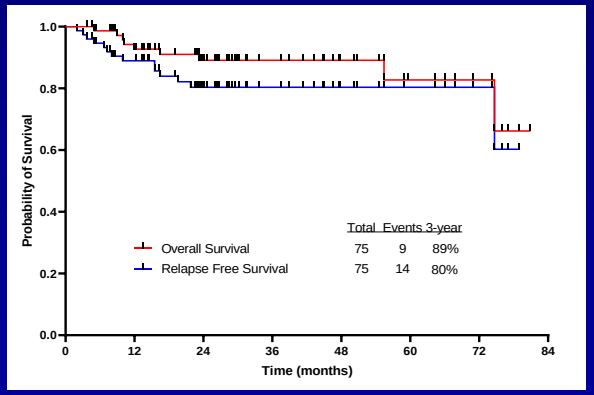
Rytting. *Cancer.* 2014;120:3660-3668; Rytting. *Am J Hematol.* 2016;91:819.

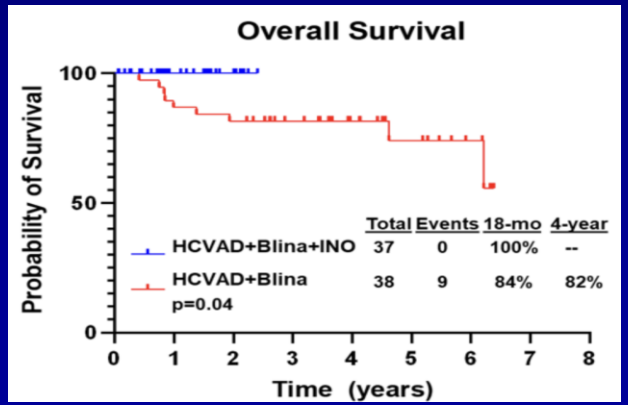
Hyper CVAD-Inotuzumab → Blina in Newly Dx Adult ALL

- 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;

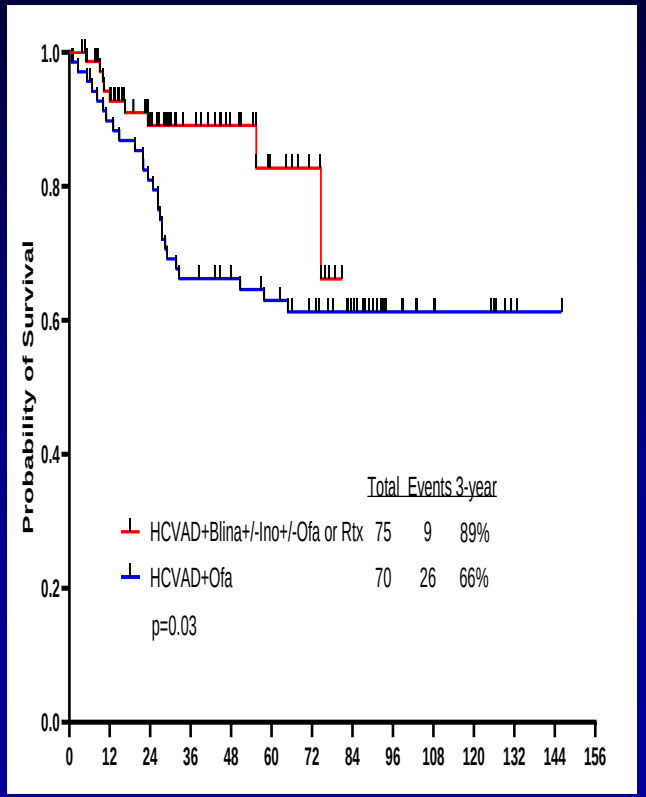






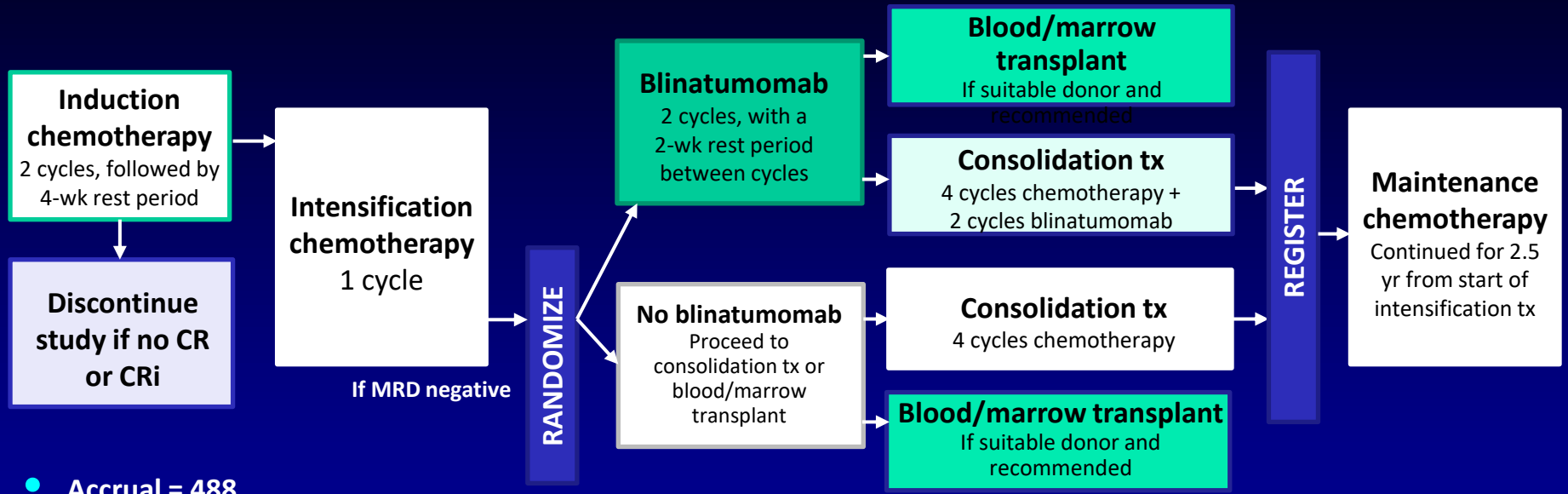


Overall Survival



Nguyen. Blood 142: abst 4245; 2023

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



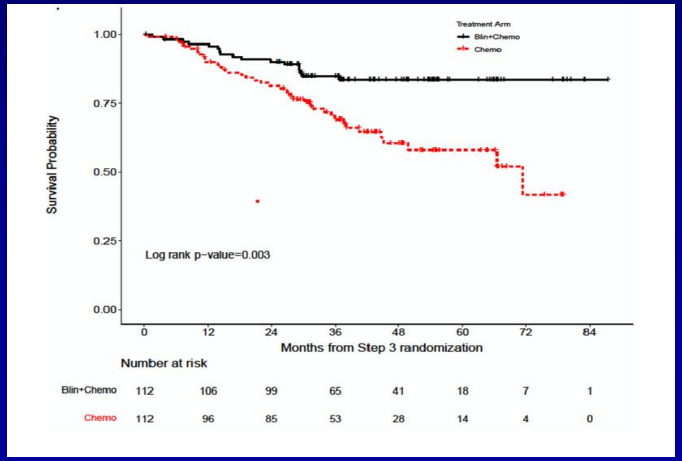
- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

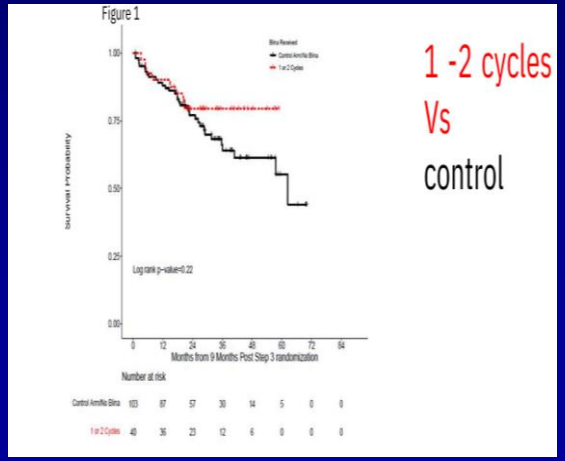
Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

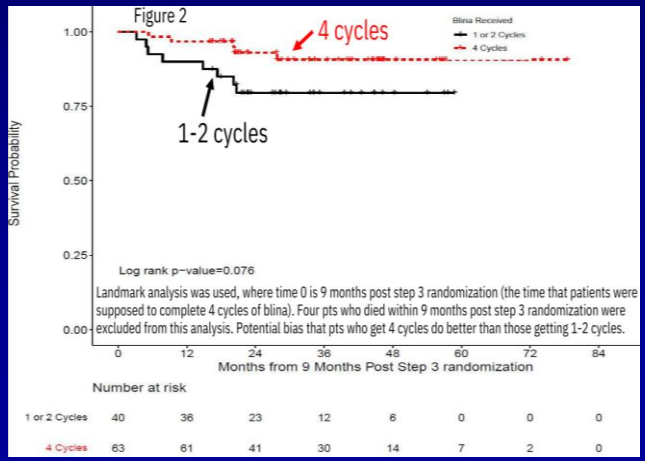
E1910 Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD–: Outcomes by Number of Cycles

- 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=0.003)**
- No difference in OS if 1-2 cycles of blina vs control (HR: 0.62; p=0.22)
- OS: 1-2 cycles vs 4 cycles (HR: 0.39; p=0.07)

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



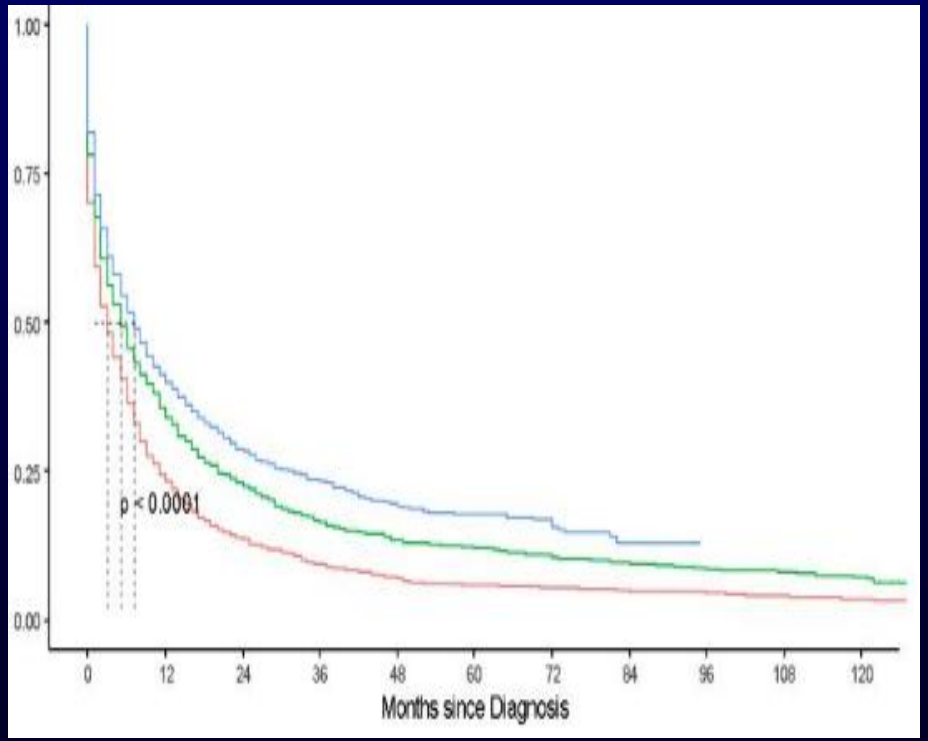


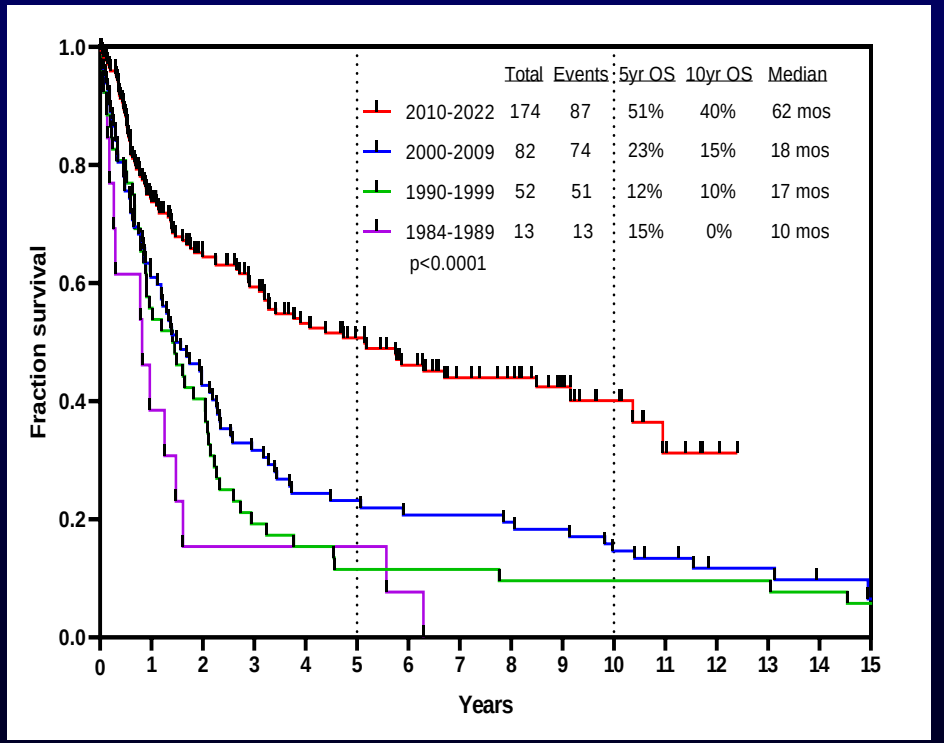


Luger. Blood 142: Abst 2877; 2023

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%

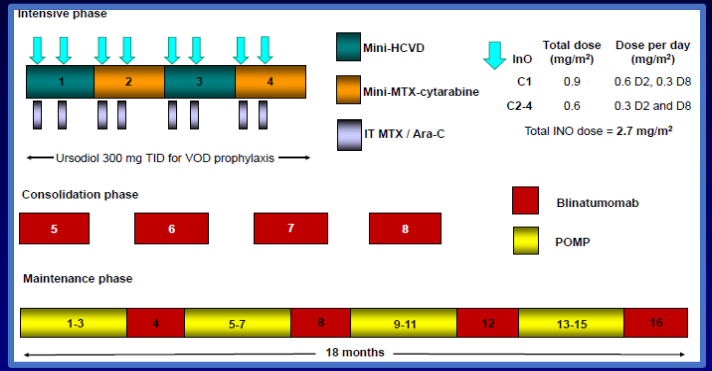




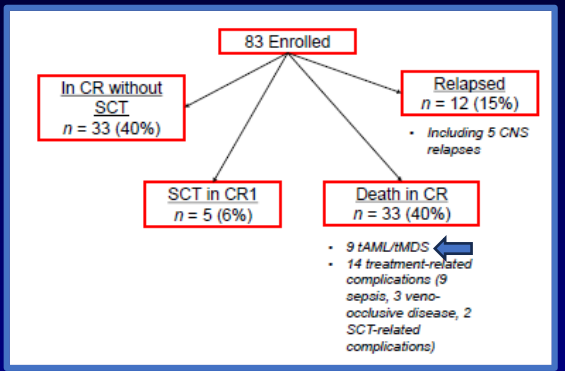
Gupta. Blood 140: abst 1379; 2022

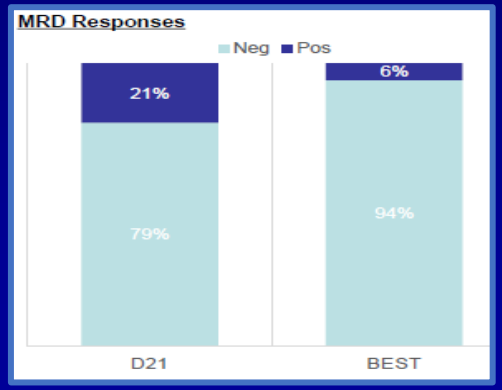
Mini-HCVD + INO ± Blina in Older ALL (N=83)

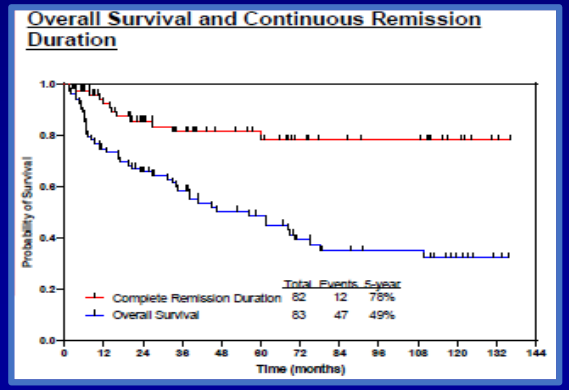
- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: *TP53* 39%; Ph-like 18%; poor cytogenetics 23%
- ORR 99% (CR 90%); MRD negativity 94% (79% at CR)



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)





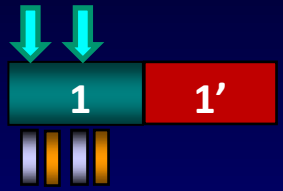


- Median F/U 88 months
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; 6%)
- Death due PD/NR: 12/83 (15%); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (11%); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: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

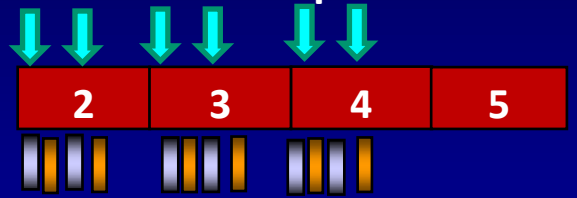
Jen. Blood 142: abst 2878; 2023

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

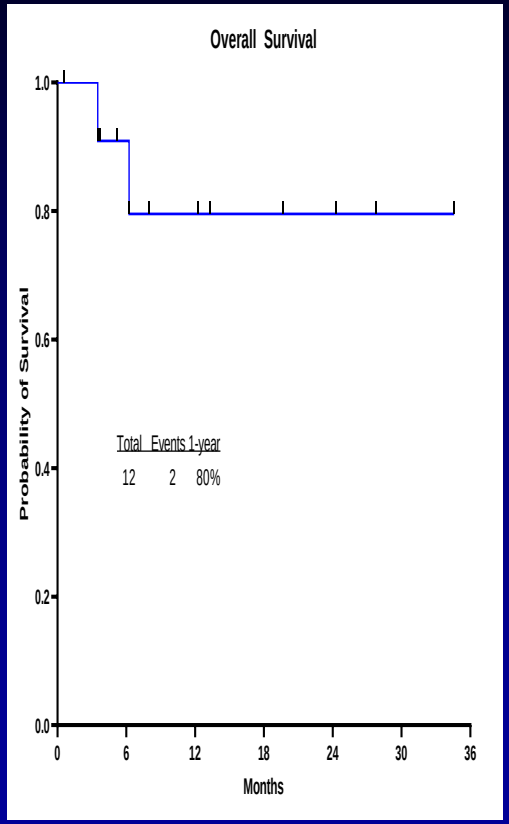
Rituximab if CD20+

1' Blinatumomab for 2 weeks

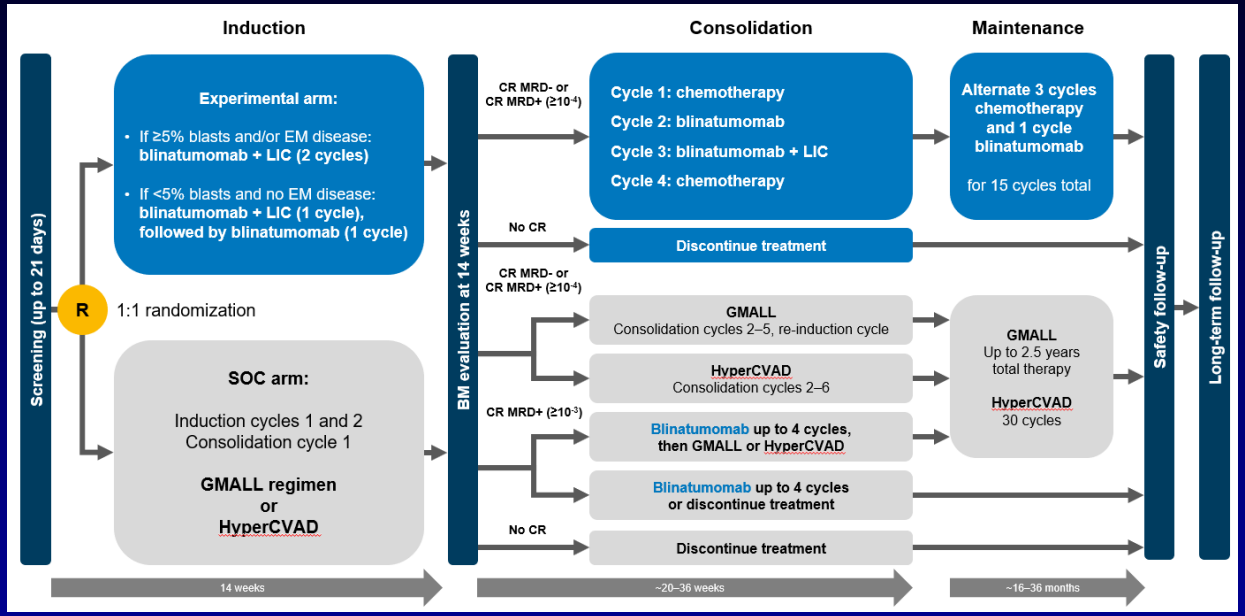
INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2-C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for VOD prophylaxis



Blina + Low-Intensity ChemoRx in Older Pre-B ALL: Golden Gate Safety Run-In Results of Phase 3



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.

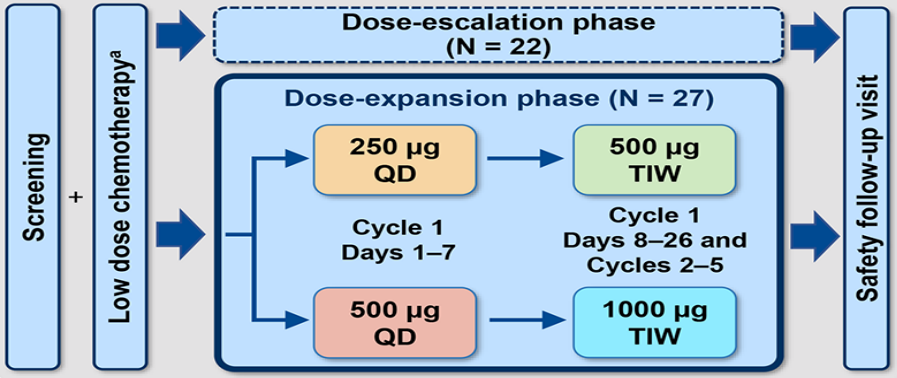
Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia

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

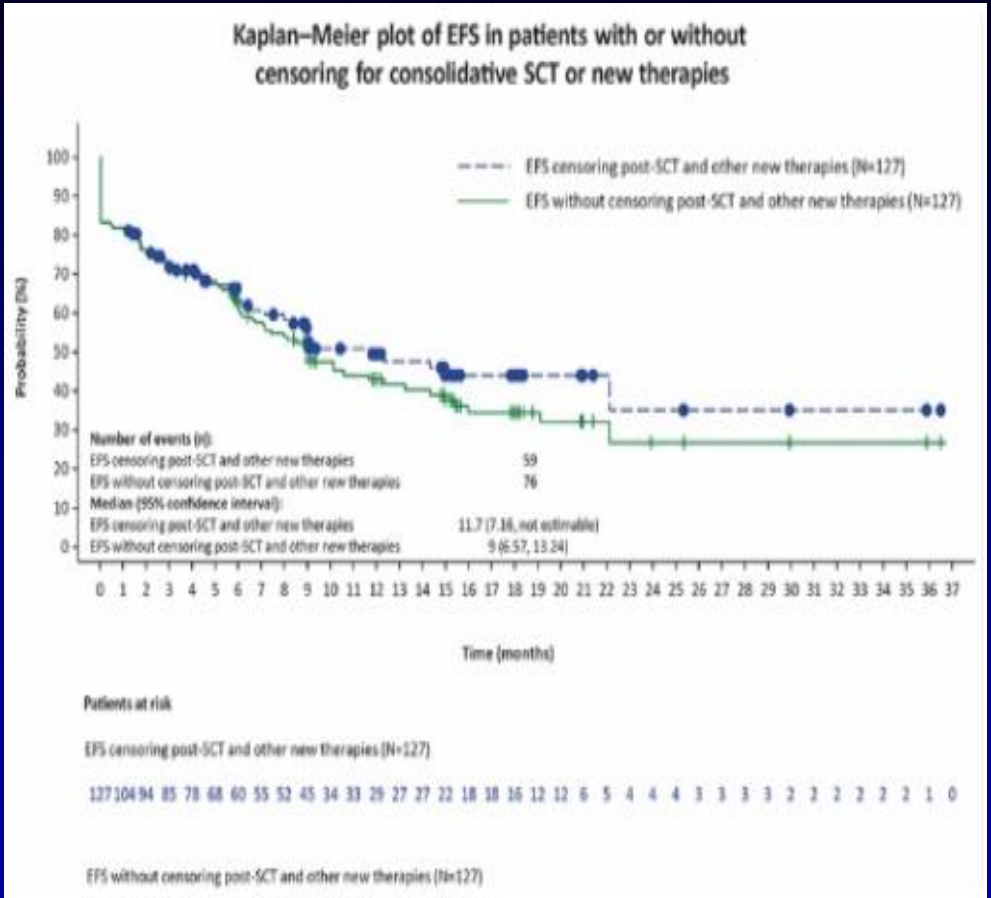
Conclusion

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, et al. AJH 2024, In press

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

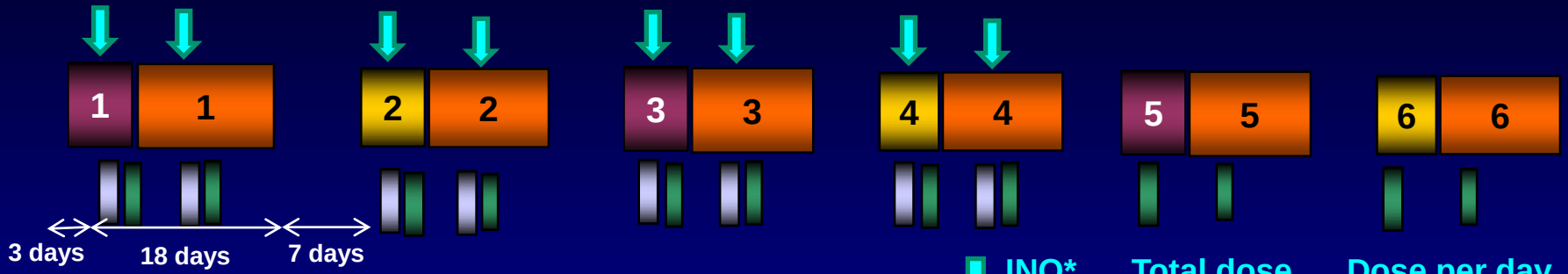
- AUTO 1 fast off-rate CD19 binder CAR T
- 153 enrolled, 127 (83%) infused. Median age 47 yrs
- Prior blina 42%, ino 31%, allo SCT 44%
- cCR-CRi 99/127 = 78% (99/153 = 65%). 19/77 allo SCT
- Loss of CAR T = HR 2.9
- 12-mos EFS 49%, 12-mos OS 61%



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

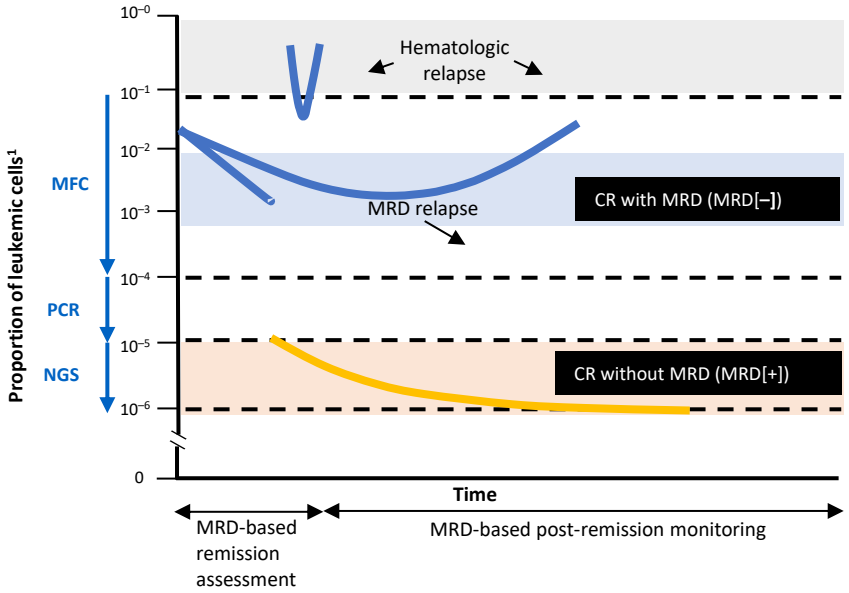
Global Leukemia Academy

Review of prognostic value of MRD in ALL and AML

Jae Park

APTITUDE HEALTH®

MRD Is a Strong Prognostic Indicator in B-ALL[1-4]



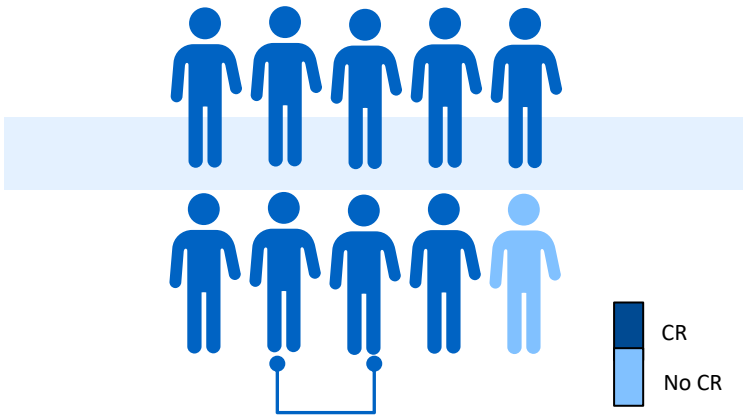
- MRD is defined as the presence of detectable leukemic cells (generally >10^{-4} or 0.01%) within the BM during remission[5,6]
- Studies collectively show the high prognostic value of MRD (both during and after initial induction therapy) in assessing relapse risk for patients with ALL[2]
- Patients who proceed to transplant with MRD-positive disease have a higher relapse rate than patients with MRD-negative disease[3,4]

ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BM, bone marrow; CR, complete remission; MFC, multiparameter flow cytometry; MRD, measurable/minimal residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction.

1. Short NJ, et al. *Am J Hematol*. 2019;94:257-265; 2. Berry DA, et al. *JAMA Oncol.* 2017;3:e170580; 3. Spinelli O, et al. *Haematologica*. 2007;92:612-618; 4. Patel B, et al. *Br J Haematol*. 2010;148:80-89; 5. Bassan R, et al. *Haematologica*. 2019;104:2028-2039; 6. Gökbuget N, et al. *Blood*. 2012;120:1868-1876.

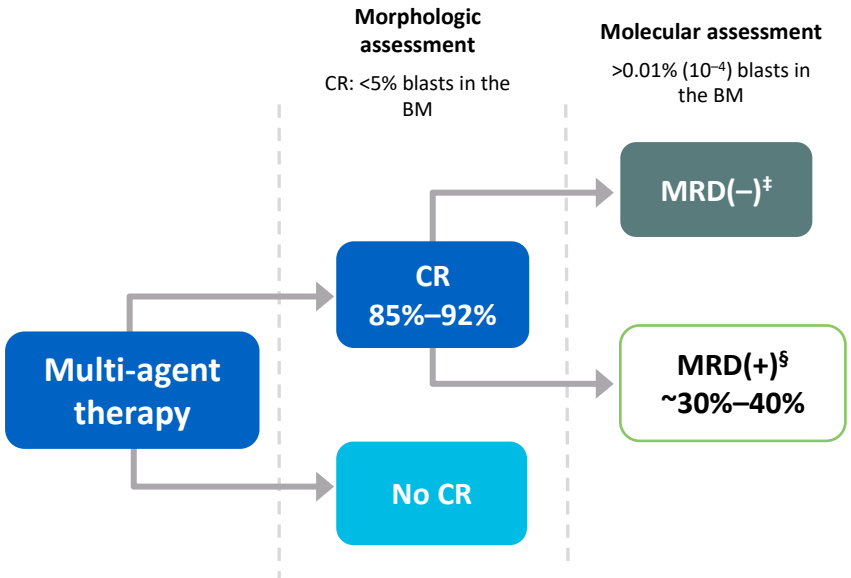
Patients Who Achieve CR May Still Harbor MRD[1-6]

85%–92% of adults* with newly diagnosed ALL will achieve CR (<5% blasts in the BM) with therapy[1,2]



But 40%–50% may experience relapse[3]

Patients Who Achieve CR May Have MRD[1-6,†]



*80%–90% of pediatric leukemia cases experience and remain in remission.[6] †Example diagram based on clinical studies.[2-5] ‡Complete MRD response refers to the absence of detectable leukemic cells confirmed in a highly sensitive assay (generally ~10^{-4} cells, or 0.01%).[2] §Range based on 3 clinical studies in which MRD was measured at different time points.[2,4,5]

ALL, acute lymphoblastic leukemia; BM, bone marrow; CR, complete remission; MRD, measurable/minimal residual disease.

1. Brüggemann M, et al. *Blood*. 2012;120:4470-4481; 2. Gökbuget N, et al. *Blood*. 2012;120:1868-1876; 3. Brüggemann M, Kotrova M. *Blood Adv.* 2017;1:2456-2466; 4. Beldjord K, et al. *Blood*. 2014;123:3739-3749; 5. Brüggemann M, et al. *Blood*. 2006;107:1116-1123; 6. Hoelzer D, et al. *Ann Oncol.* 2016;27(suppl 5):v69-v82.

MRD Is a Strong Predictor of Outcomes in ALL

- MRD is prognostic for both adults and children in all ALL subtypes, including[1]
  - B- and T-cell lineage
  - Ph-positive and -negative disease
- Post-treatment detection of MRD in B-ALL[2]
  - MRD status has been shown to predict relapse and has been associated with treatment response

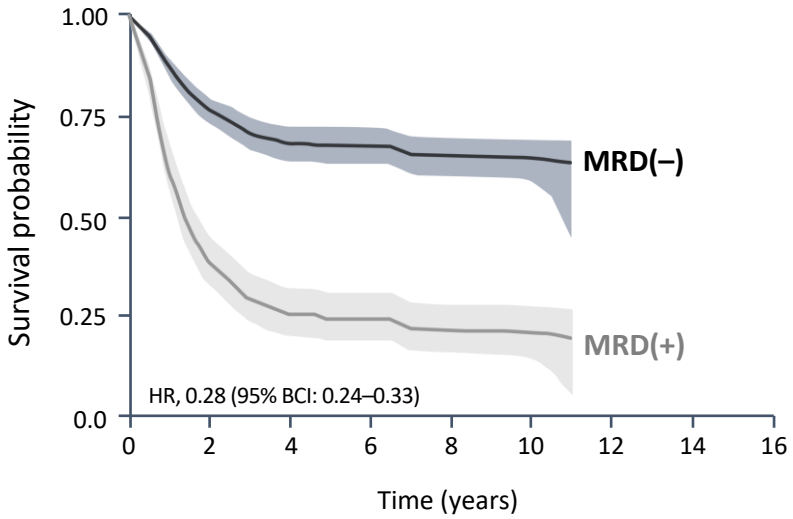
ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome.

1. Abou Dalle I, et al. *Ther Adv Hematol*. 2020;11:1-13; 2. Vora A, et al. *Lancet Oncol*. 2013;14:199-209.

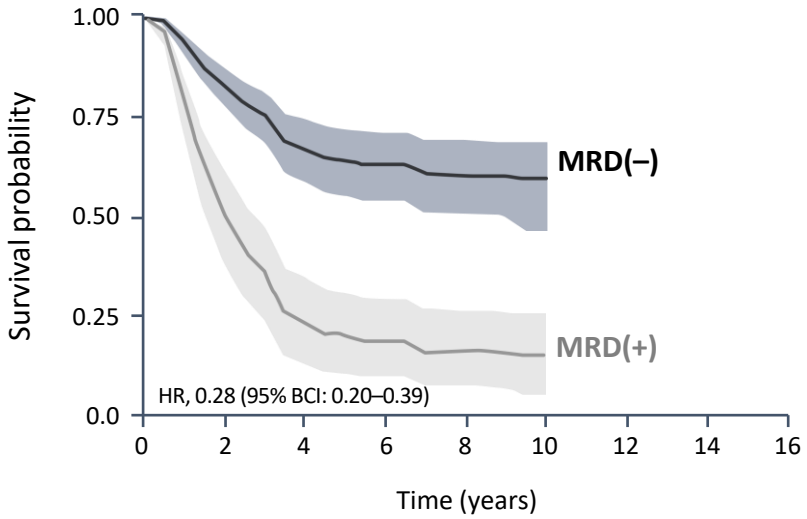
MRD Status Has Been Shown to be a Predictor of EFS and OS in Adult Patients With ALL

Meta-analysis: Estimated Survival Curves for Adult Patients With ALL

EFS for Adult ALL: 16 Studies With 2,065 Patients



OS for Adult ALL: 5 Studies With 806 Patients



These data include various treatments and are not intended to make any sort of survival claim, nor is the benefit specific to any treatment.

This information is presented for the purpose of demonstrating the utility of MRD testing as a prognostic indicator in B-ALL. Treatment decisions are the sole discretion of the healthcare provider.

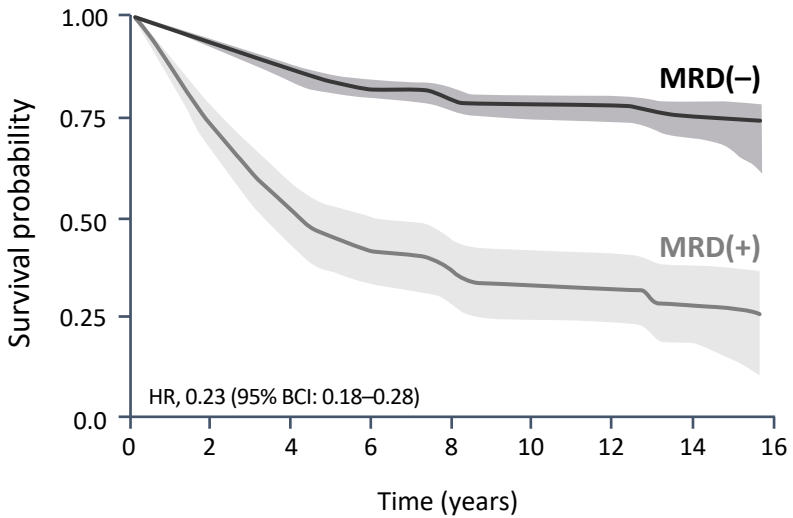
ALL, acute lymphoblastic leukemia; BCI, Bayesian credible intervals; EFS, event-free survival; HR, hazard ratio; MRD, measurable/minimal residual disease; OS, overall survival.

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

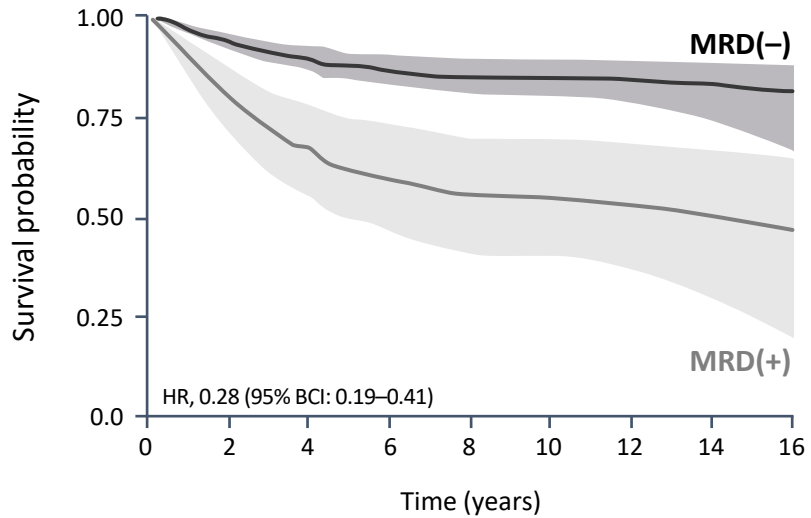
MRD Status Has Been Shown to be a Predictor of EFS and OS in Pediatric Patients With ALL

Meta-analysis: Estimated Survival Curves for Pediatric Patients With ALL

EFS for Pediatric ALL: 20 Studies With 11,249 Patients



OS for Pediatric ALL: 5 Studies With 2,876 Patients



These data include various treatments and are not intended to make any sort of survival claim, nor is the benefit specific to any treatment.

This information is presented for the purpose of demonstrating the utility of MRD testing as a prognostic indicator in B-ALL. Treatment decisions are the sole discretion of the healthcare provider.

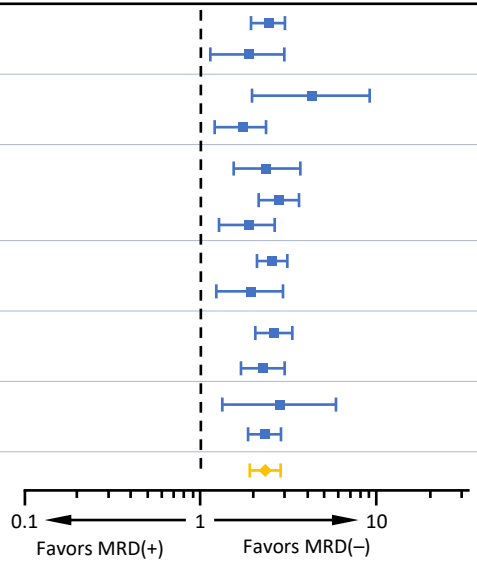
ALL, acute lymphoblastic leukemia; BCI, Bayesian credible intervals; EFS, event-free survival; HR, hazard ratio; MRD, measurable/minimal residual disease; OS, overall survival.

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

MRD Negativity Was Favored Across a Variety of Parameters

Subset Analysis of RFS for Adults With ALL (With 95% CIs)

Parameter	Subgroup	Studies, n	HR (95% CI)
Disease stage	CR1	21	2.39 (1.93–2.98)
	CR2 or later	2	1.84 (1.14–2.95)
Timing of MRD	After HSCT	2	4.18 (1.93–9.03)
	Before HSCT	6	1.69 (1.23–2.31)
MRD level	10^{-3}	2	2.36 (1.50–3.70)
	10^{-4}	12	2.74 (2.12–3.56)
	10^{-5}	4	1.82 (1.28–2.59)
MRD testing location	Central	10	2.55 (2.06–3.14)
	Local	7	1.92 (1.27–2.92)
Timing of MRD	≤3 months	14	2.60 (2.05–3.31)
	>3 months	5	2.23 (1.67–2.97)
MRD methodology	Flow	4	2.84 (1.35–5.94)
	PCR	17	2.30 (1.84–2.87)
Overall		**23**	**2.34 (1.91–2.86)**



ALL, acute lymphoblastic leukemia; CI, confidence interval; CR, complete remission; HR, hazard ratio; HSCT, hematopoietic stem cell transplant; MRD, measurable/minimal residual disease; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; RFS, relapse-free survival.

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

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Recommend MRD Testing for ALL

NCCN Guidelines® recommend MRD assessment upon completion of initial induction, at the end of consolidation, and at additional timepoints guided by the regimen used[1]

- Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden[1]
- When possible, therapy aimed at reducing MRD before alloHSCT should be considered[1]

NCCN Guidelines® state that the optimal sample for MRD testing is the first pull of the bone marrow aspirate[1]

- Experts recommend ≤3 mL of the bone marrow aspirate to avoid hemodilution of the specimen[2]
- It is suggested that a test that has been validated to quantify ALL to a sensitivity of at least 10^{-4} is used[2]

NCCN makes no warranties of any kind whatsoever regarding its content, use of application and disclaims any responsibility for their application or use in any way.
ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; MRD, measurable/minimal residual disease; NCCN, National Comprehensive Cancer Network.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia V.1.2022. © National Comprehensive Cancer Network, Inc 2022. All rights reserved. Accessed July 27, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. 2. Nucleus ASTCT. Best Practices in MRD Quantification: The Importance of the First Bone Marrow Pull. https://nucleus.astct.org/Full-Article/best-practices-in-mrd-quantification-the-importance-of-the-first-bone-marrow-pull. Accessed September 7, 2022.

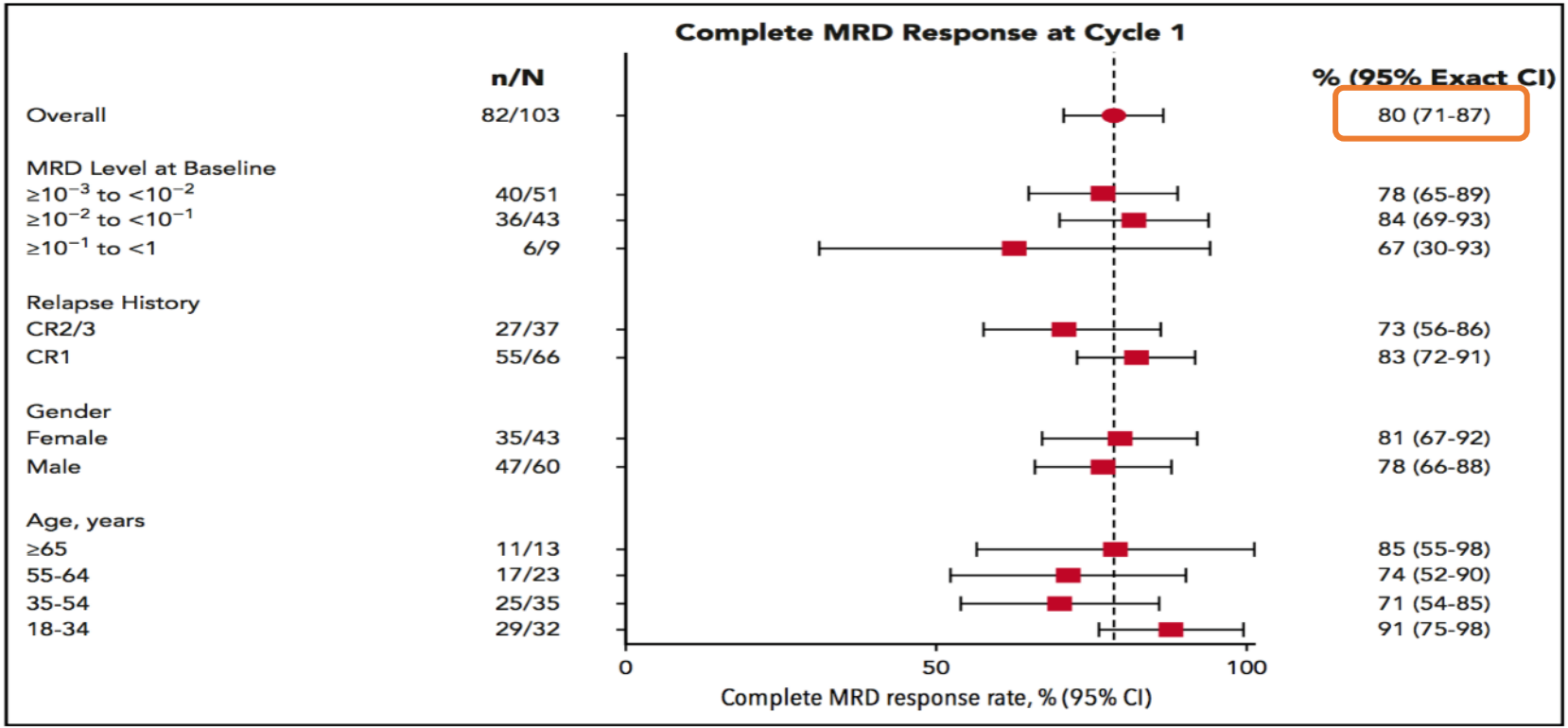
Blinatumomab in MRD+ B-ALL

- **Eligibility criteria**
  - First *or later* CR *AND*
  - Persistent or recurrent **MRD ≥10^{-3}** after minimum 3 blocks of intense chemo
- **Primary endpoint**
  - MRD-CR after 1 cycle
- **Secondary endpoint**
  - RFS at 18 months

Characteristic	Patients (n = 116)
Relapse history, n (%)	
In first CR	75 (65)
In second CR	39 (34)
In third CR	2 (2)
Baseline MRD levels	
≥10^{-1} to <1	9 (8)
≥10^{-2} to <10^{-1}	45 (39)
≥10^{-3} to <10^{-2}	52 (45)
<10^{-3}	3 (3)

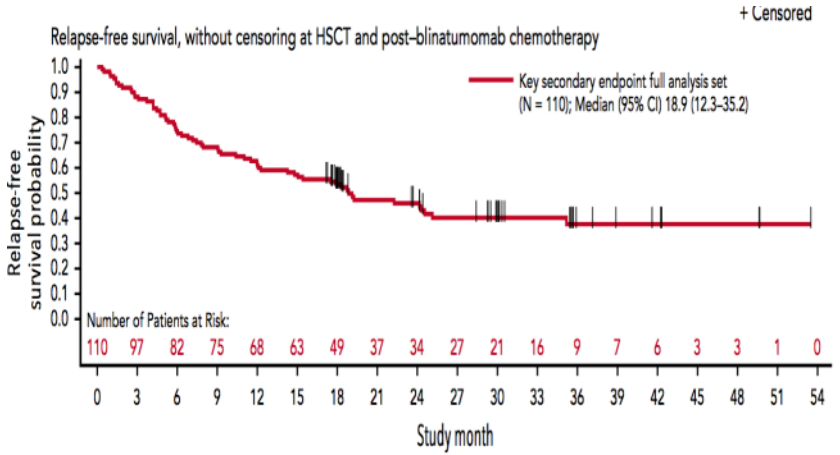
Gökbuget N, et al. *Blood.* 2018;131:1522-1531.

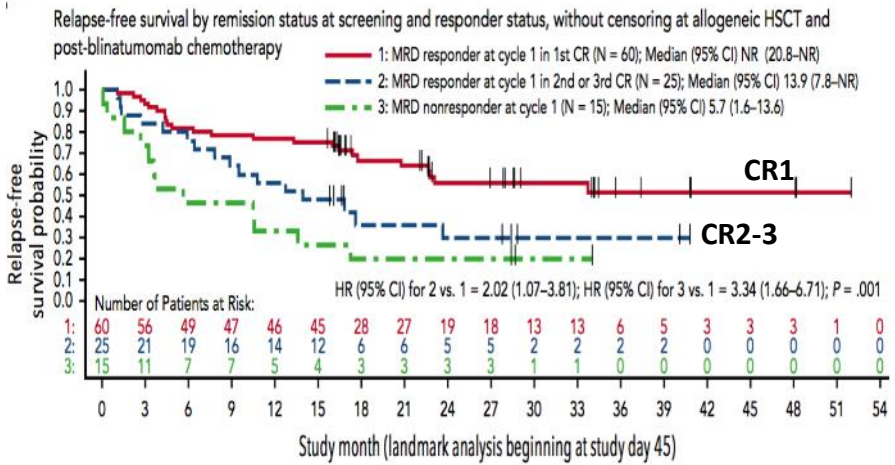
CR Rates by Subgroups in MRD+ B-ALL



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

RFS of MRD+ ALL Patients After Blinatumomab





70% of patients proceed to allo-HSCT

Response	First CR (N = 60)	Second CR (N = 26)
cMRD*	85.2%	72%
hRFS†	35.2 months	12.3 months

*Complete MRD response is defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 0.01%; †Time from start of blinatumomab to hematologic or extramedullary relapse, secondary leukemia, or death due to any cause; includes time after transplantation; Kaplan-Meier estimate.

Gökbuget N, et al. *Blood.* 2018;131:1522-1531; Jen EY, et al. *Clin Cancer Res.* 2019;25:473-477.

FDA Approval of Blinatumomab for MRD+ B-ALL in US

- Blinatumomab approved for the treatment of B-ALL in first or second complete remission with MRD ≥0.1%
- Prior to the approval, MRD results did not change disease management
- With the approval, the incorporation of MRD is standard of care for all subtypes of ALL
- In January 2020, the FDA released guidance for industry on the use of MRD in the development of investigational agents for hematologic malignancies
  - FDA accepts MRD levels of <0.01% as evidence of efficacy
  - ALL is the only disease in which MRD has been used as a surrogate endpoint supporting drug approval

US Food and Drug Administration. Resources – Drugs. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment – Guidance for Industry. Jan 2020. Accessed Sep 8, 2023. https://www.fda.gov/media/134605/download

Current Challenges With MRD

- When to measure?
  - Currently, MRD is focused (generally) on a single time point: EOI
  - ALL therapy extends well beyond a day-29 endpoint
  - Very little data on serial monitoring
- MRD assays differ
  - Multiparameter flow (FCM)
  - Next-generation sequencing (NGS)
  - Quantitative PCR (qPCR)
- Limited data on concordance of the different assays and risk stratification

MRD Detection Methods Vary in Their Target, Sensitivity, Benefits, and Limitations[1-6]

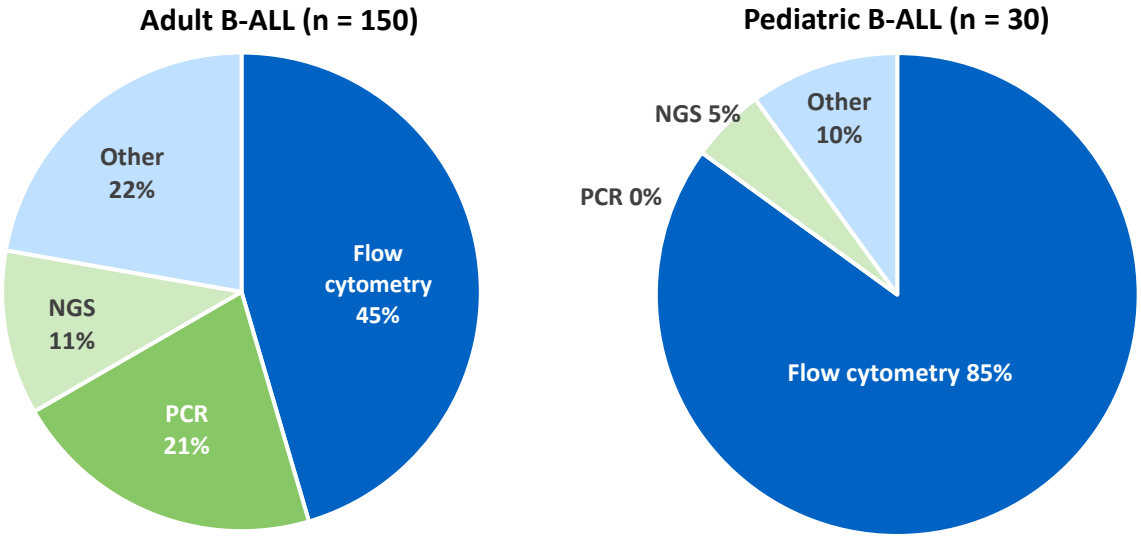
Method	Target	Sensitivity	Some Potential Benefits	Some Potential Limitations
Flow cytometry[1-5]	Leukemia-associated immunophenotypes	3–4 color: 10^{-3} to 10^{-4} 6–9 color: 10^{-4} to 10^{-5}	• Rapid • Target Ag information	• Limited sensitivity/standardization • Difficult to interpret
PCR[1-5]	RT-qPCR: Abnormal gene fusions (eg, *BCR-ABL)*	10^{-4} to 10^{-5}	• High sensitivity • Specific	• Only possible in leukemias that harbor fusion transcripts • Risk of cross-contamination
	ASO-PCR: Ig and TCR gene rearrangements		• High sensitivity • Standardized	• Time-consuming • Patient-specific primers needed
NGS[5,6]	Ig and TCR gene rearrangements	10^{-6}	• High sensitivity • No patient-specific primers required • Available via reference lab • Some are FDA-cleared[7]	• Turnaround time (~7 days) • Need initial diagnostic sample

ASO-PCR, allele-specific oligonucleotide PCR; FDA, Food and Drug Administration; Ig, immunoglobulin; MRD, measurable/minimal residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-qPCR, real-time quantitative PCR; TCR, T-cell receptor.

1. Campana D. *Am Soc Hematol Educ Progr*. 2010;2010:7-12; 2. Brüggemann M, et al. *Blood*. 2012;120:4470-4481; 3. Schrappe M. *Am Soc Hematol Educ Progr.* 2012;2012:137-142; 4. van Dongen JJ, et al. *Blood*. 2015;125:3996-4009; 5. Chen X, Wood B. *Best Pract Res Clin Haematol*. 2017;30:237-248; 6. Thol F, et al. *Genes Chromosomes Cancer.* 2012;51:689-695; 7. FDA Decision Summary for ClonoSEQ®. https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170080.pdf. Accessed September 7, 2022.

Flow Cytometry Is the Most Commonly Used Method of MRD Detection in the USA

Most Frequently Used Method of MRD Detection Reported by US Physicians[1,*]



While flow cytometry is frequently used in the USA, RT-qPCR is the most widely used technique in European MRD clinical studies[2]

*Based on a survey. To be included in this analysis, physicians were required to be treating ≥ 5 patients with B-ALL and to conduct MRD testing.
The 'Other' category included cytogenetics, FISH, immunological testing, and 'Not sure'.[1]
B-ALL, B-cell acute lymphoblastic leukemia; FISH, fluorescence in situ hybridization; MRD, measurable/minimal residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-qPCR, real-time quantitative PCR.

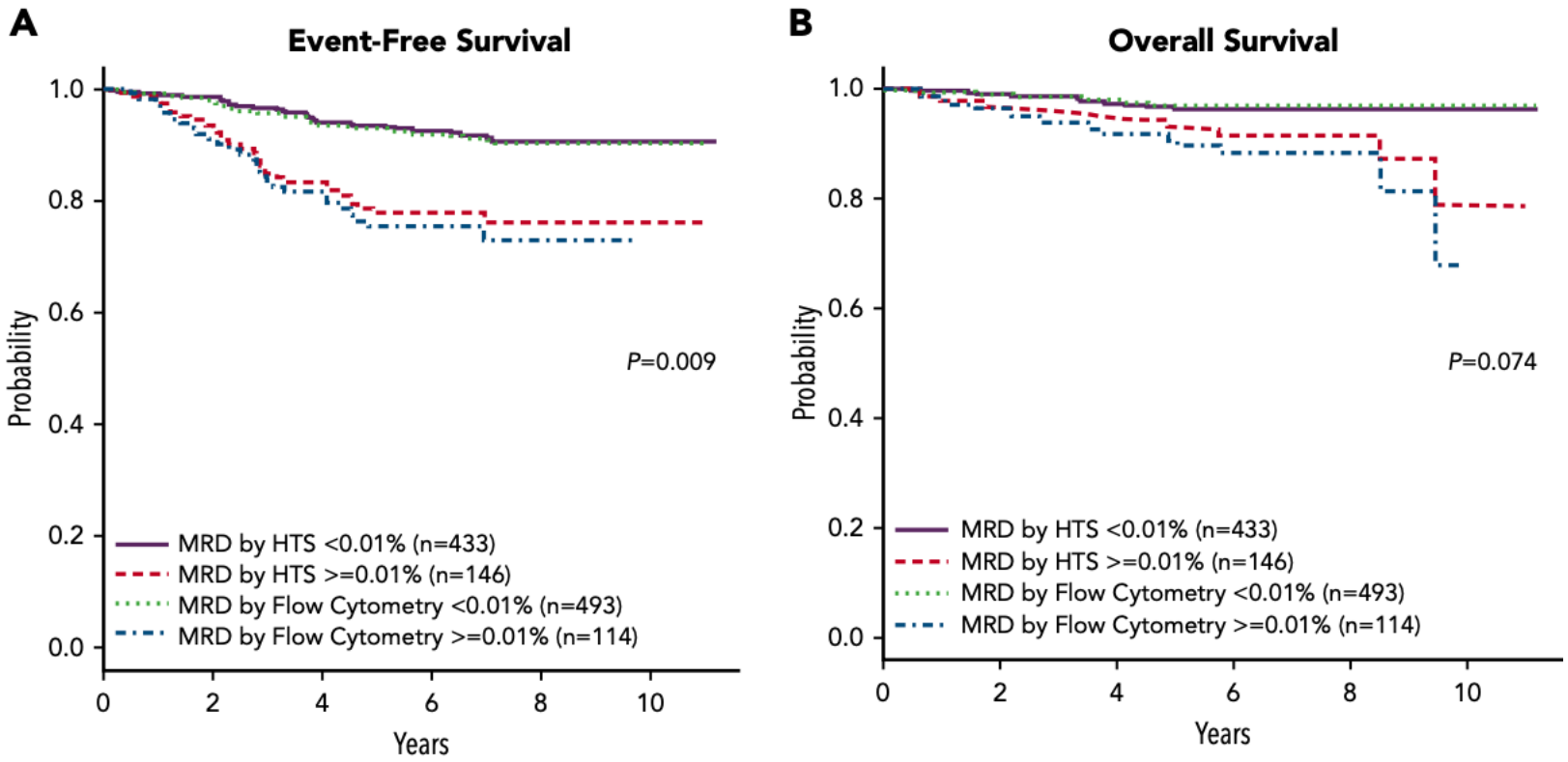
1. Kim C, et al. *Hematology*. 2019;24:70-78 and supplemental data; 2. Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

Children's Oncology Group
Comparison of MRD by FCM and NGS

- Paired pretreatment and EOI (day 29) samples from 619 patients enrolled on AALL0331 (standard-risk protocol) and AALL0232 (high-risk protocol) were used for the analysis
  - 315 samples were high risk
  - 304 samples were standard risk
- FCM MRD done at University of Washington or Johns Hopkins
- Tissue-banked specimens were sent to Adaptive Biotechnologies for DNA extraction and immunosequencing
  - *IGH* and *TRC* CDR3 regions were amplified and sequenced
  - ImmunoSEQ platform was used
- EFS and OS were evaluated and compared with MRD assays

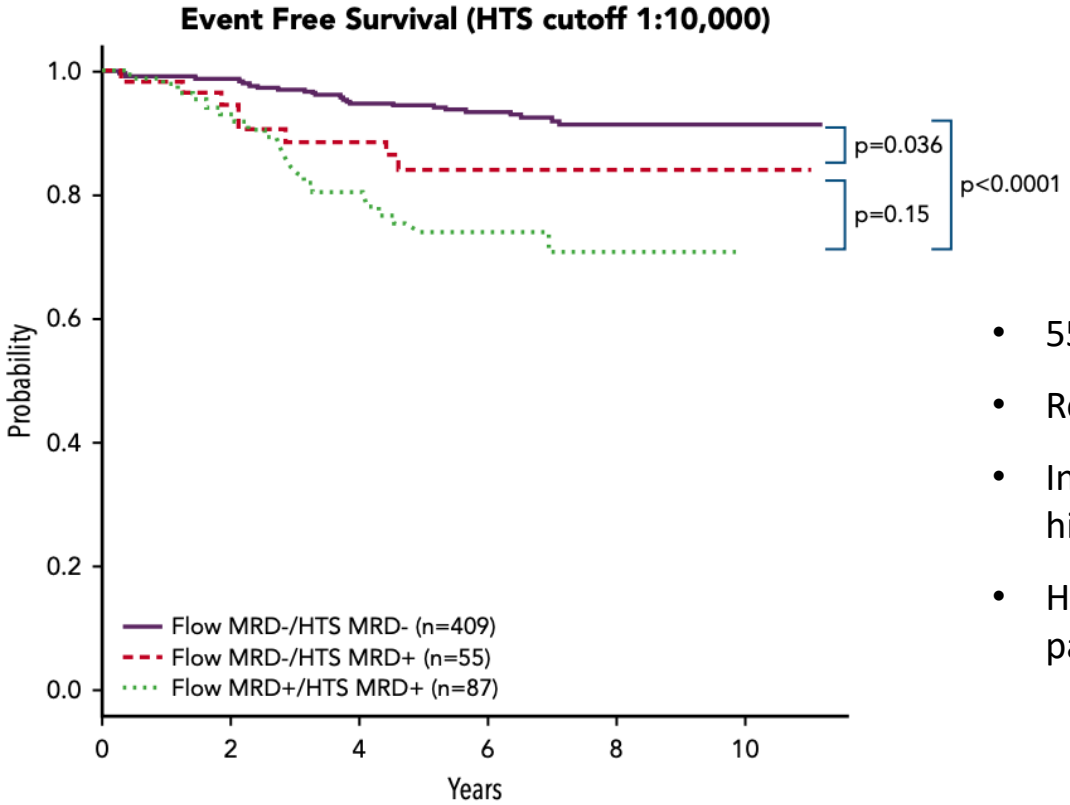
Wood B, et al. *Blood*. 2018;131:1350-1359.

Strong Correlation Between MRD by HTS or FCM (0.01%)



Wood B, et al. *Blood*. 2018;131:1350-1359.

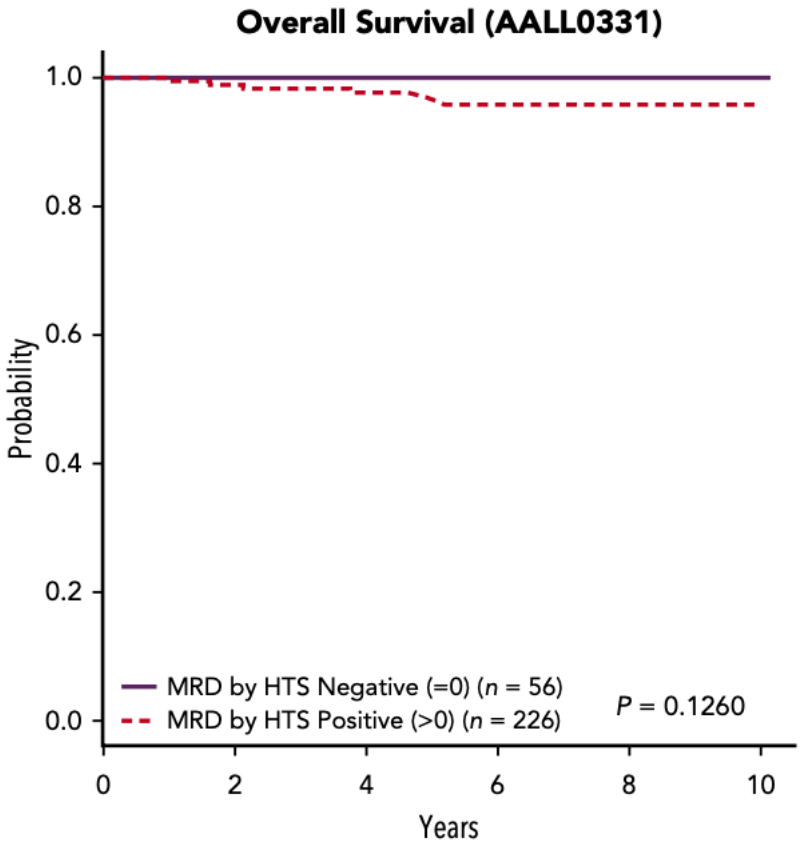
Discordant MRD by HTS or FCM Has Intermediate Prognosis



- 55 patients with **FCM MRD–/HTS MRD+**
- Represented ~**38% of patients in SR group**
- Inferior 5-year EFS, so may be considered as higher-risk and ? intensification of therapy
- HTS in this study can identify higher-risk patients

Wood B, et al. *Blood*. 2018;131:1350-1359.

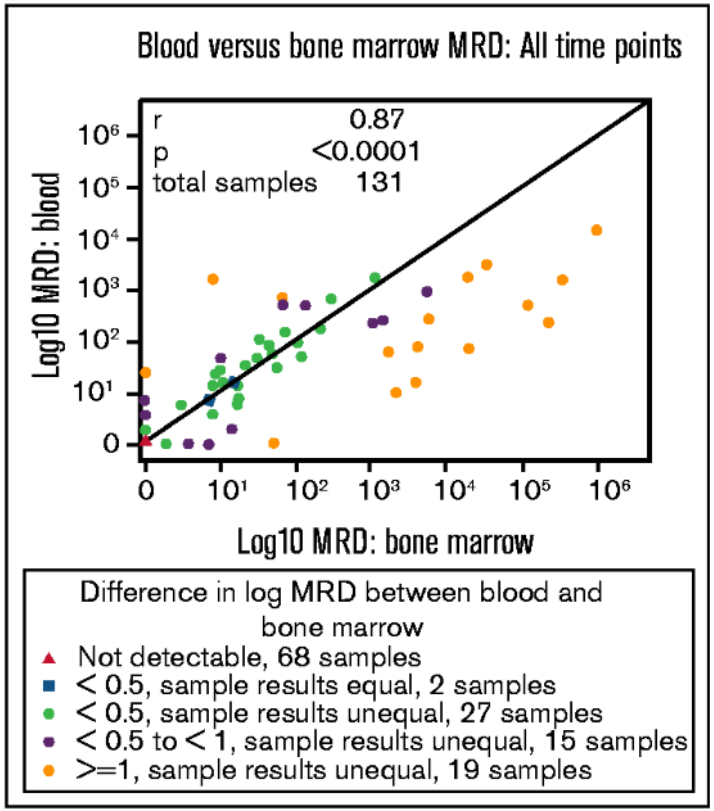
HTS Can Identify Patients With Excellent Outcomes



- 56 patients **HTS MRD– at EOI** down to a cutoff of 0.0001%
- Represented ~20% of patients in SR group
- 8-year OS of 100%
- These patients require no further therapy intensification or novel therapy to attain cure
- Will not contribute to further randomized questions
- May be candidates for treatment reductions instead
- Importantly, the HTS MRD– patients in the HR population did NOT show the uniformly 100% OS

Wood B, et al. *Blood*. 2018;131:1350-1359.

Concordance of BM and PB MRD Assessment



Prospective observational study evaluating MRD in patients receiving HSCT or CAR T-cell therapy (n = 69)

- Strong correlation between PB and BM MRD: sensitivity 87% and specificity 90% in PB vs BM
- Median time from MRD to clinical relapse
  - Post-HSCT 90 days
  - Post-CAR 60 days
- PB MRD NGS monitoring appears to be adequate alternative to BM

Muffly L, et al. *Blood Adv.* 2021;5:3147-3151.

MRD Monitoring in AML

Although MRD is emerging as a potential predictive factor of treatment effectiveness and likelihood of disease recurrence, consensus on the utility of evaluating MRD in clinical practice has yet to be achieved. The ELN guidelines currently recommend MRD assessment before consolidation treatment and throughout disease monitoring as part of the standard of care for AML patients. NCCN guidelines recommend MRD after induction chemotherapy to help inform choice of consolidation treatment.

ELN Recommendations for MRD Assessment

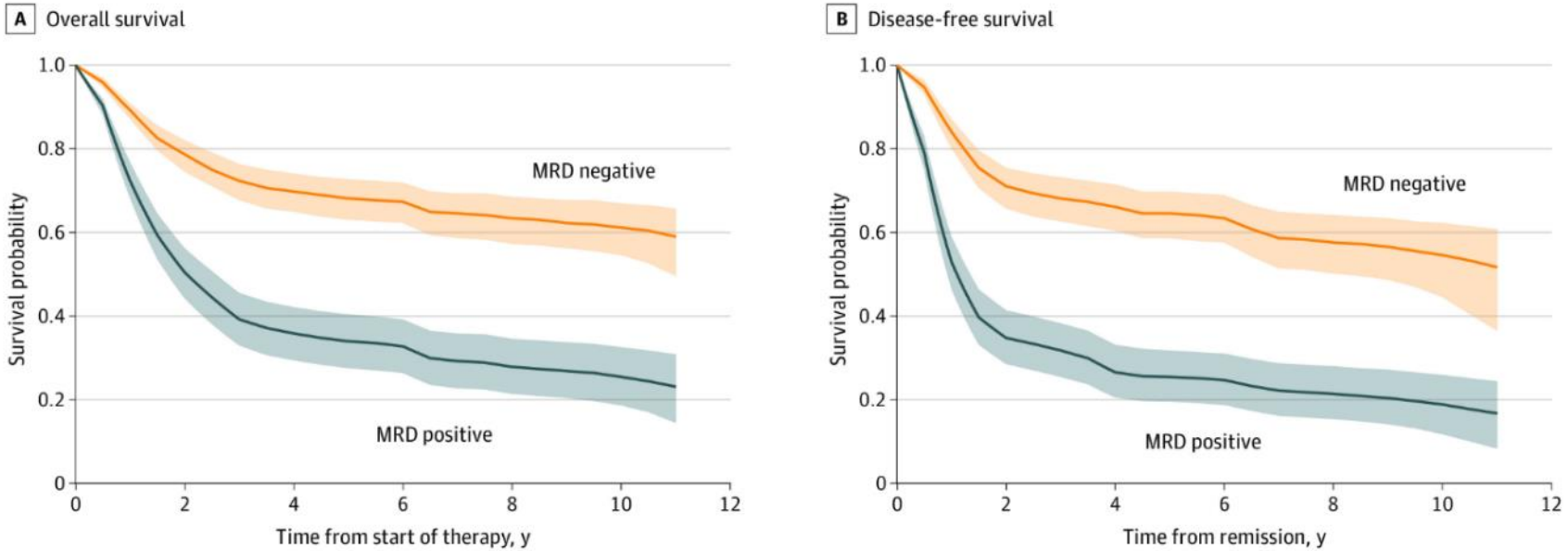
Flow Cytometry	Molecular Biology
Aspirate 5−10 mL BM and use the first pull for MRD assessment	Aspirate 5−10 mL BM and use the first pull for MRD assessment
Use 500,000 to 1,000,000 white blood cells	Patients with mutant *NPM1*, *RUNX1-RUNX1T1*, *CBFB-MYH11*, or *PML-RARA* should have molecular assessment of residual disease at informative clinical time points
Use the following markers in a MRD panel: CD7, CD11b, CD13, CD15, CD19, CD33, CD34, CD45, CD56, CD117, HLA-DR	*WT1* expression should not be used as an MRD marker unless no other MRD marker is available
Single-center studies with no extensive experience on multiparameter flow cytometry MRD are strongly discouraged	Do not use mutations in *FLT3*, *NRAS*, *KRAS*, *DNMT3A*, *ASXL1*, *IDH1/2*, or *MLL-PTD* and expression levels of *EVI1* as single MRD markers

Döhner H, et al. *Blood.* 2017;129(4):424-447; NCCN clinical practice guidelines in oncology: acute myeloid leukemia (Version 2.2021). National Comprehensive Cancer Network® website. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Updated November 12, 2020. Accessed November 19, 2020.

MRD in AML

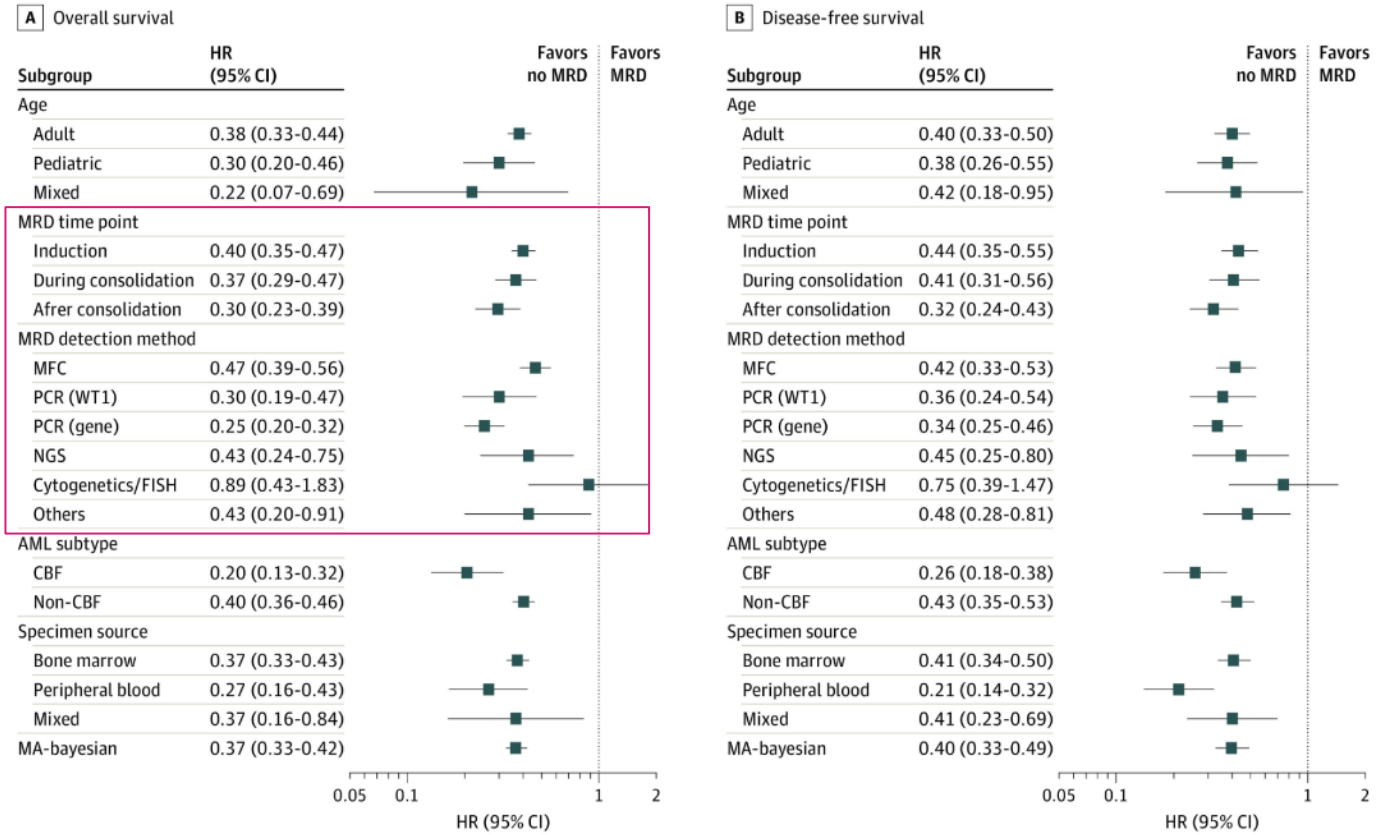
- In the context of MRD assessment, targeted NGS is commonly used for serial assessment of mutations found at diagnosis
- Caution, as several AML-associated mutations (eg, *DNMT3A, TET2, ASXL1*) are associated with CHIP (DTA)
- A meta-analysis of 81 trials with over 11,000 patients found strong associations between MRD negativity and superior disease-free survival

Prognostic Impact of MRD in AML (Meta-analysis)



Short N, et al. *JAMA Oncol.* 2020; 6(12): 1890-1899.

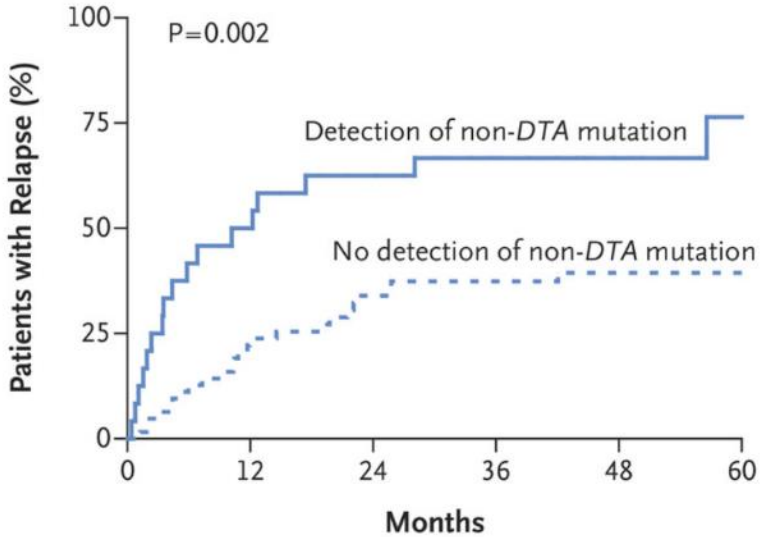
Prognostic Impact of MRD in AML (Meta-analysis)



Short N, et al. *JAMA Oncol.* 2020; 6(12): 1890-1899.

MRD Presence After Induction Is Prognostic in AML

A Relapse among Patients with Persistent *DTA* Mutations

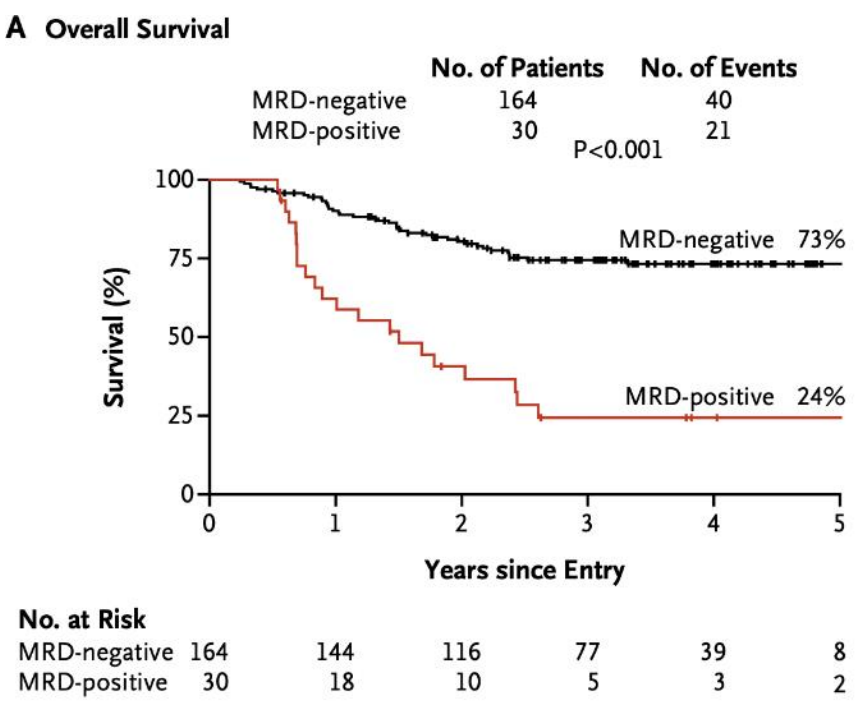


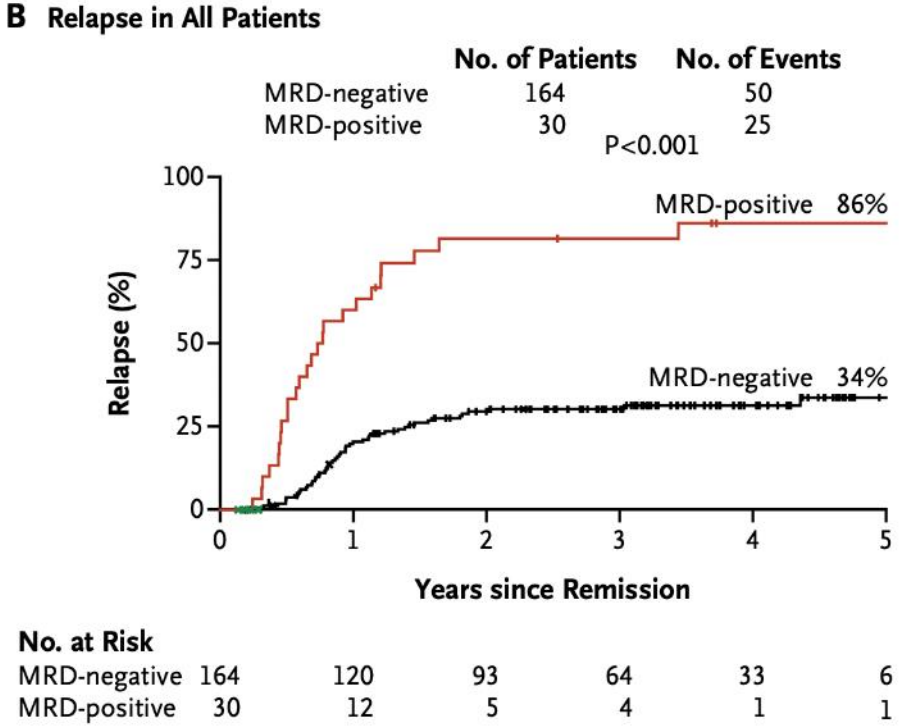
No. at Risk						
Detection	24	11	8	5	4	2
No detection	63	45	33	29	22	17

DTA mutations = *DNMT3A, TET2, ASXL1*

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

NPM1 PB MRD Is Associated With Worse Survival





Ivey A, et al. *N Engl J Med.* 2016;374:422-433.

Conclusions

- MRD monitoring throughout therapy is needed *and* critical to guide prognosis and risk-directed treatments in ALL; should be standard of care

- MRD monitoring should include early assessment of response to therapy (EOI) and post-treatment monitoring for early relapse detection and to guide therapeutic intervention prior to overt relapse, ie, continued assessment vs one-time

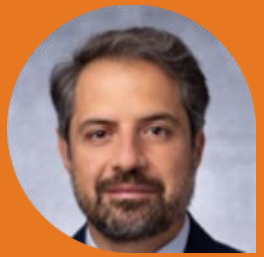
- NGS/HTS is a robust clinical platform for MRD determination

- More data demonstrate prognostic importance of MRD in AML but no specific therapeutic interventions yet

Global Leukemia Academy

Best practices for first-line treatment in ALL

Elias Jabbour



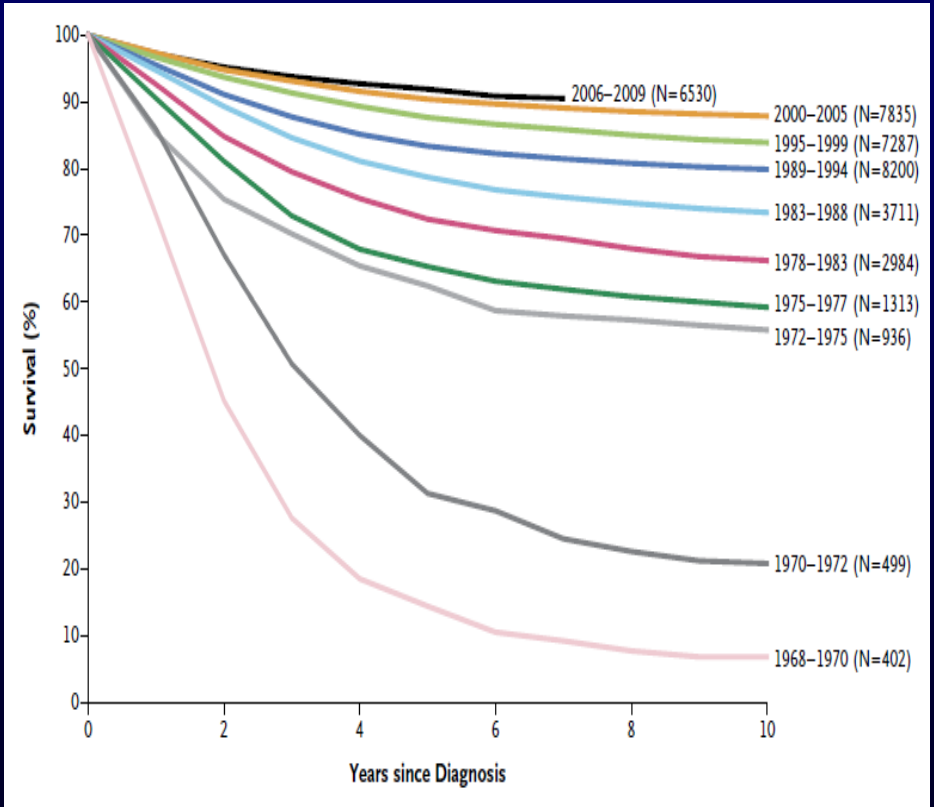
APTITUDE HEALTH

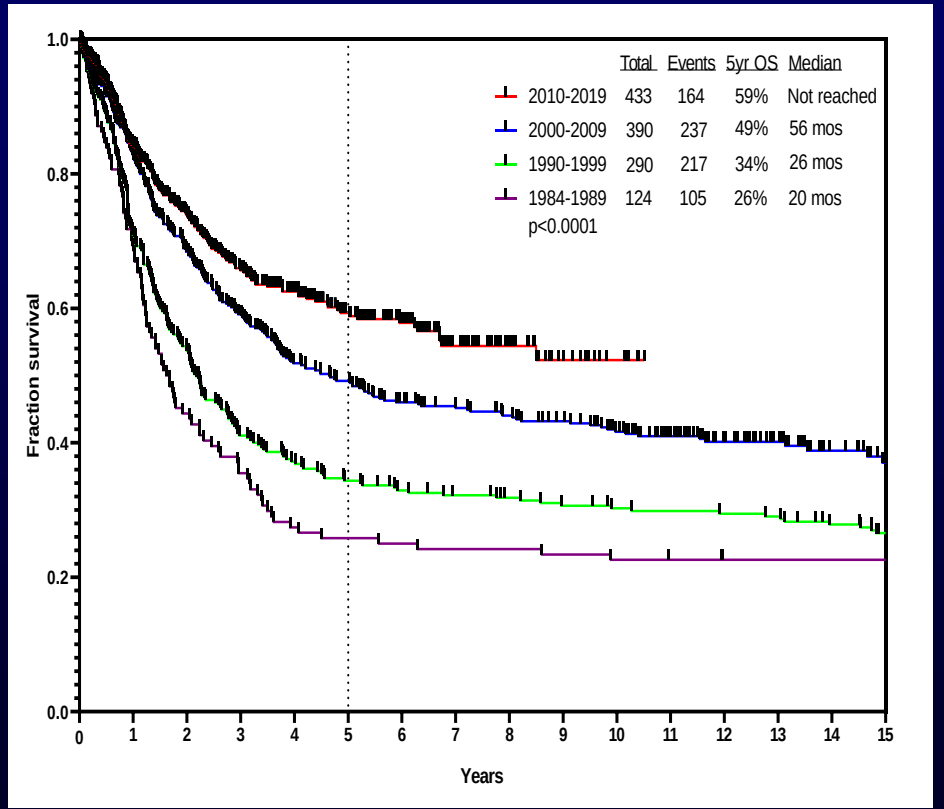
Integration of Immunotherapy in Newly Diagnosed ALL

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

Summer 2024

Survival in Pediatric and Adult ALL with Classical Intensive ChemoRx Regimens

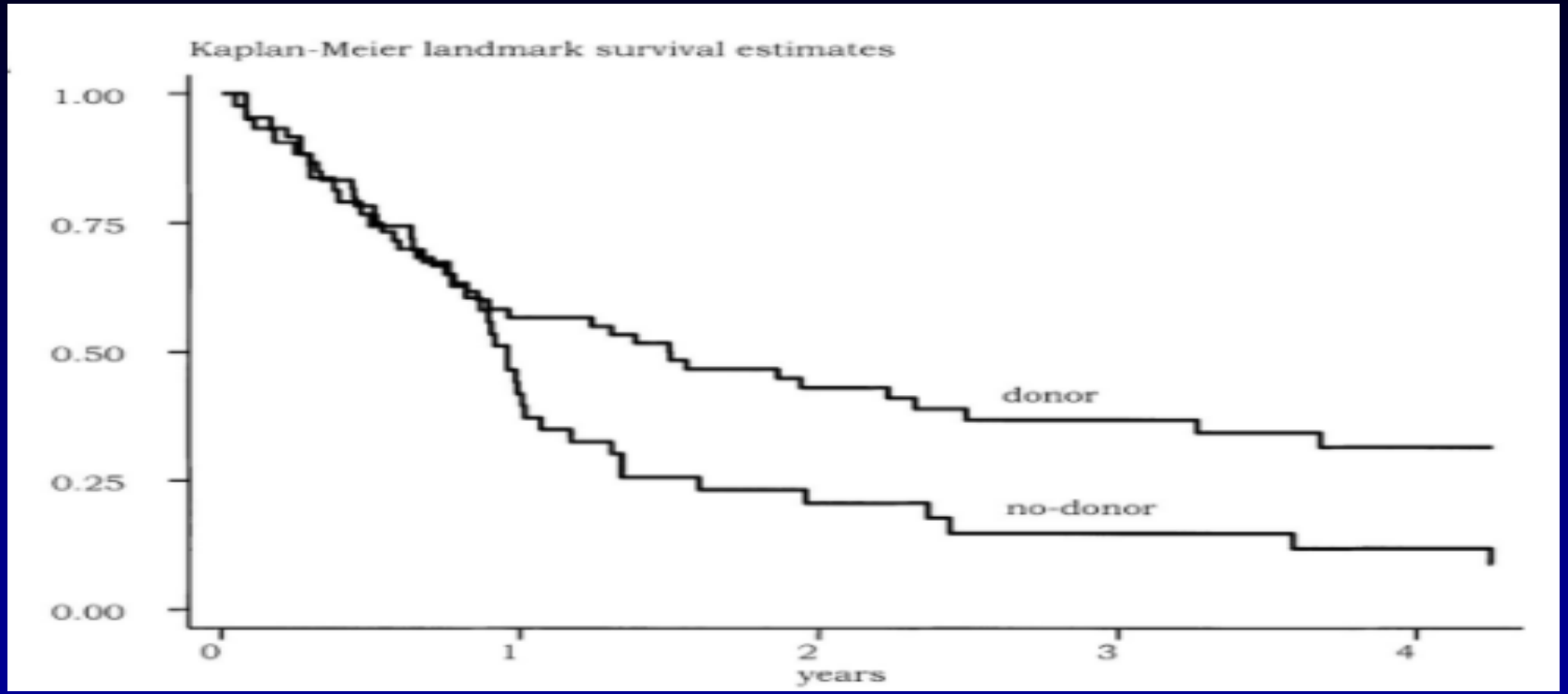




Hunger et al. *N Engl J Med.* 2015;373(16):1541-1552.

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

SCT for Ph+ ALL: Pre-TKI



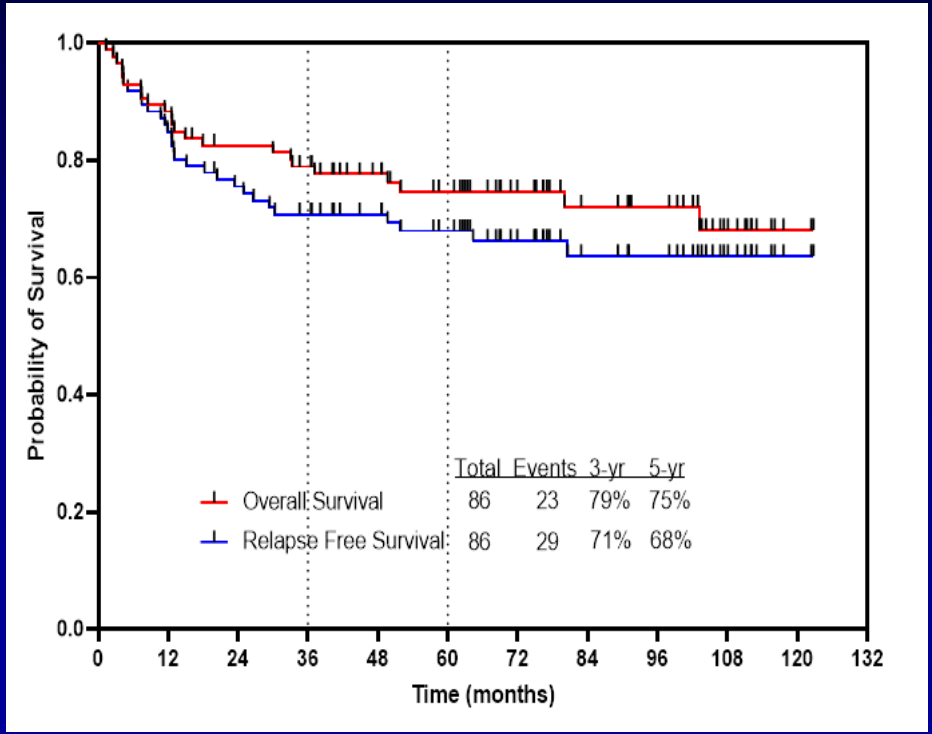
- Donor (n=60) – 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

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

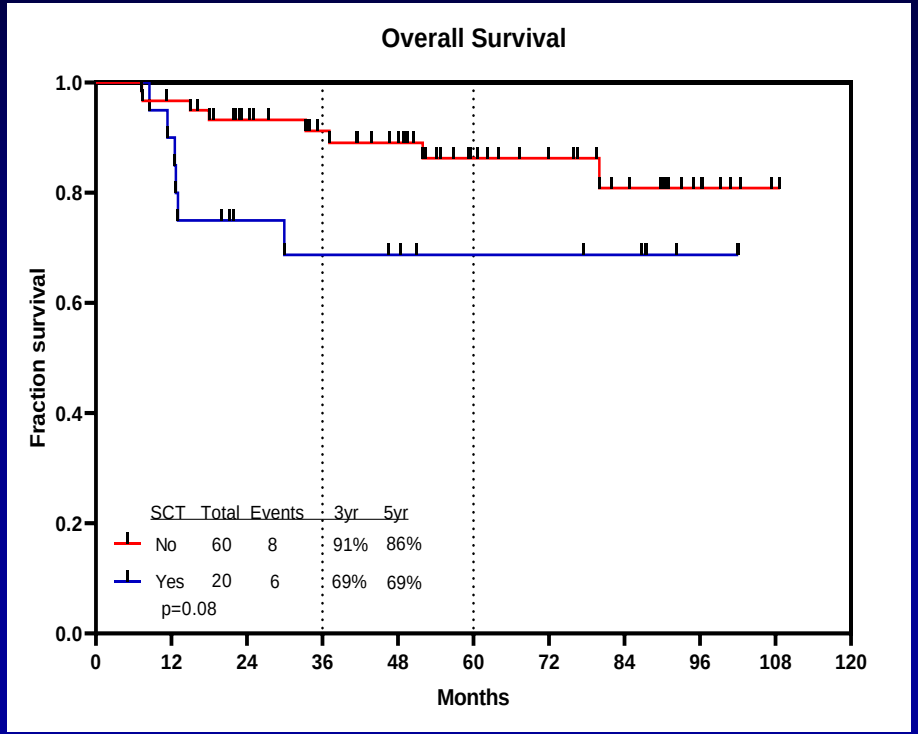
HyperCVAD + Ponatinib in Ph+ ALL

- 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



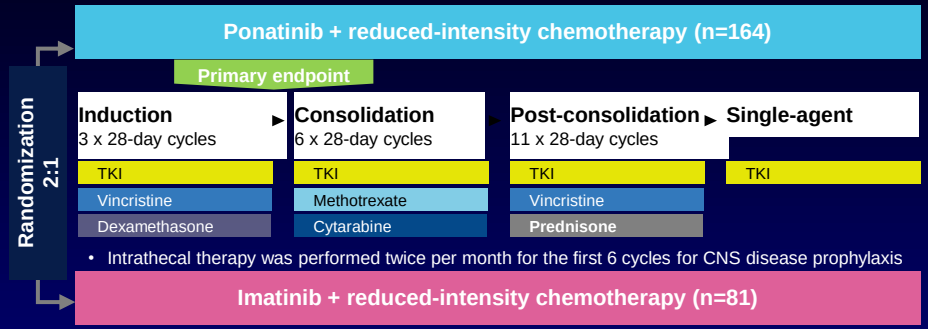
6-month Landmark



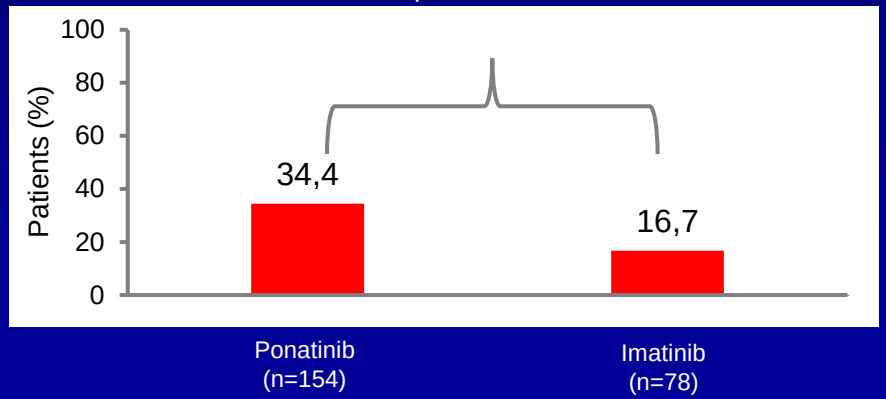
Kantarjian. Am J Haematol 98:493-501;2023

Ponatinib vs Imatinib With Rx in Ph+ ALL: PhALLCON

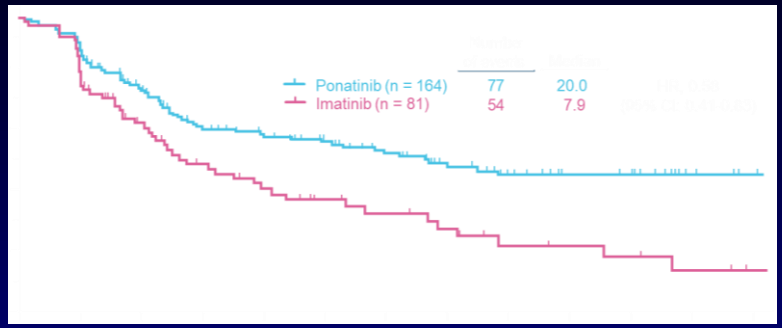
Study design



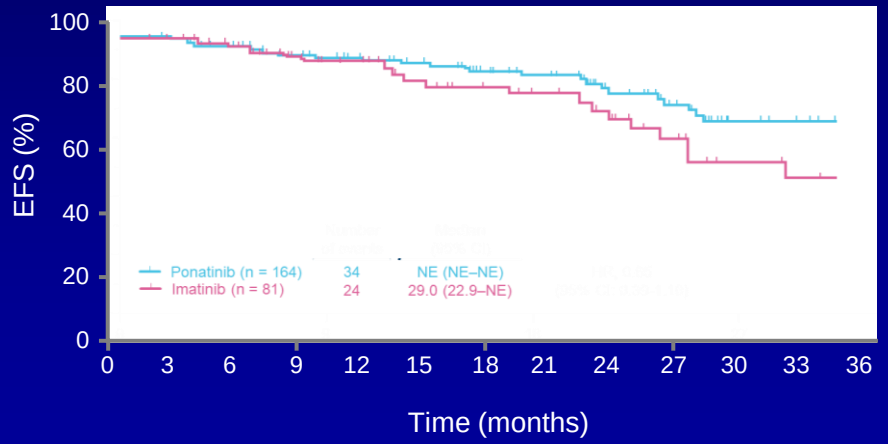
Primary endpoint:
MRD– (MR4) CR at end of induction
RR: 2.06 (95% CI=1.19–3.56)
p=0.0021



PFS

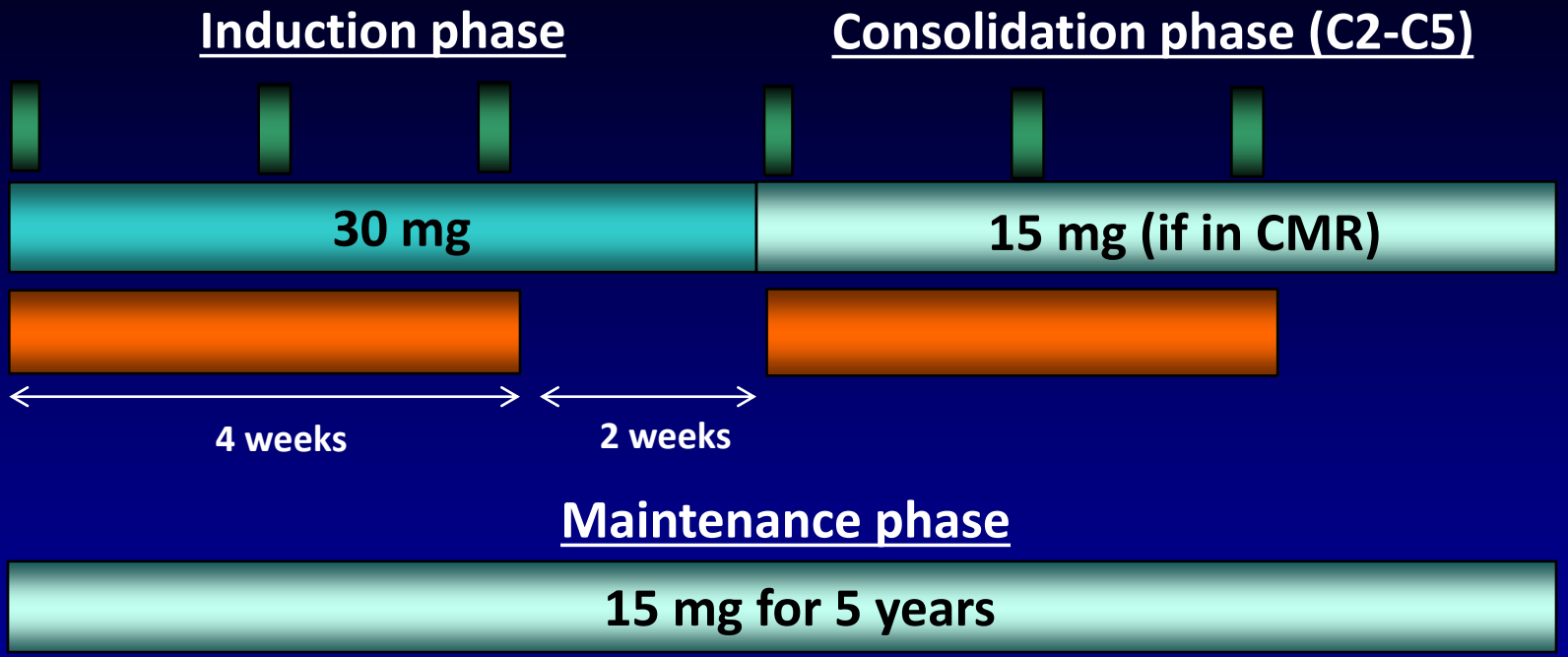


EFS



Jabbour. JAMA. 2024 May 9:e244783.

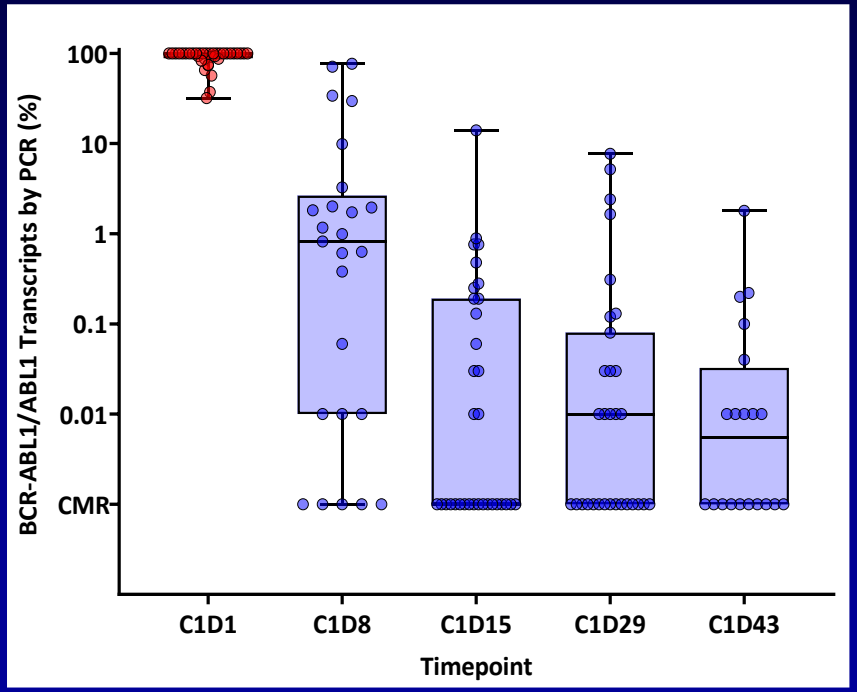
Ponatinib + Blinatumomab in Ph+ ALL: Regimen

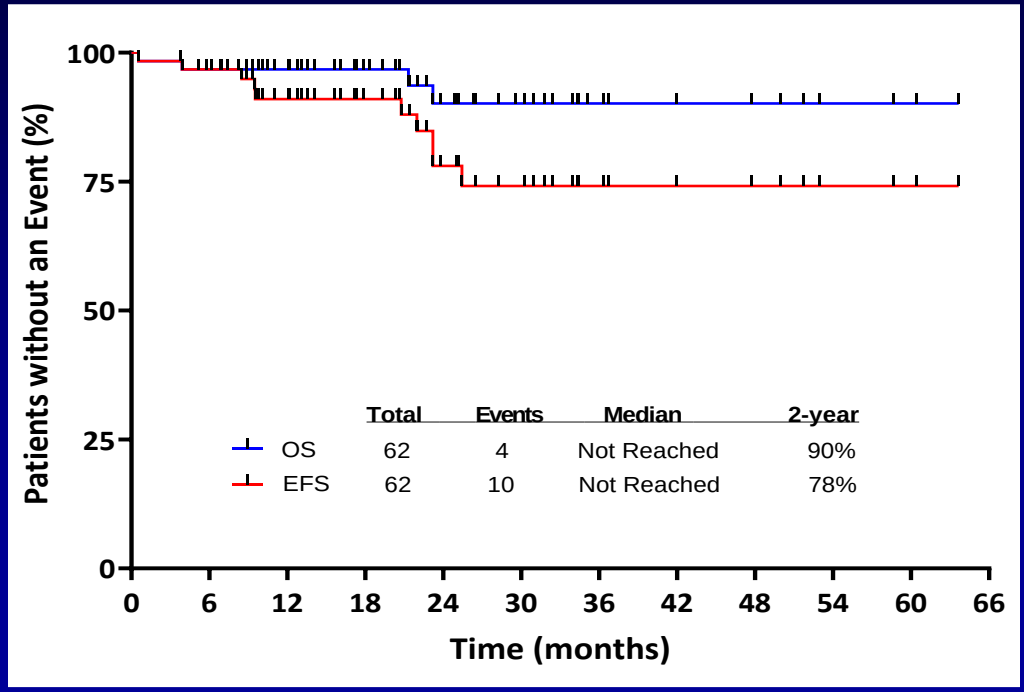


Jabbour. Lancet Haematol. 2023;10(1):e24-e34

Ponatinib and Blinatumomab in Newly Dx Ph+ ALL

- 62 pts Rx with simultaneous ponatinib 30-15 mg/D and blinatumomab x 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. Lancet Haematol. 2023;10(1):e24-e34.

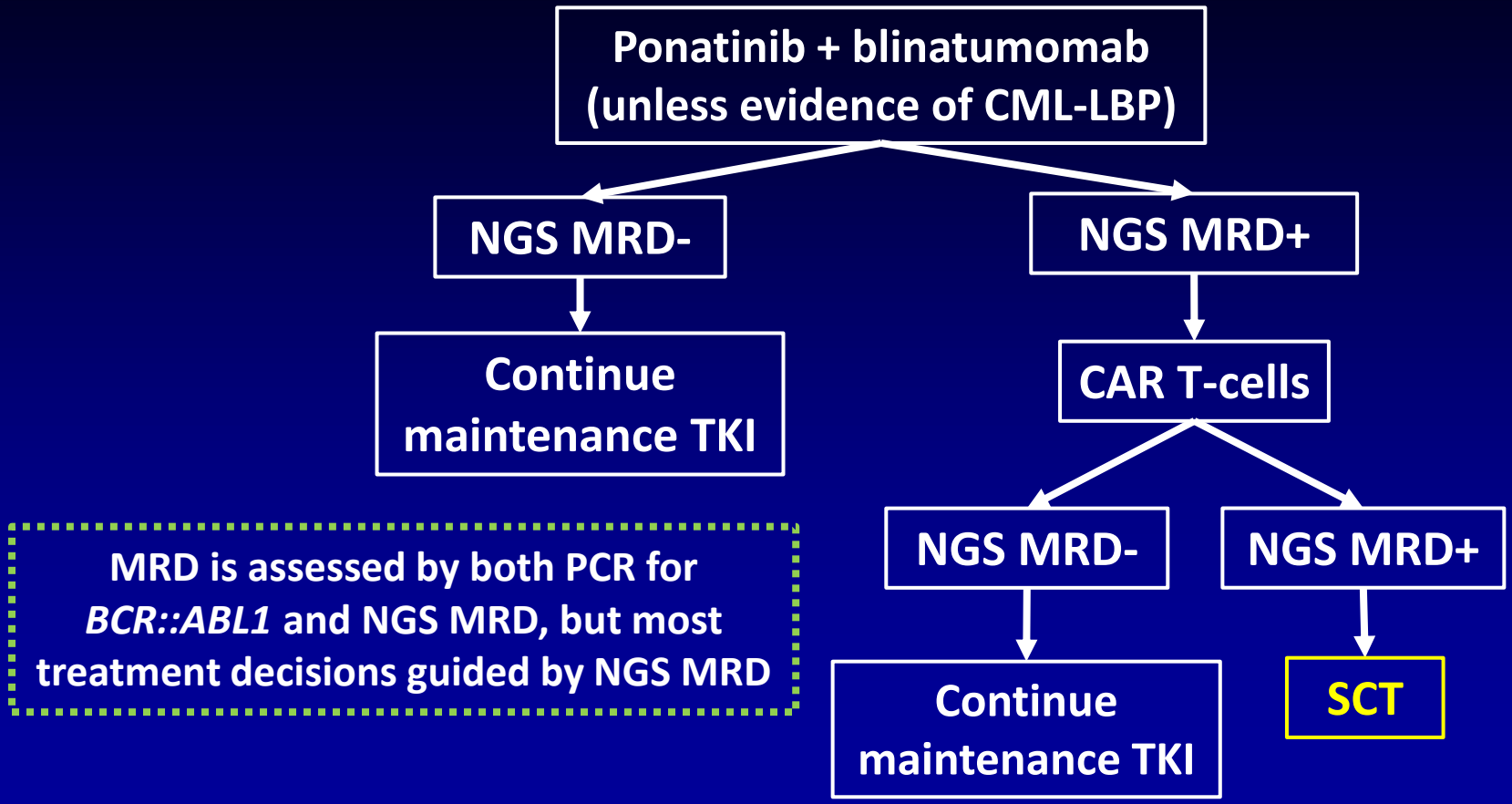
Haddad. Blood 142: abstr 2827;2023

Ponatinib vs Dasatinib + Blinatumomab in Ph+ ALL

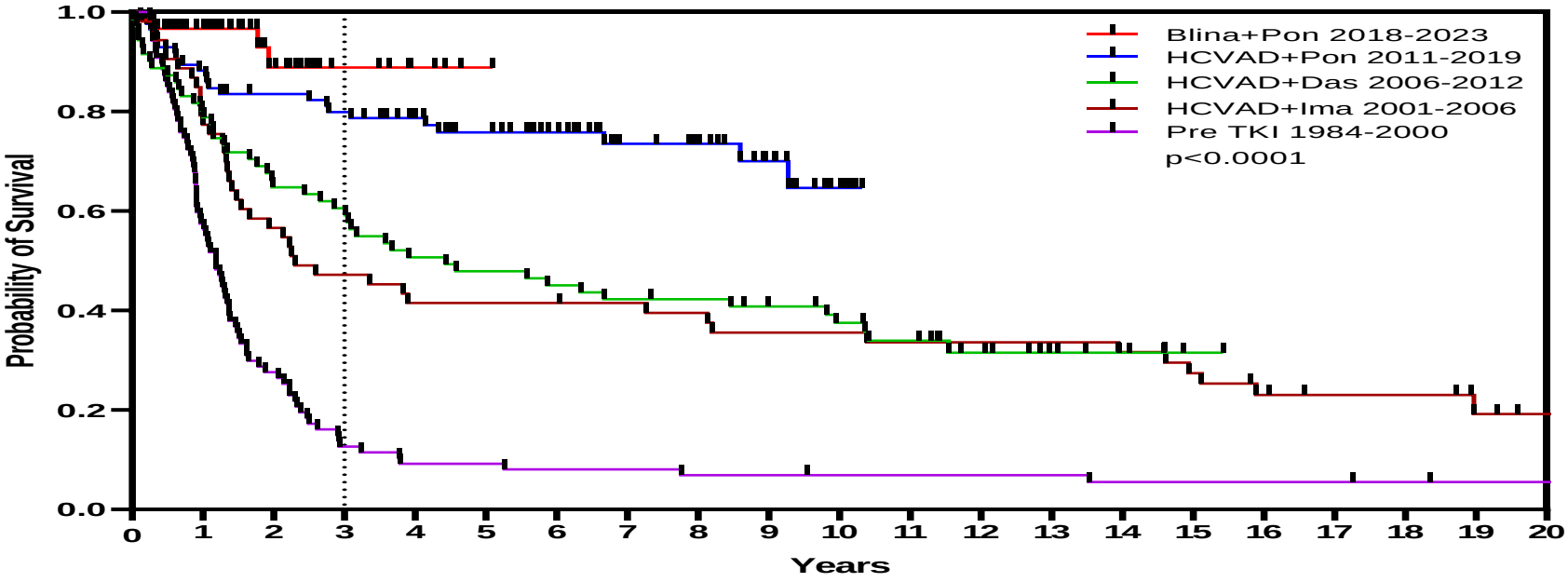
Parameter	Pona+Blina (n=62; 5 blina)	Dasa+Blina (n=63; 2+blina)	Dasa+ Blina (n=24; 3 blina)
Median age (yrs)	58	54	73
% PCR neg % NGS-clonoSEQ neg	84 94	93 (+PNQ)	63
% 4-yr OS	90	82	75
% allo SCT	3	48	5
Relapses (CNS)	7 (4)	9 (4)	8 [3 T315I]

Jabbour. Lancet Haematol. 2023;10(1):e24-e34. Foa. JCO online, December 23; 2023. Advani. Blood 142: Abst 1499; 2023

Research Rx Algorithm for Ph+ ALL



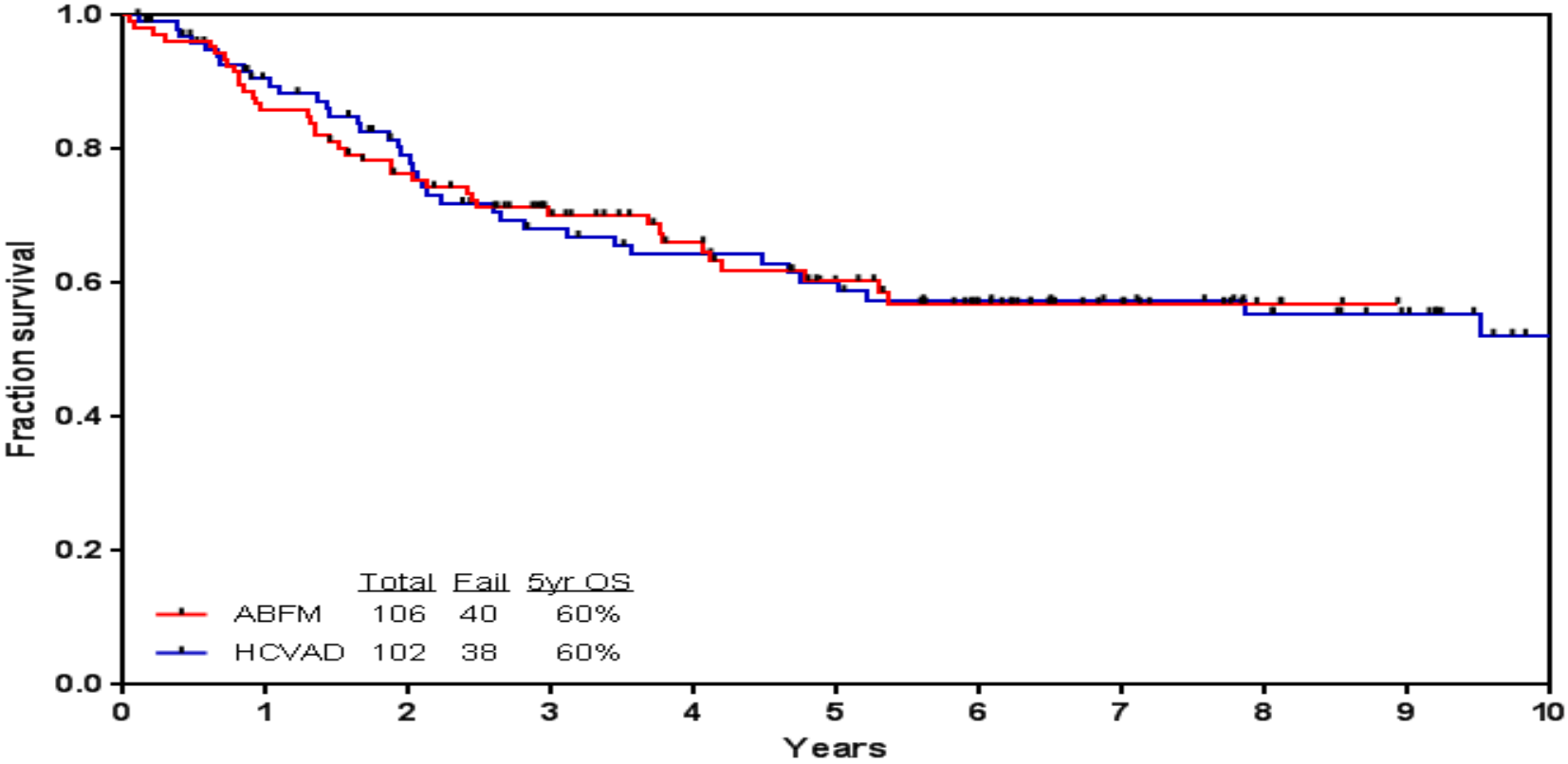
Ph+ ALL: Survival by Decade (MDACC 1984-2023)



	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

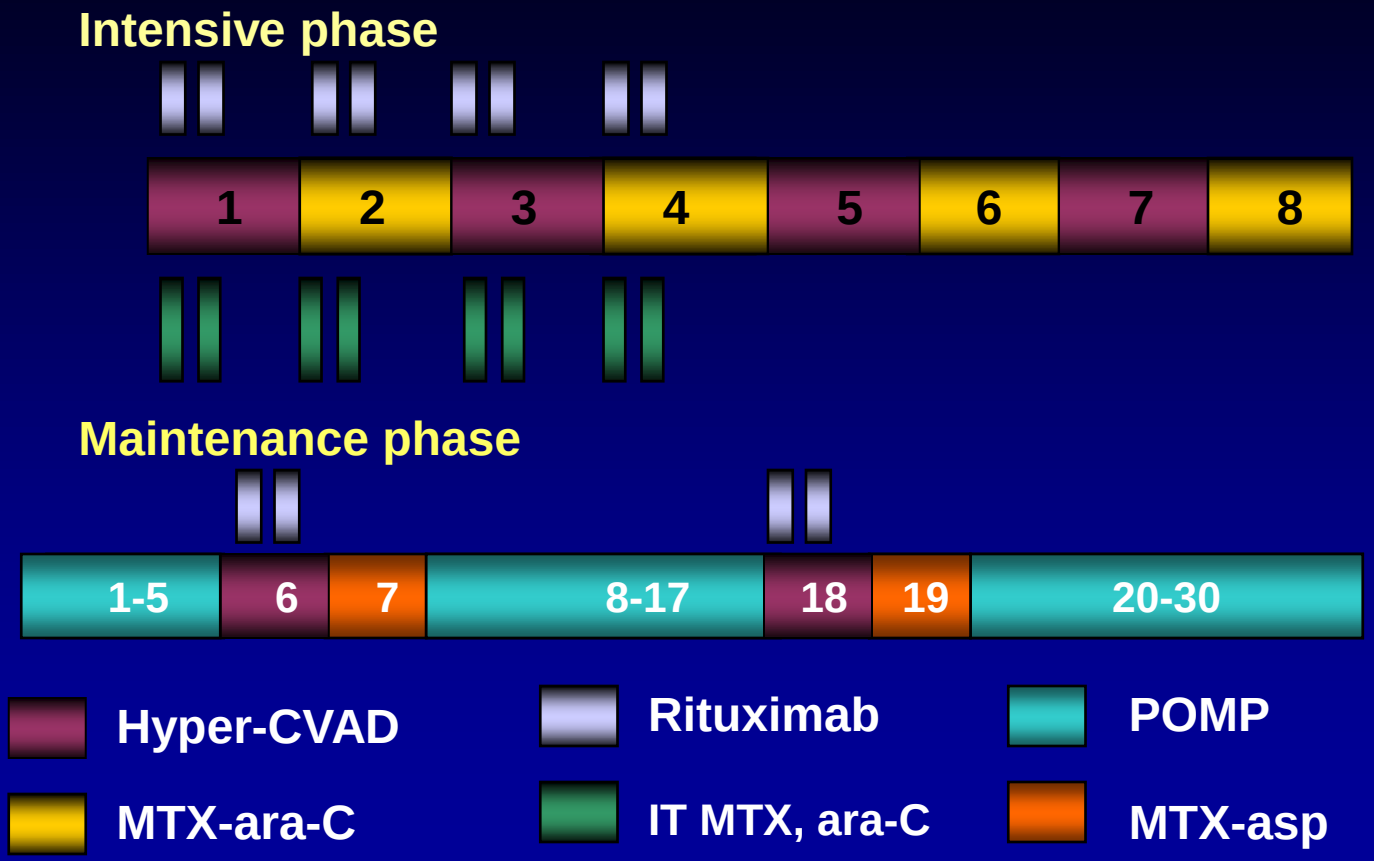
p<0.0001

Hyper-CVAD vs ABFM: Overall Survival



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

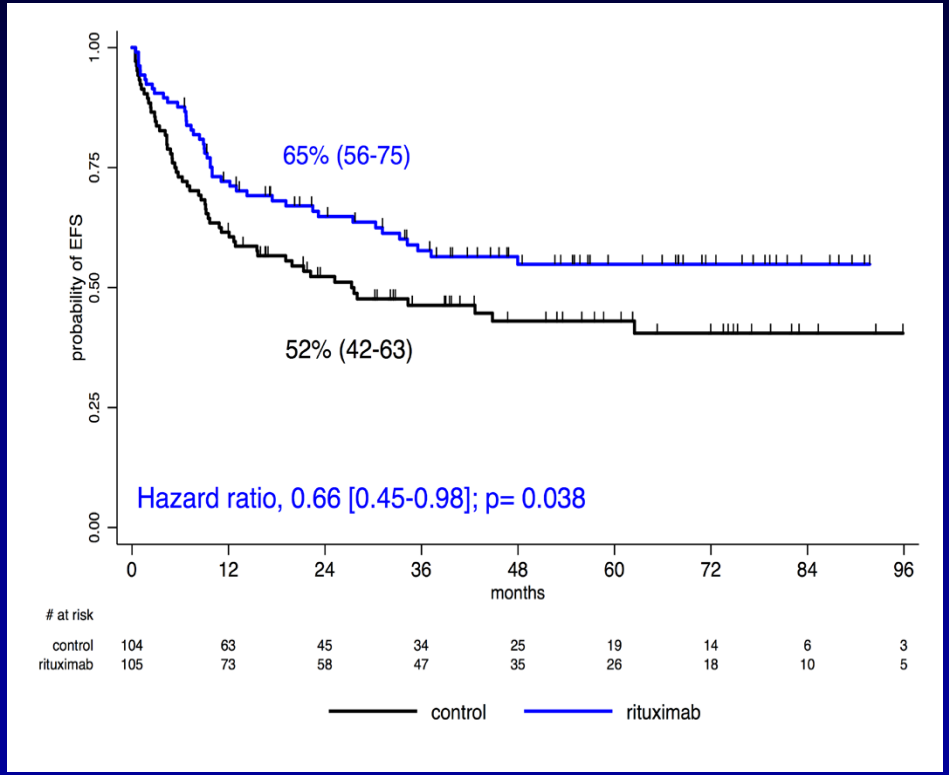
Hyper-CVAD + Rituximab in Precursor B-ALL

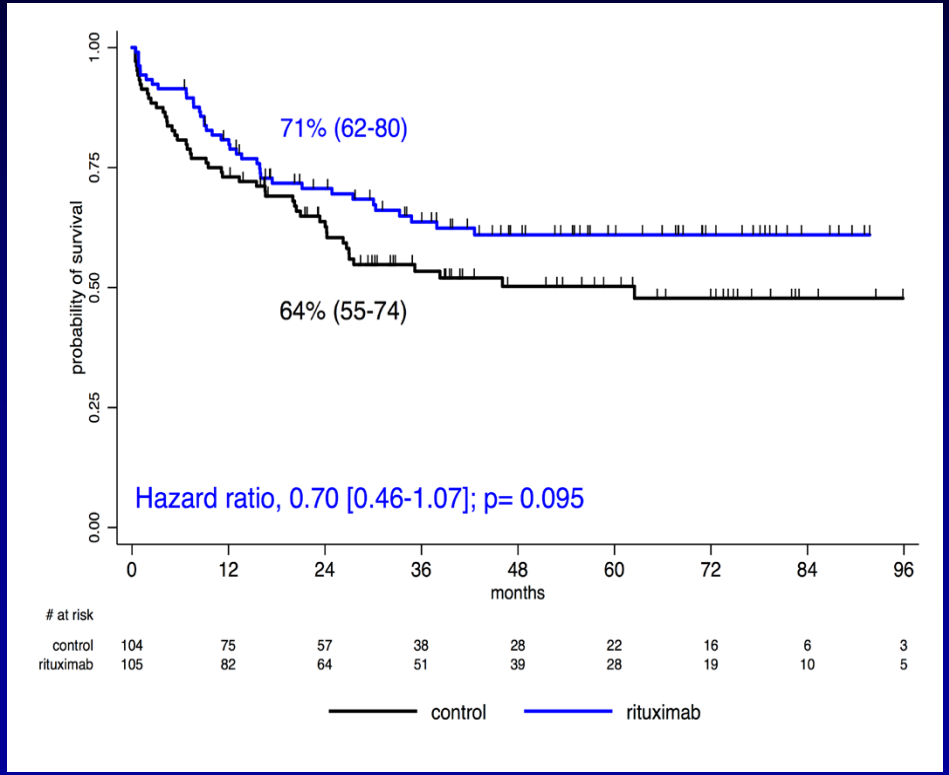


Thomas. JCO 2010; 28:3880-9

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

- Median follow-up 30 months

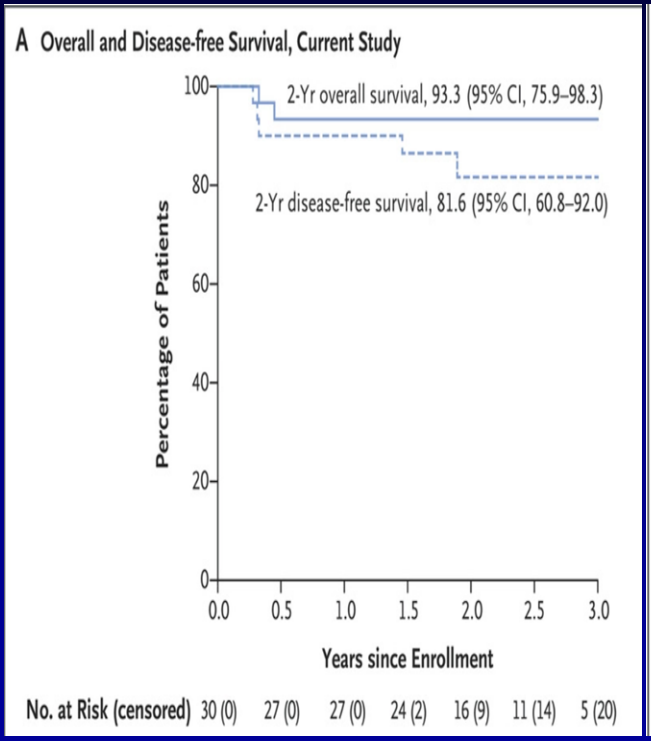


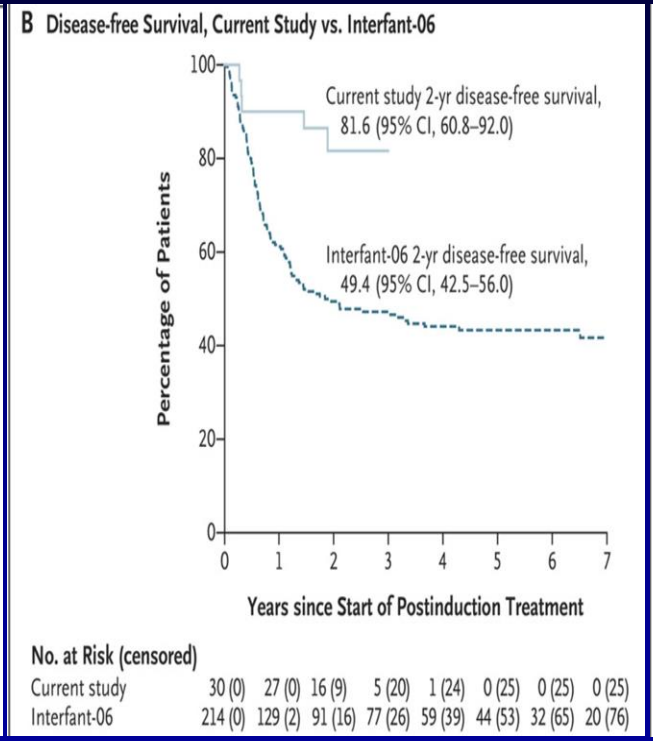


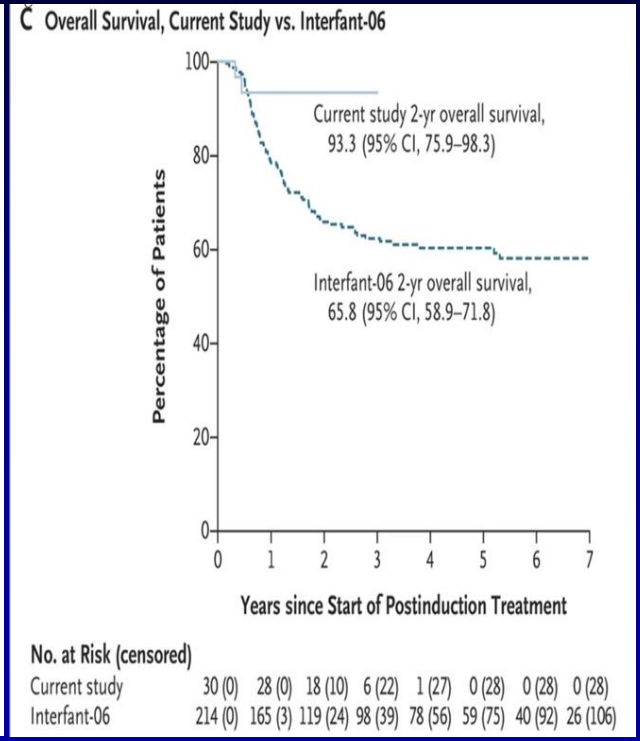
Maury. N Engl J Med. 2016;375:1044-53

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 x 28), then chemoRx continuation



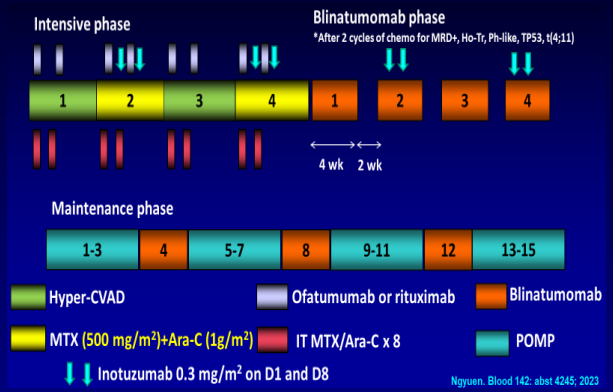


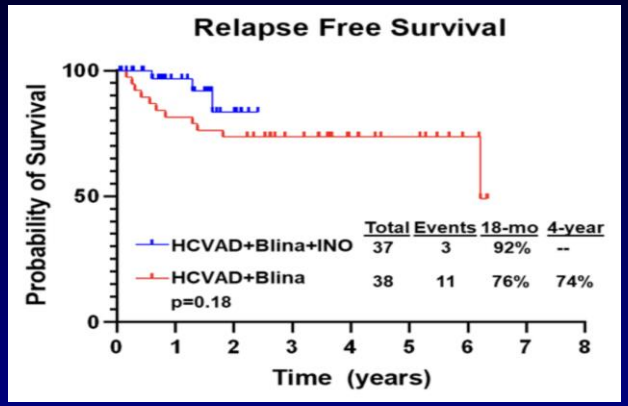


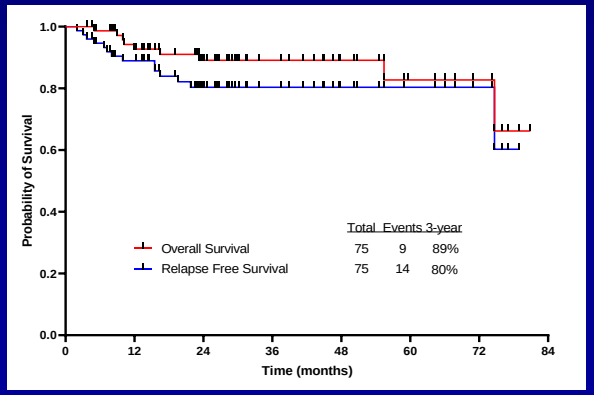
Vam der Sluis. NEJM 388:1572-1581; 2023

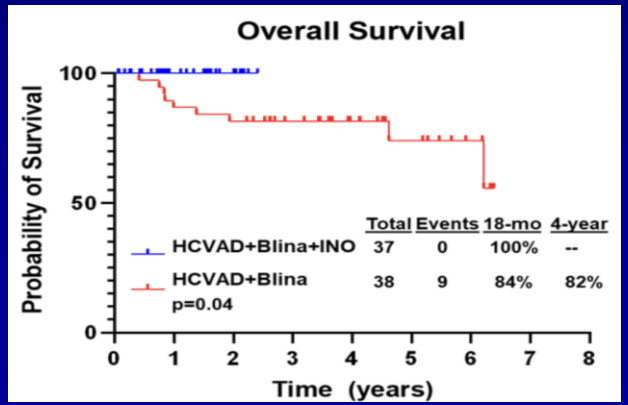
Hyper CVAD-Inotuzumab → Blina in Newly Dx Adult ALL

- 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;

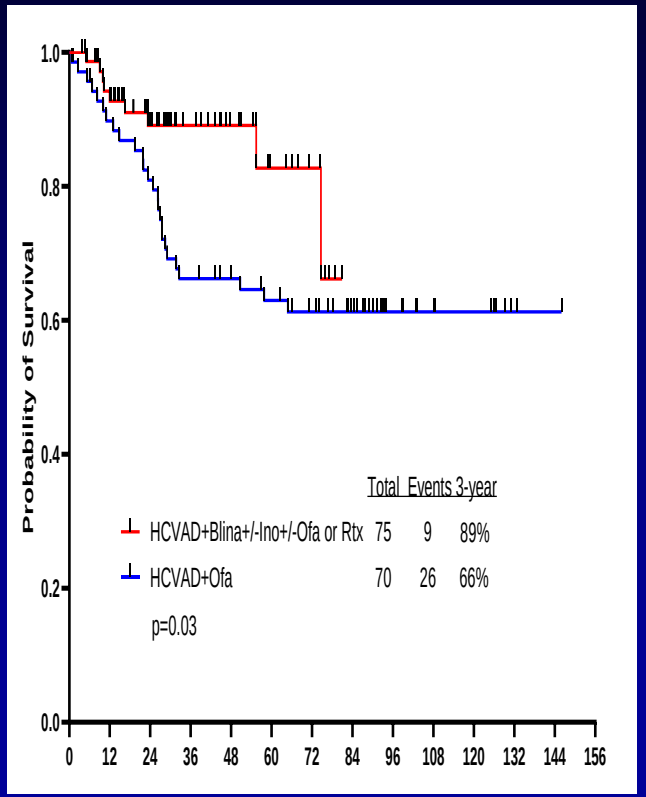








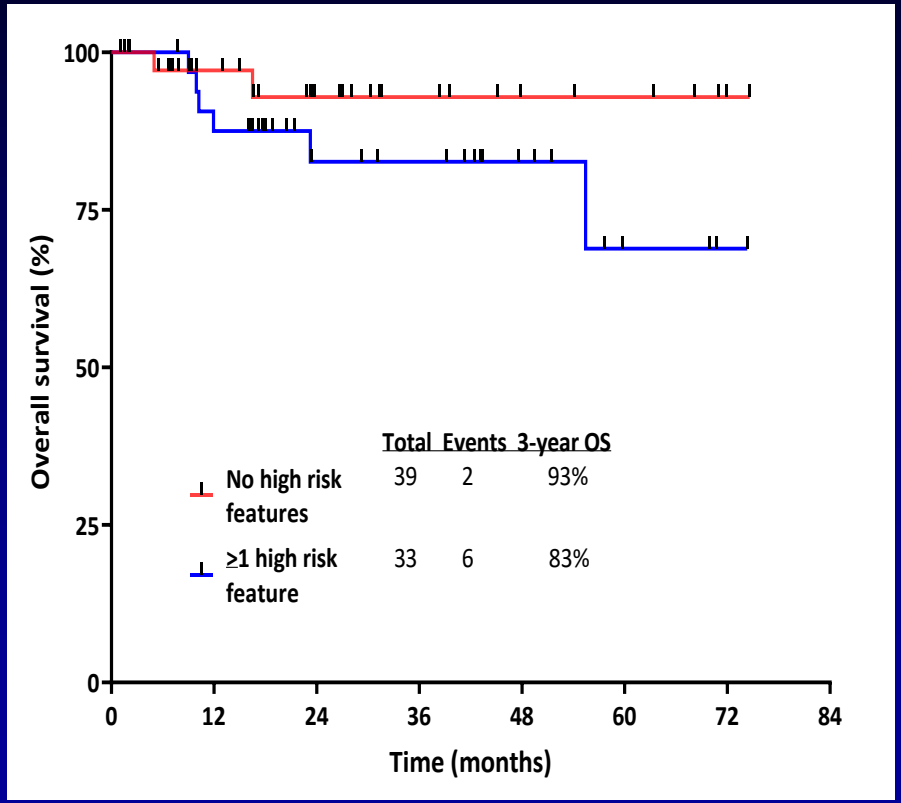
Overall Survival



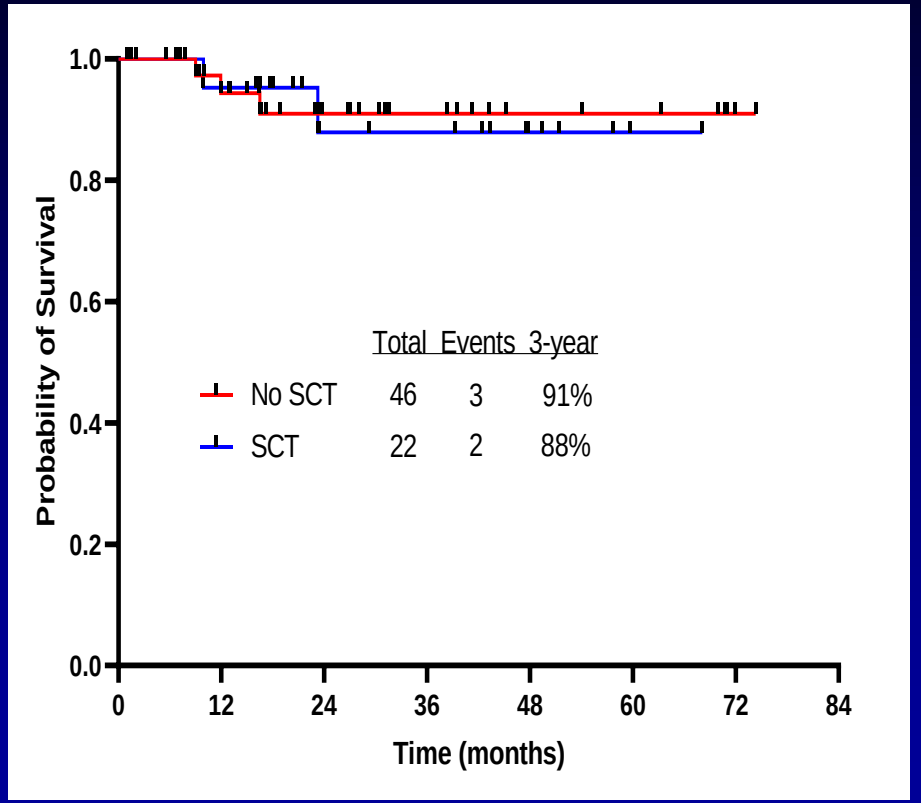
Nguyen. Blood 142: abst 4245; 2023

Hyper-CVAD + Blinatumomab + Inotuzumab in B-ALL

Outcome by ALL Risk

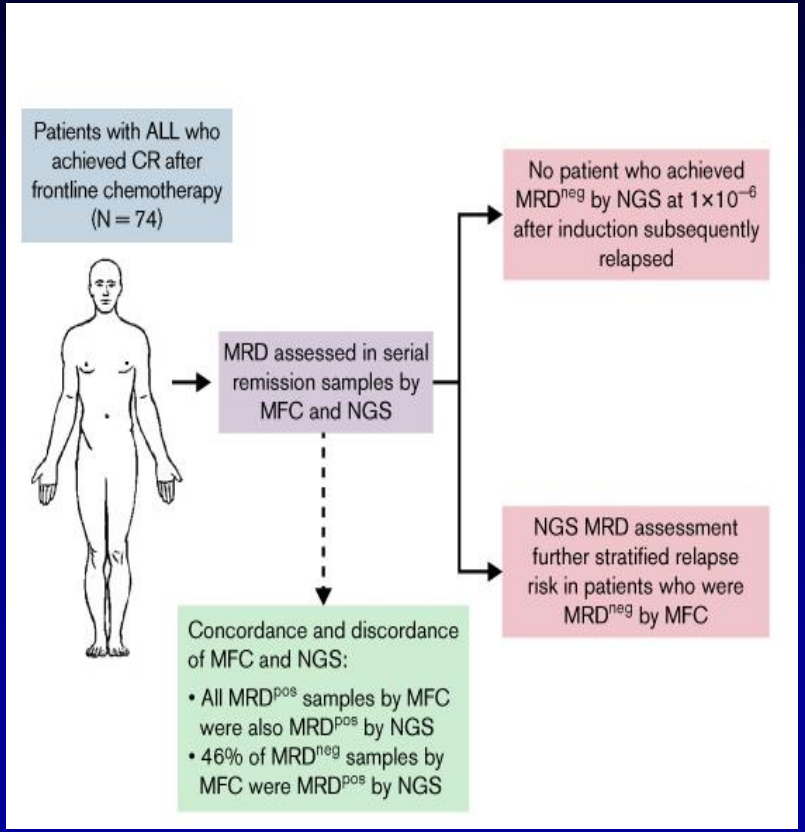


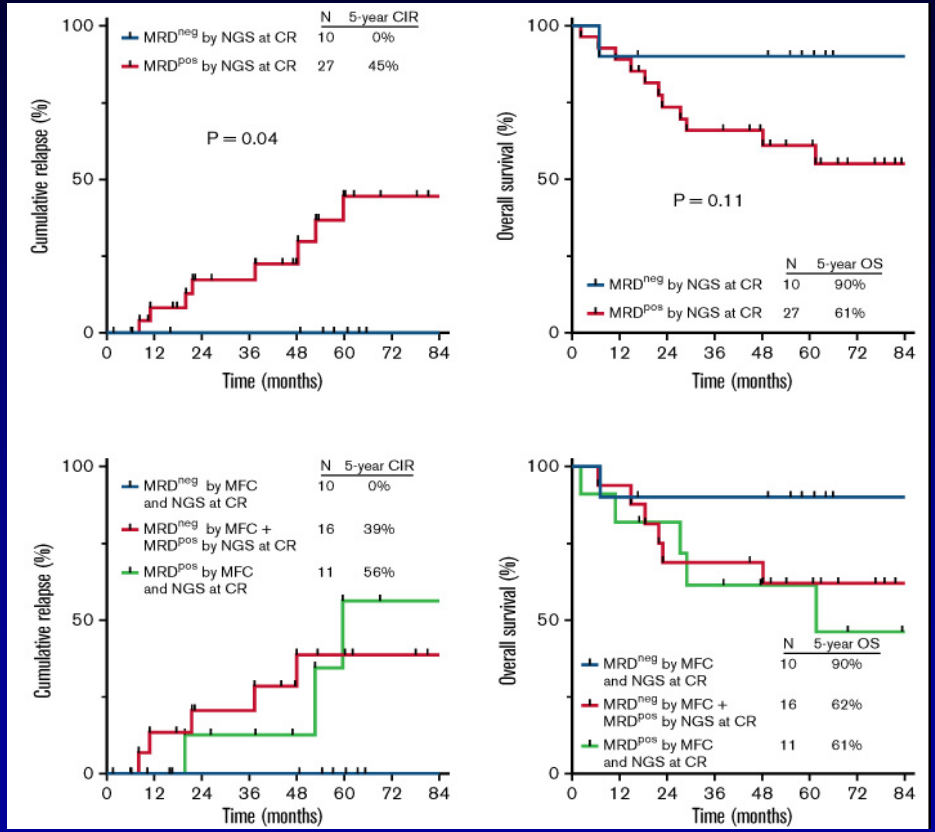
Outcome by ASCT (5-mo landmark)



Jabbour. Lancet Haematology 9 : e 878-e885; 2023

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





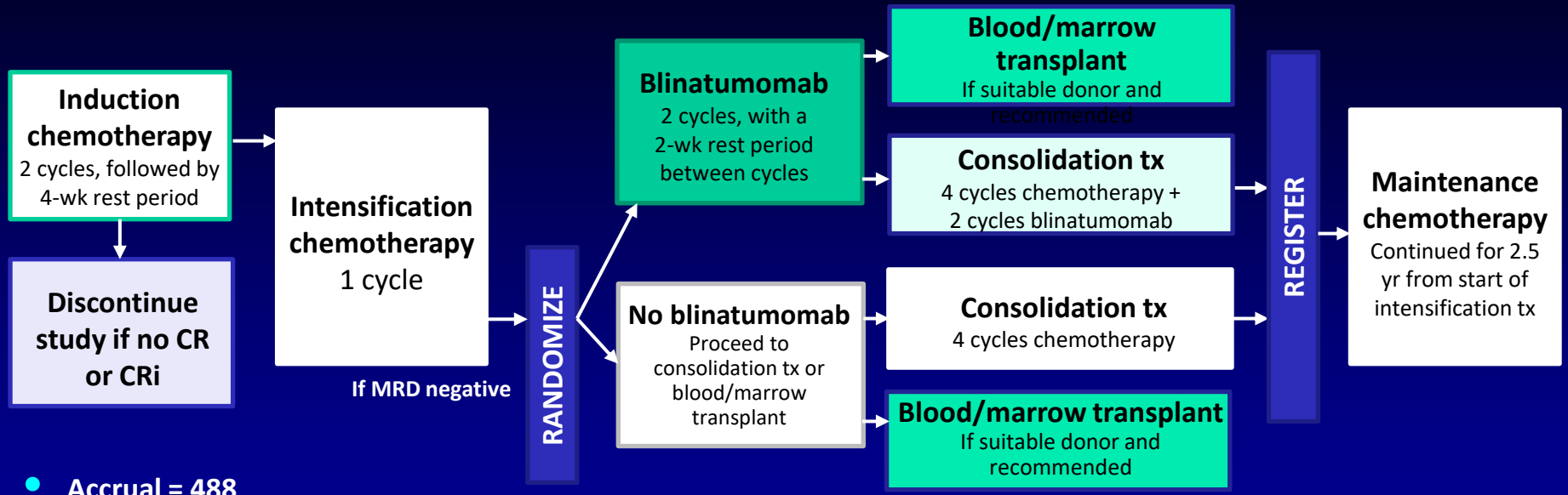
Short. Blood Adv. 2022; 6: 4006-14

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. Lancet Haematology 9: e878-e885;2023. Chiaretti. Blood 142: abst 826; 2023. Boissel. Blood 140: abst 1232; 2021. Fleming. Blood 138:1224; 2021

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



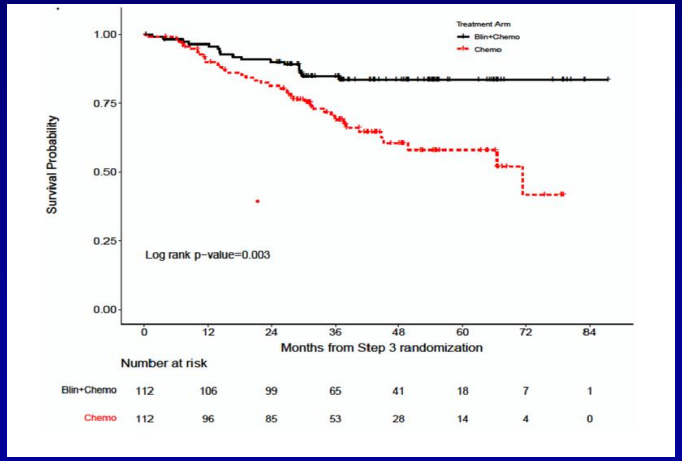
- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

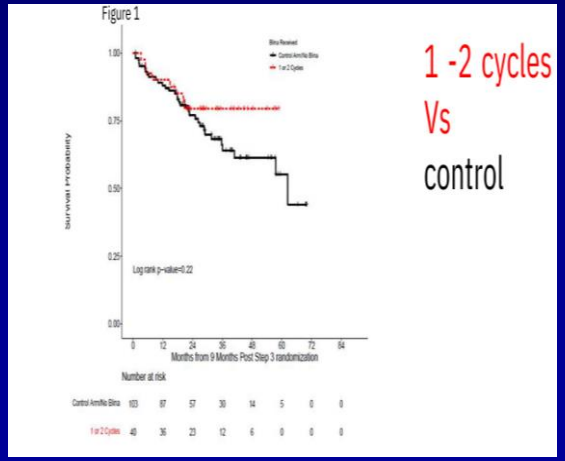
Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

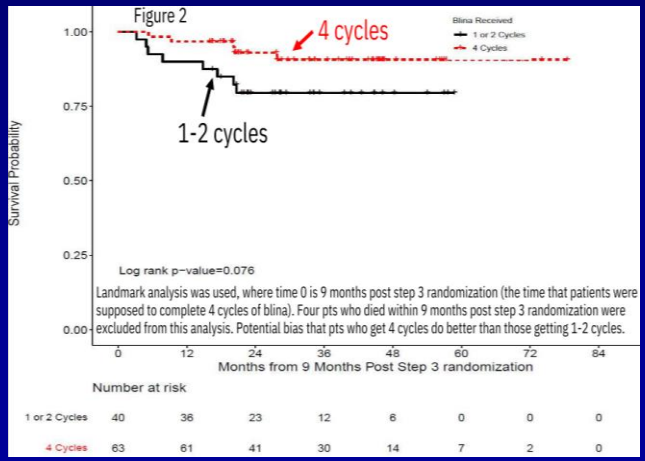
E1910 Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD–: Outcomes by Number of Cycles

- 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=0.003)**
- No difference in OS if 1-2 cycles of blina vs control (HR: 0.62; p=0.22)
- OS: 1-2 cycles vs 4 cycles (HR: 0.39; p=0.07)

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

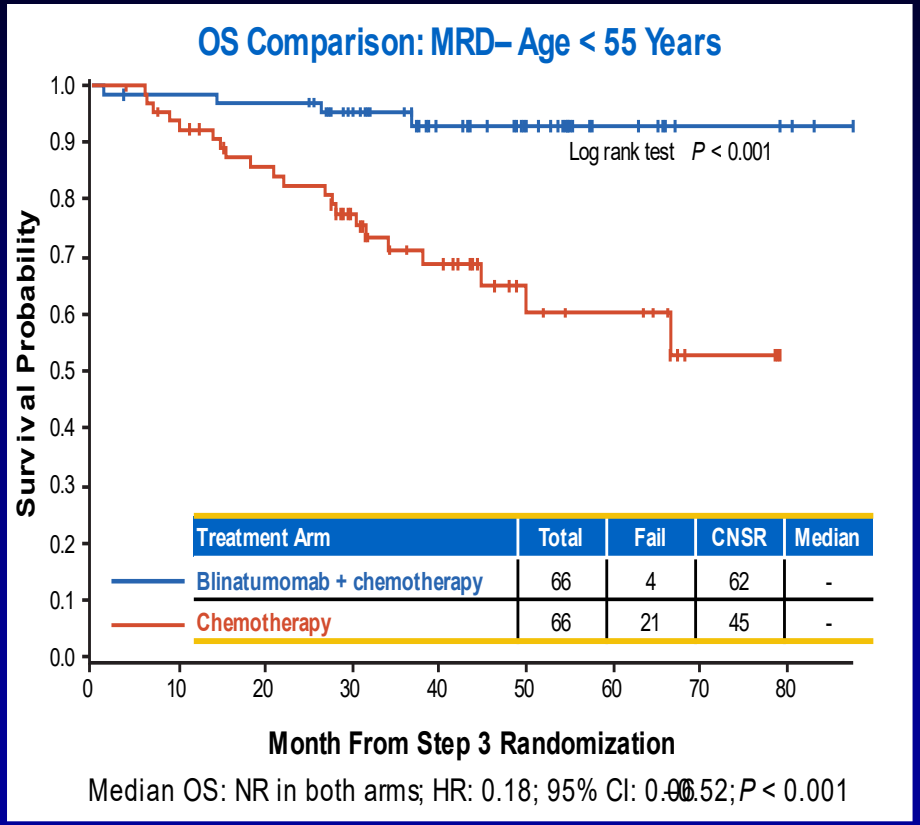


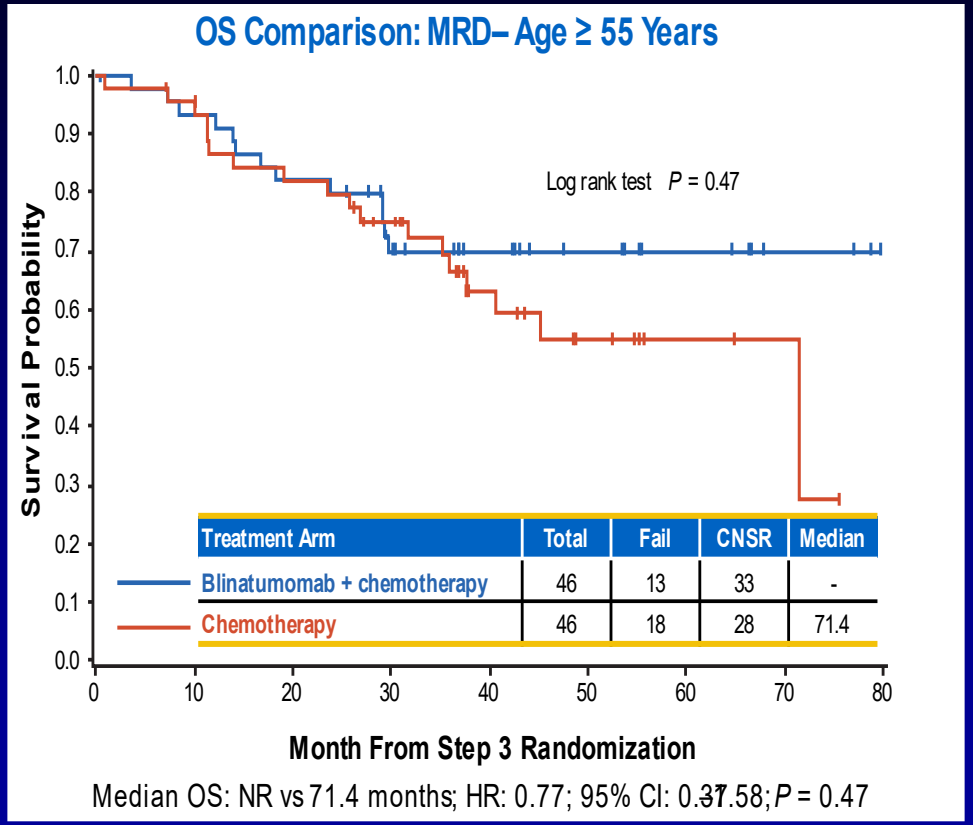




Luger. Blood 142: Abst 2877; 2023

E1910 Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD–: Outcomes by Age

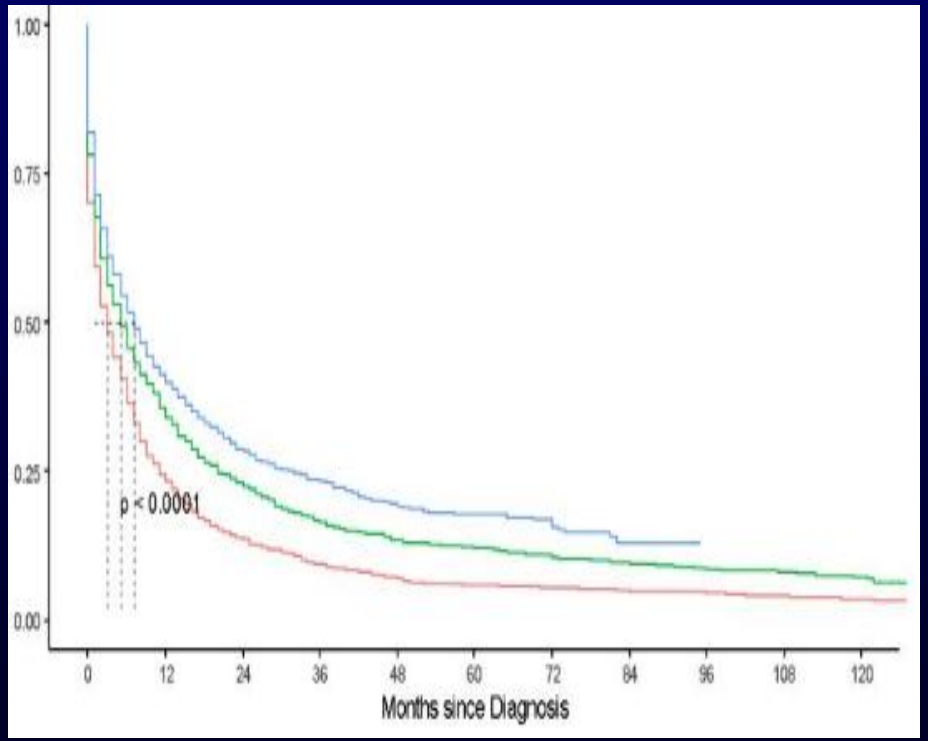


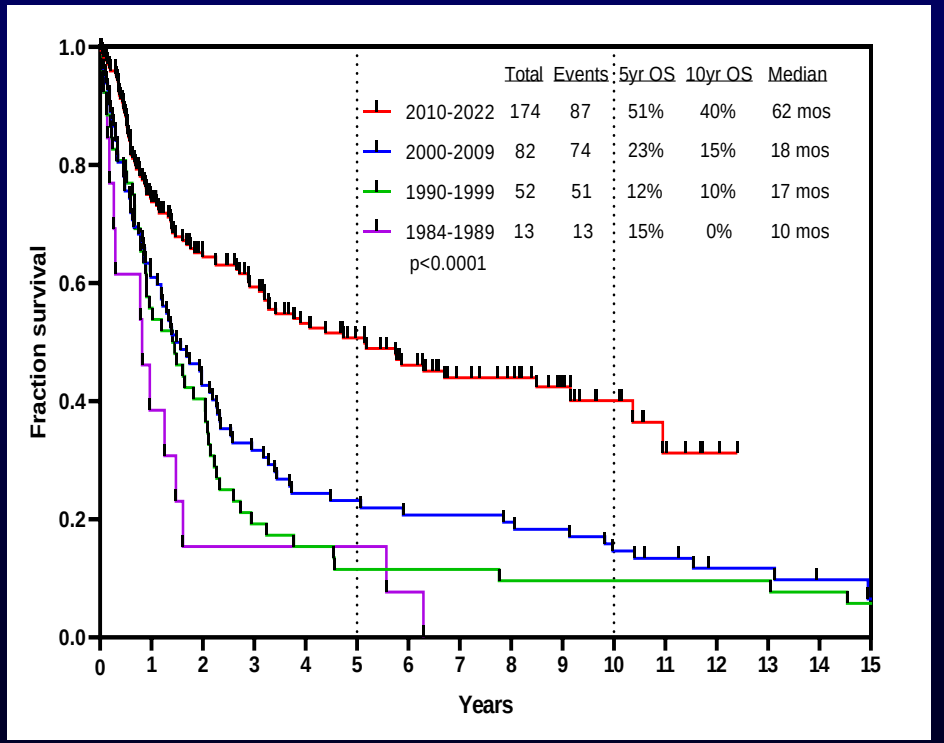


Mattison R, et al. EHA 2023; Abstract S115

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%

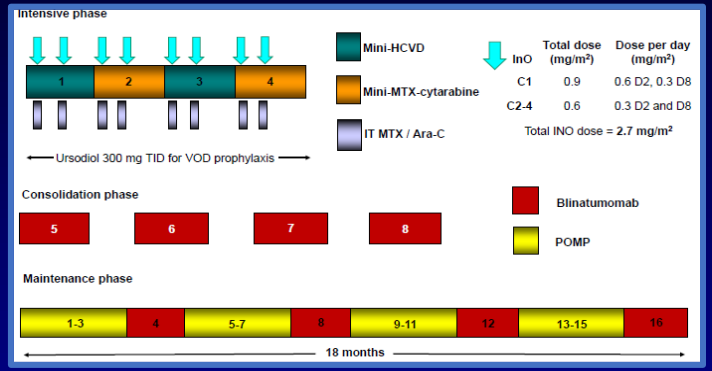




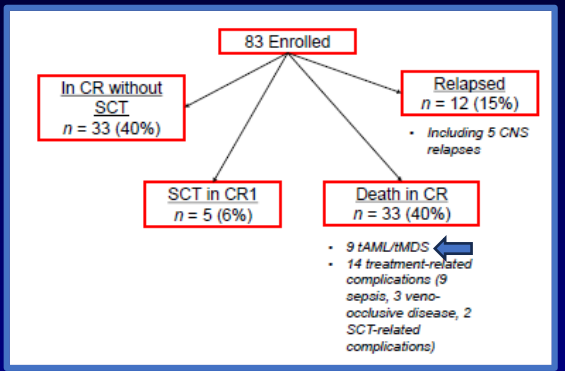
Gupta. Blood 140: abst 1379; 2022

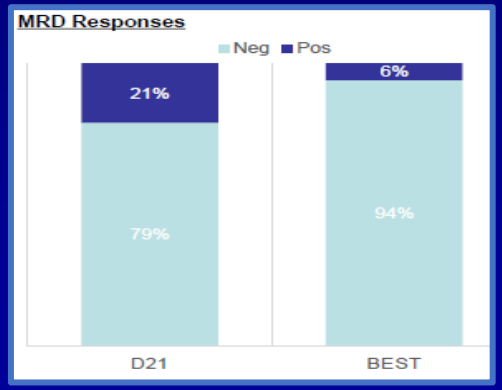
Mini-HCVD + INO ± Blina in Older ALL (N=83)

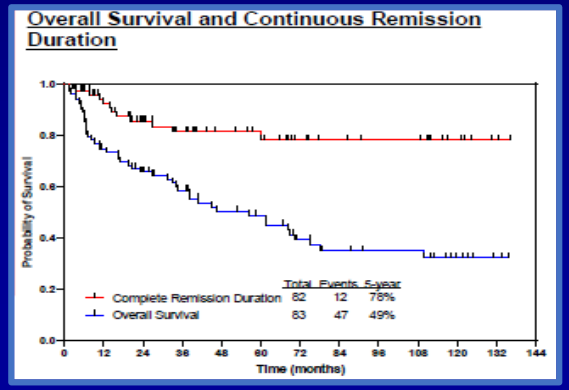
- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: *TP53* 39%; Ph-like 18%; poor cytogenetics 23%
- ORR 99% (CR 90%); MRD negativity 94% (79% at CR)



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)





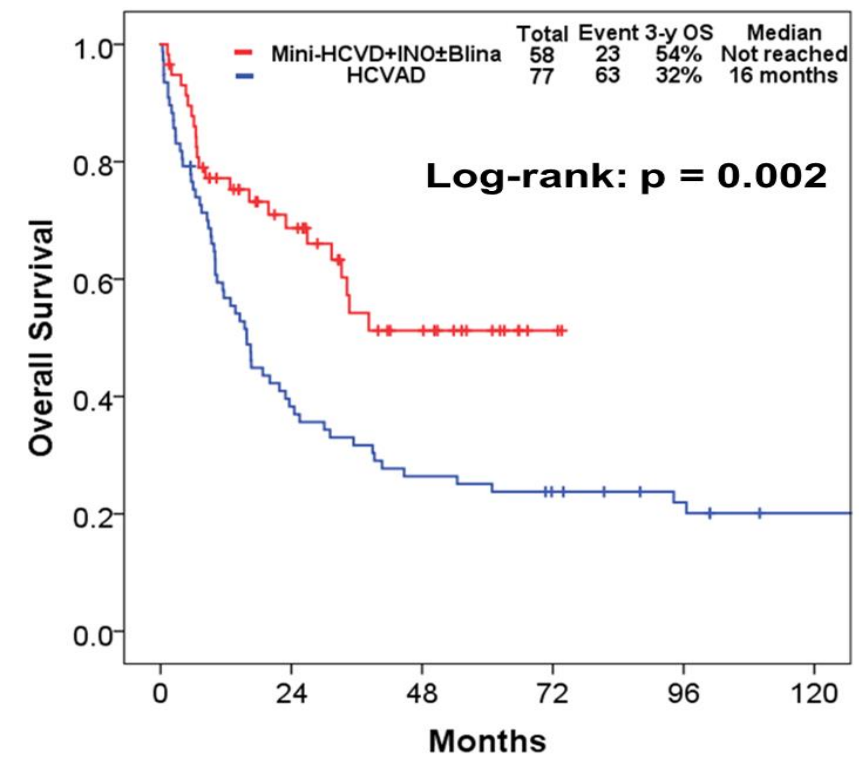


- Median F/U 88 months
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; 6%)
- Death due PD/NR: 12/83 (15%); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (11%); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: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

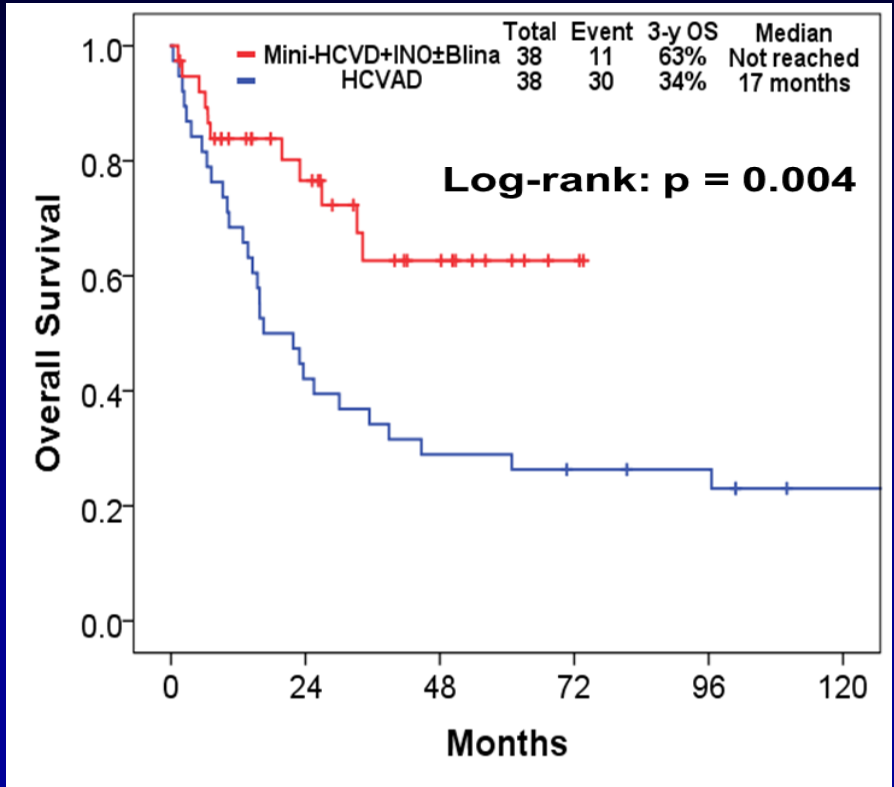
Jen. Blood 142: abst 2878; 2023

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

Pre-matched



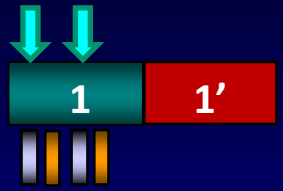
Matched



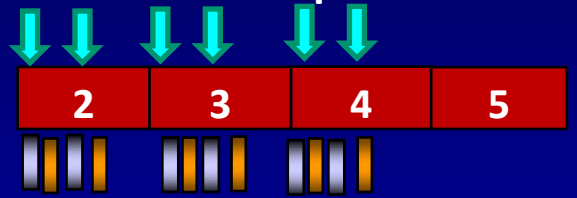
Jabbour E. Cancer. 2019;125(15):2579-2586.

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

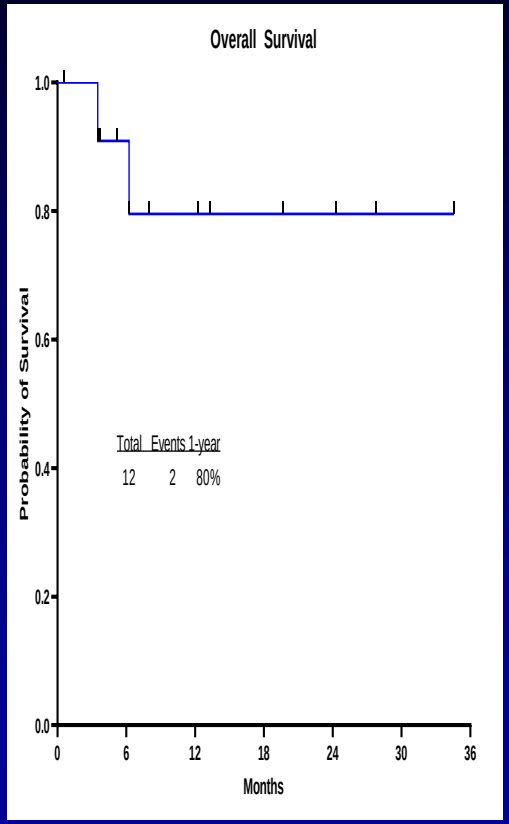
Rituximab if CD20+

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 300mg tid for VOD prophylaxis

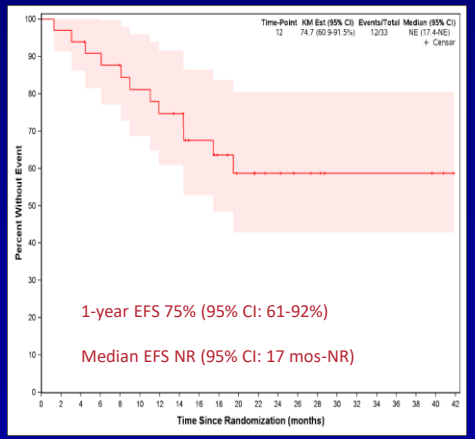


Chemo Rx-Free Inotuzumab + Blinatumomab in Pre–B-ALL (Alliance A 041703)

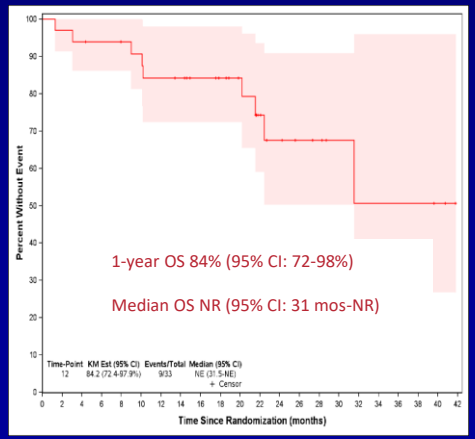
- 33 pts; median age 71 yrs (60-84). Median CD22 92%. F/U 22 months
- Induction: INO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 & 15 (1.8 mg/m^2)
- Maintenance: If CR-CRi INO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) x 2 then BLINA x 2
- If no CR-CRi—BLINA 28m cg/D x21 then x 28 x 3
- IT x 8
- CR 85% post INO x 3; cumulative 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

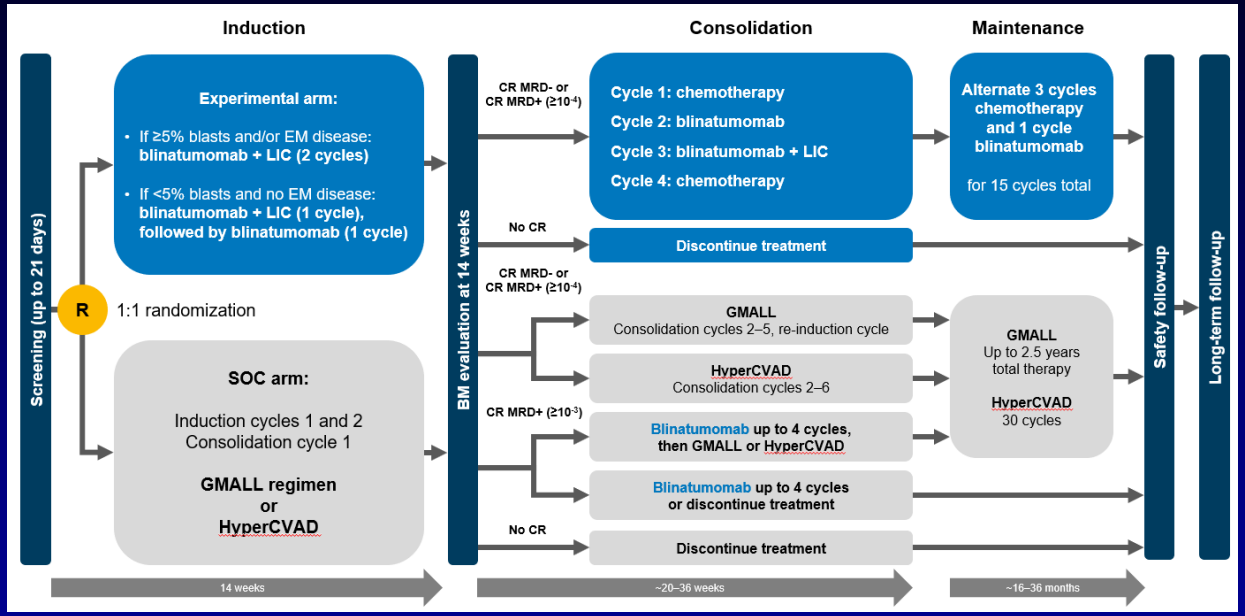


OS



Wieduwilt. HemaSphere 7: abst S117: 2023

Blina + Low-Intensity ChemoRx in Older Pre-B ALL: Golden Gate Safety Run-In Results of Phase 3



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

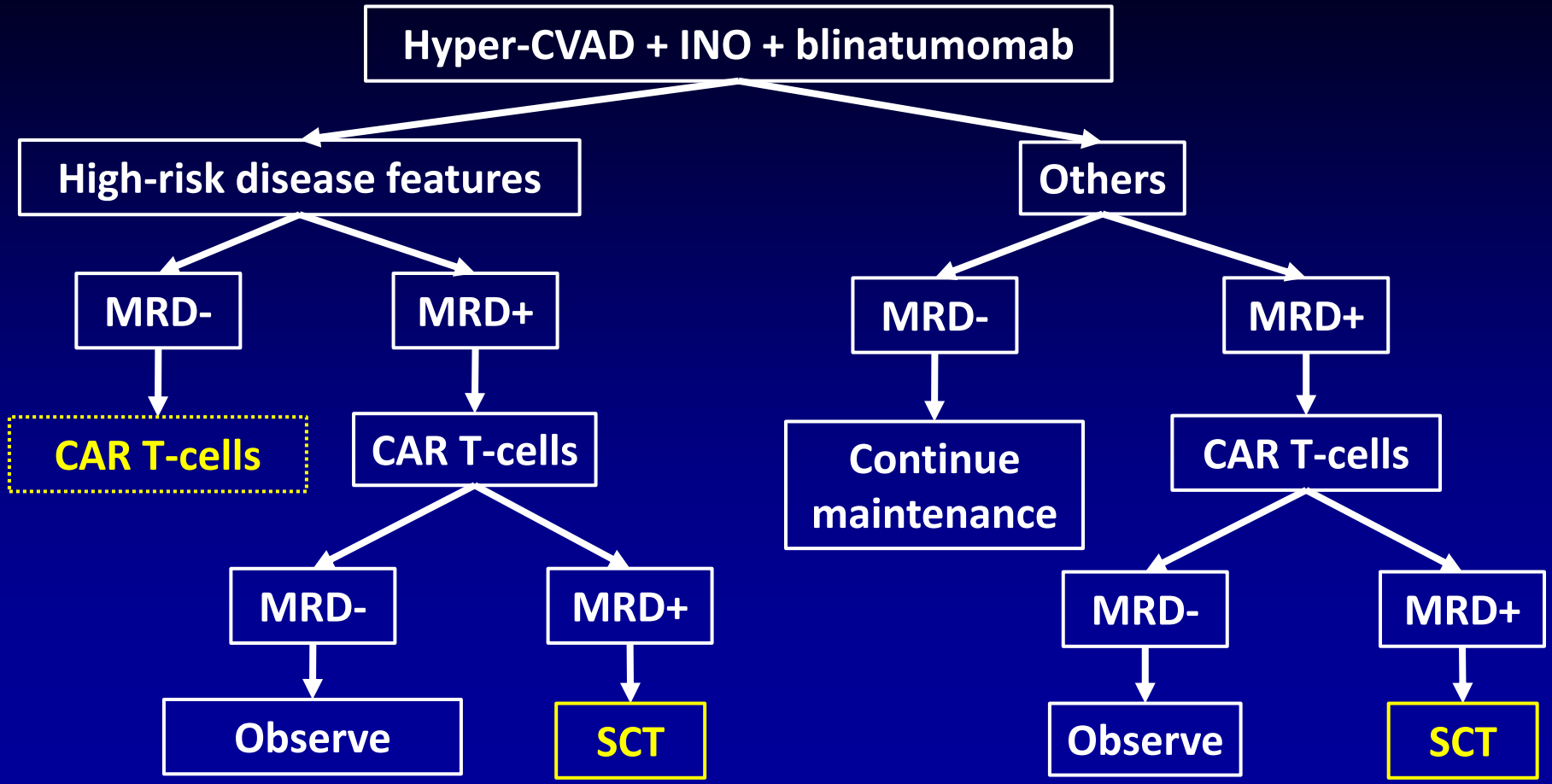
Jabbour E, et al. ASH 2022; Abstract 2732;
NCT04994717. Available at https://clinicaltrials.gov/ct2/show/NCT04994717. Accessed January 2024.

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

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Global Leukemia Academy

AYA patients with ALL :

What is the current treatment approach for this diverse patient population?

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

Roberta Demichelis

APTITUDE HEALTH

Global Leukemia Academy

2024

Adolescent and young adult patients with acute lymphoblastic leukemia

Roberta Demichelis

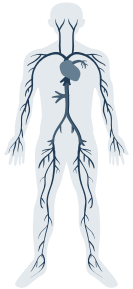
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

México

Disclosures

- Honoraria: AbbVie, Amgen, Bristol, Astellas, Pfizer, Servier, Teva
- Advisory board: Astellas, Chinoin, Pfizer, Servier, Teva

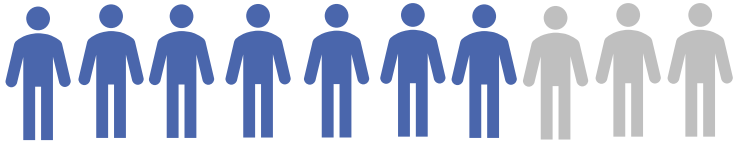
Why is it important to talk about this?

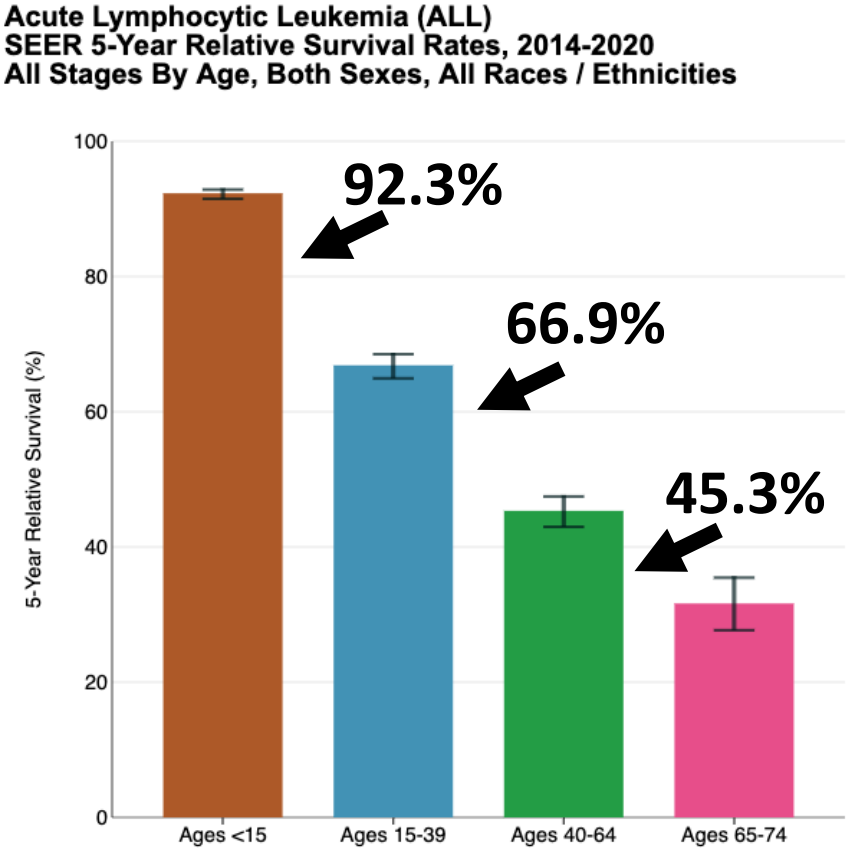


Adolescent and young adults (AYA): 15–39 years

In a large cohort of adults with ALL:

67.3% AYA





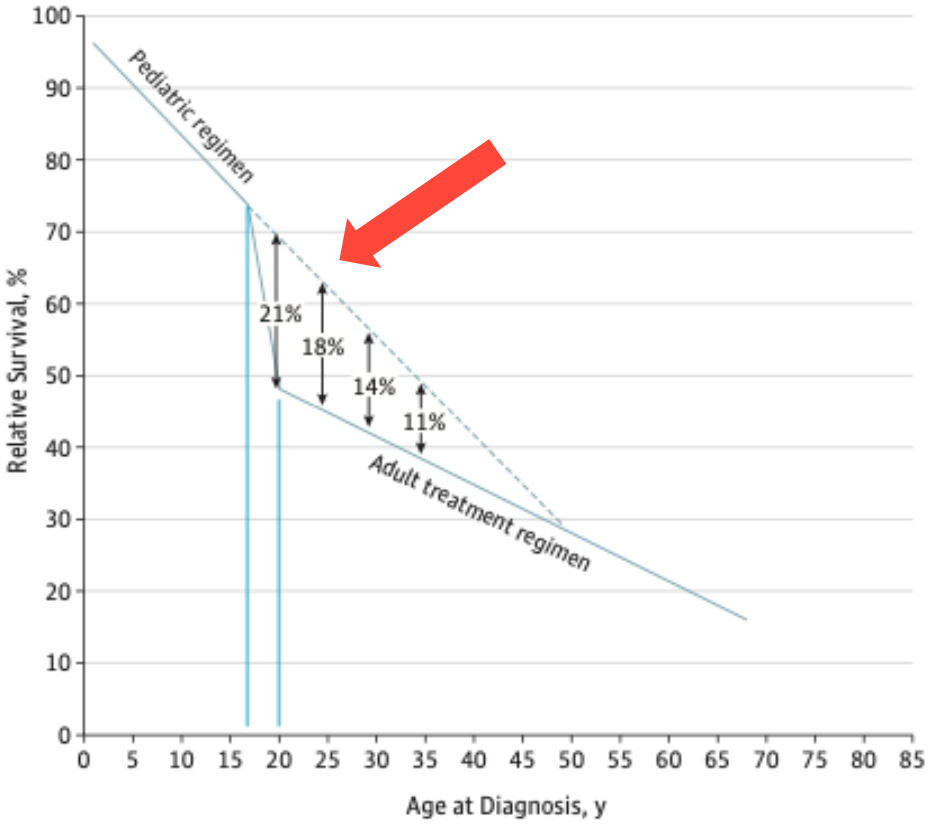
Crespo-Solis E, et al. *Cancer Med.* 2018;7:2423-2433; National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Updated April 17, 2024. https://seer.cancer.gov/explorer/application.html

What is happening?

More high-risk genetics

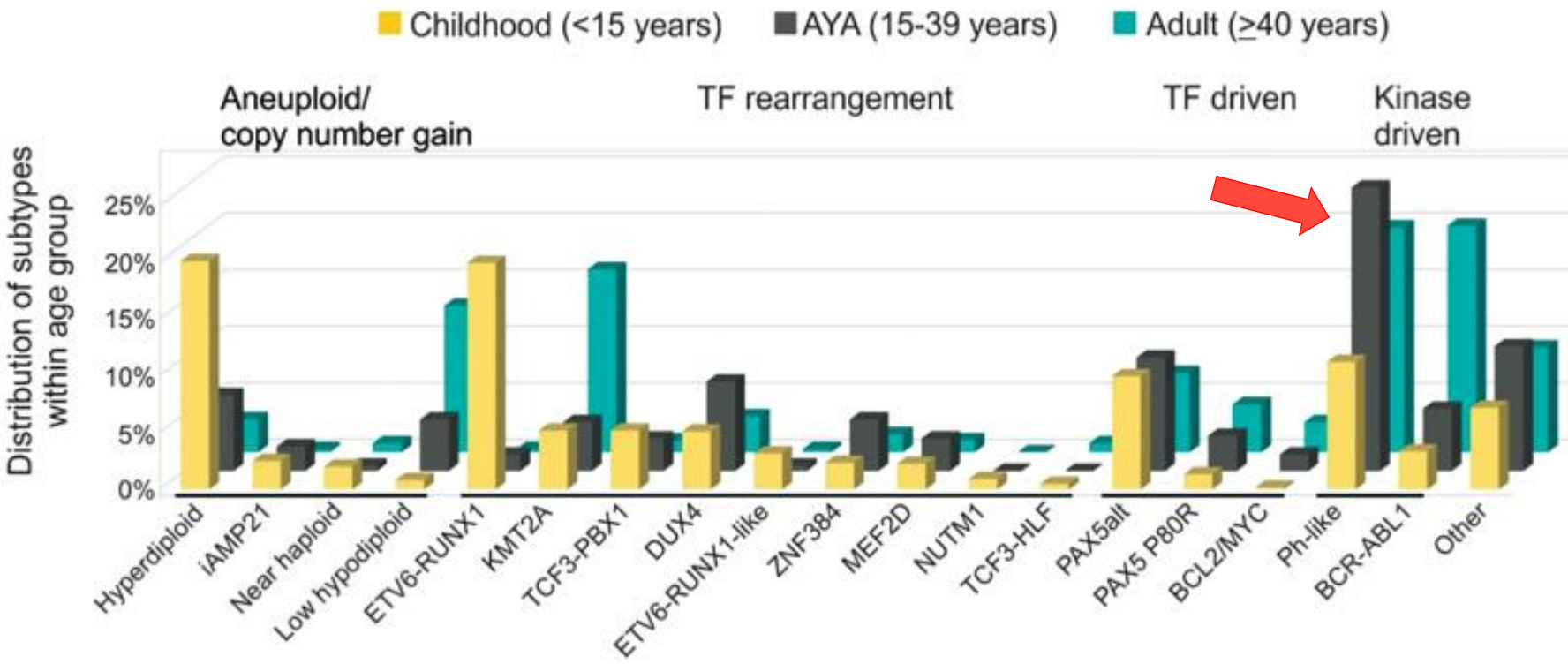
Less tolerance of treatment

Psychosocial factors



Siegel SE, et al. *JAMA Oncol.* 2018;4:725-734.

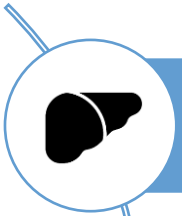
Genetic aberrations in ALL



Roberts KG, et al. *Hematology Am Soc Hematol Educ Program.* 2018;2018:137-145.

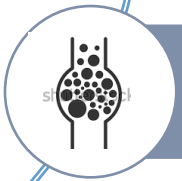
More asparaginase-related toxicity in AYA vs children

Pediatric ALL cohort (up to 20 years)



More grade ≥3 liver toxicity: 45.8% vs 25.6%

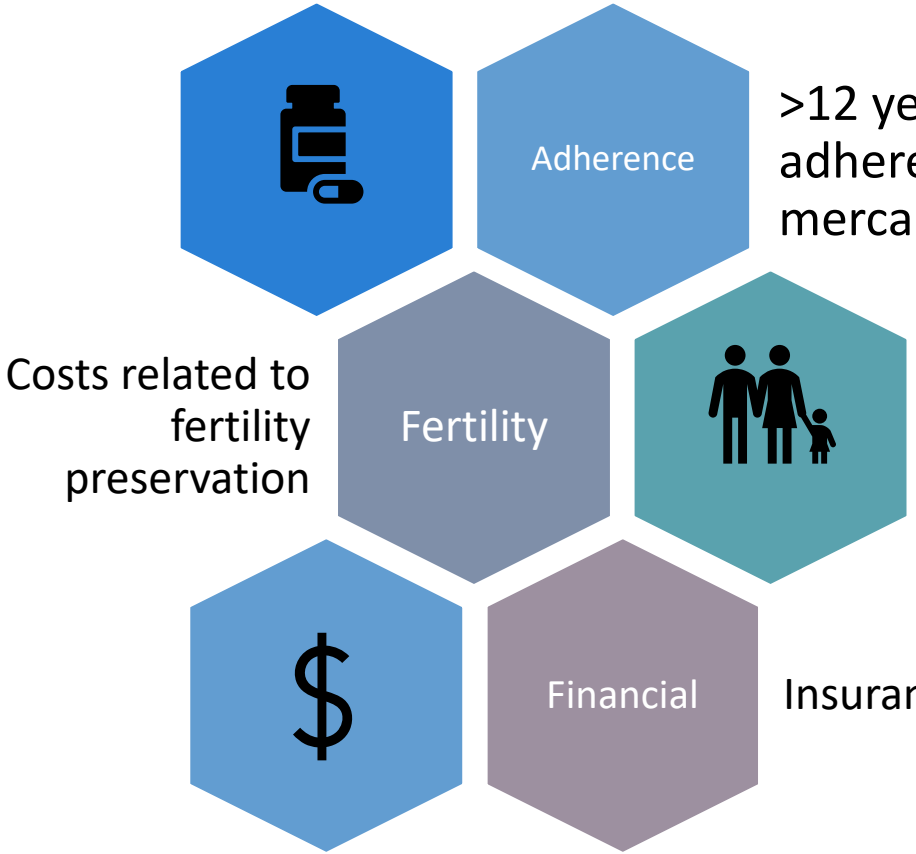
More grade ≥3 hyperglycemia: 27.1% vs 14.8%



More thrombosis: 15.3% vs 6.8%

West ZE, et al. *Leuk Lymphoma.* 2021;62:899-908.

Psychosocial barriers



>12 years: less adherence to 6-mercaptopurine

Costs related to fertility preservation

Insurance

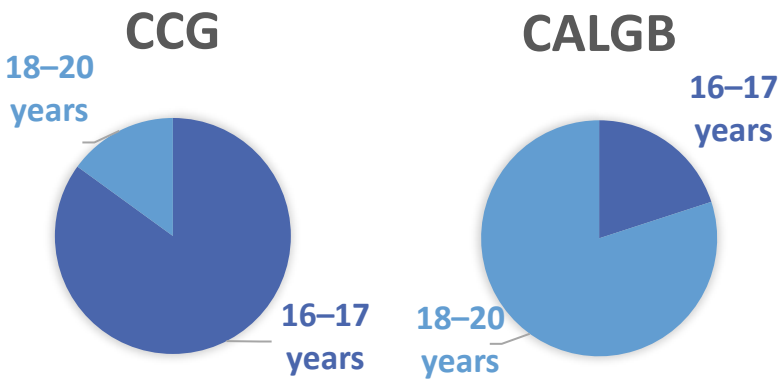
Inclusion in clinical trials

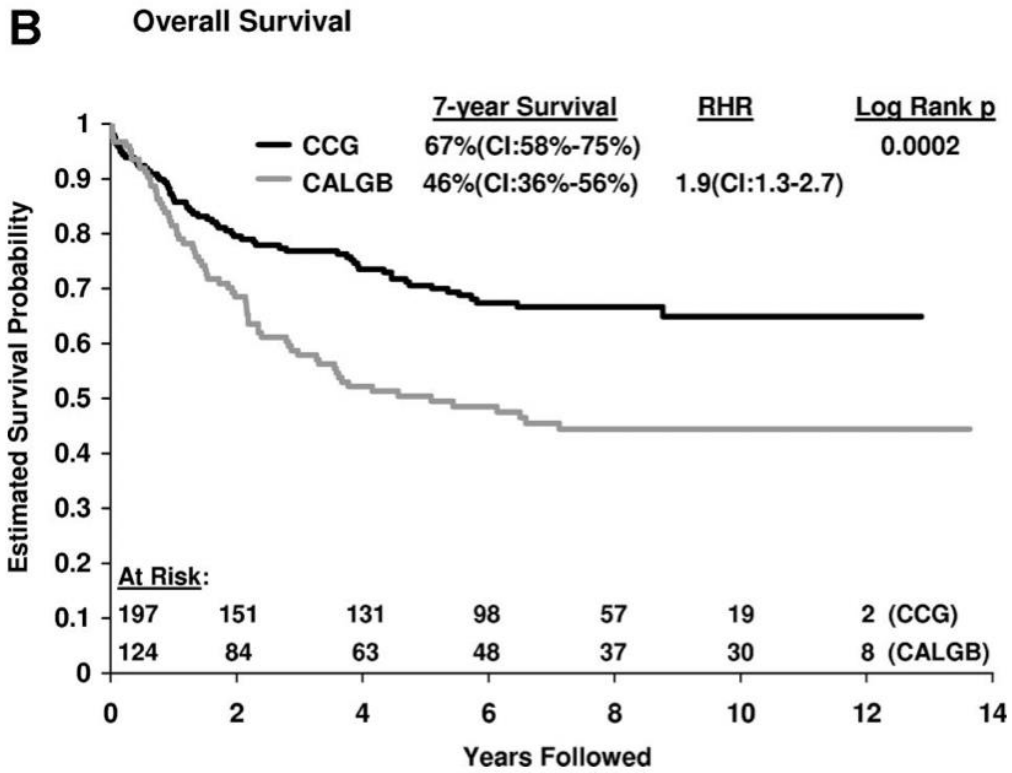
Bhatia S, et al. *J Clin Oncol.* 2012;30:2094-2101.

More than 15 years ago . . .

Retrospective study
CCG vs CALGB

- ✓ Aged 16–20 years
- ✓ Treatment between 1988–2001

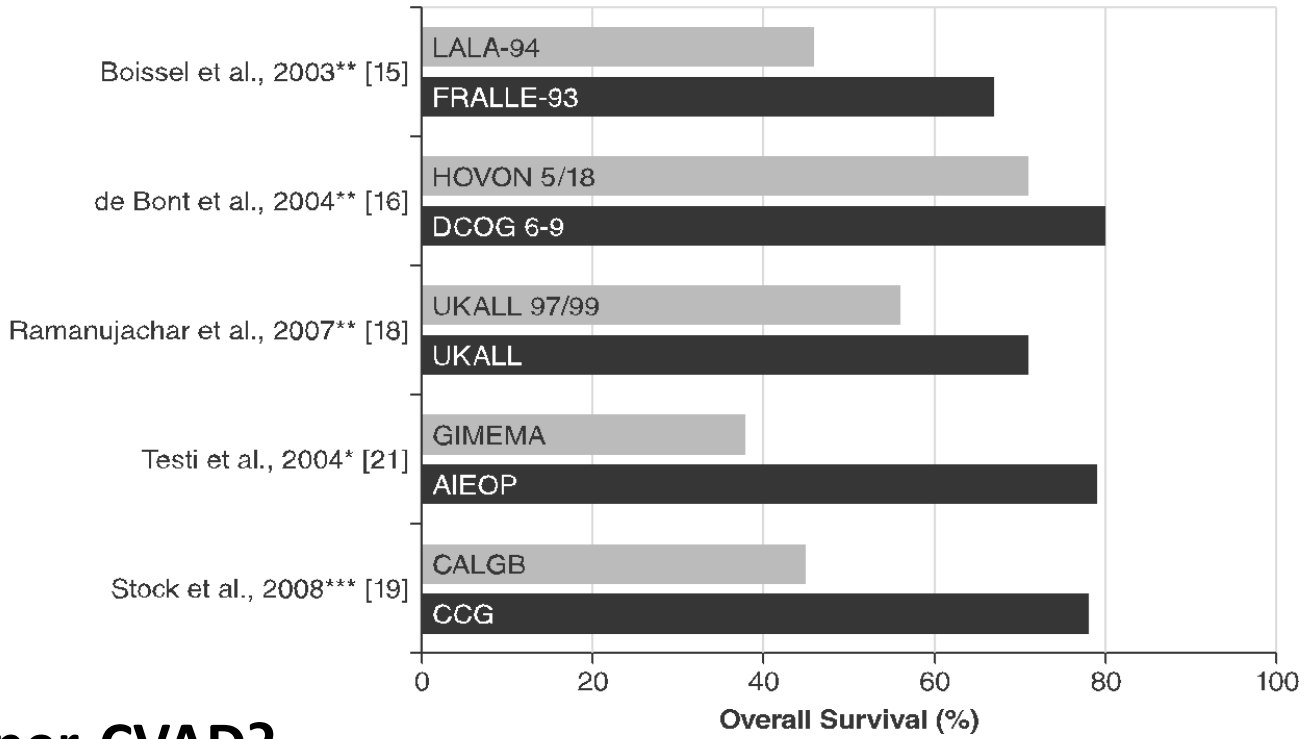




CCG, Children´s Cancer Group; CALGB, Cancer and Leukemia Group B.

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

Retrospective analysis by different groups



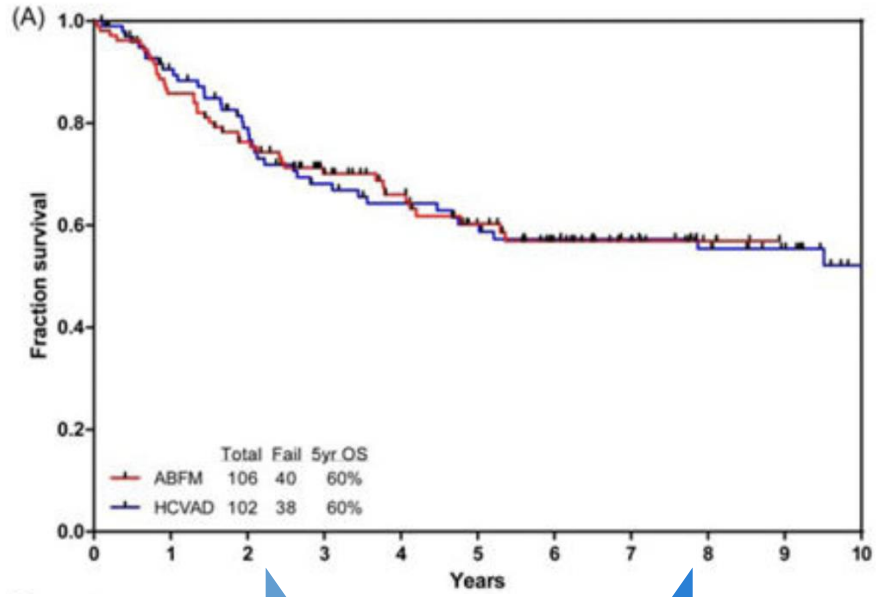
Hyper-CVAD?

Boissel N, Sender LS. *J Adolesc Young Adult Oncol.* 2015;4:118-128.

Hyper-CVAD?

MD Anderson, AYA up to 40 years

- ✓ **Augmented-BFM** (n = 106) vs
- ✓ Historical **Hyper-CVAD** (n = 102)



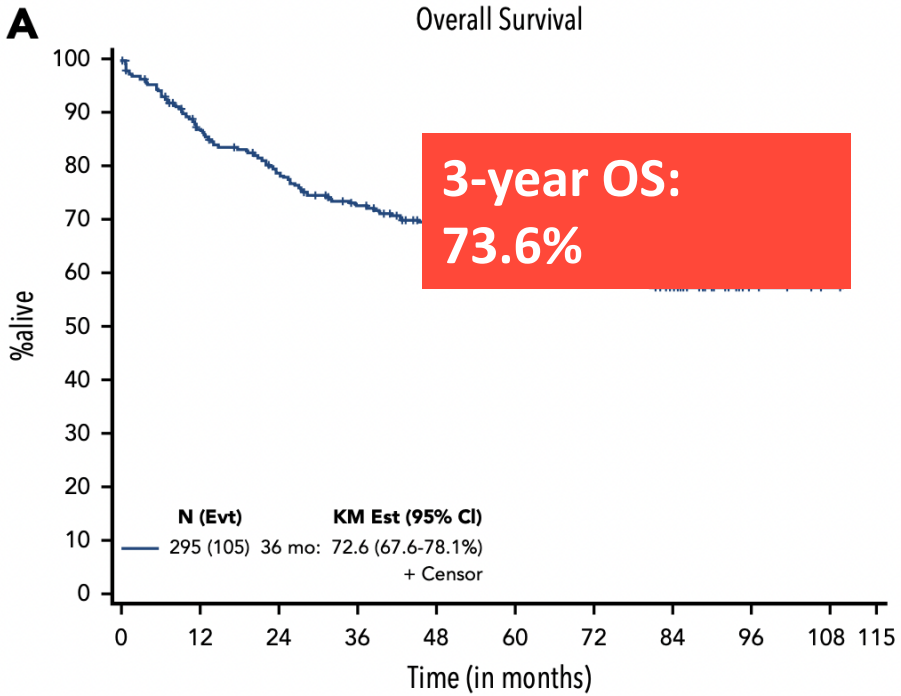
ABFM: liver toxicity, pancreatitis, and thrombosis

Hyper-CVAD: myelosuppression

Rytting ME, et al. *Am J Hematol.* 2016; 91: 819-823.

CALGB 10403: a pediatric regimen for older AYAs with ALL

- **Based on Children's Oncology Group study AALL0232**
- **N = 318**



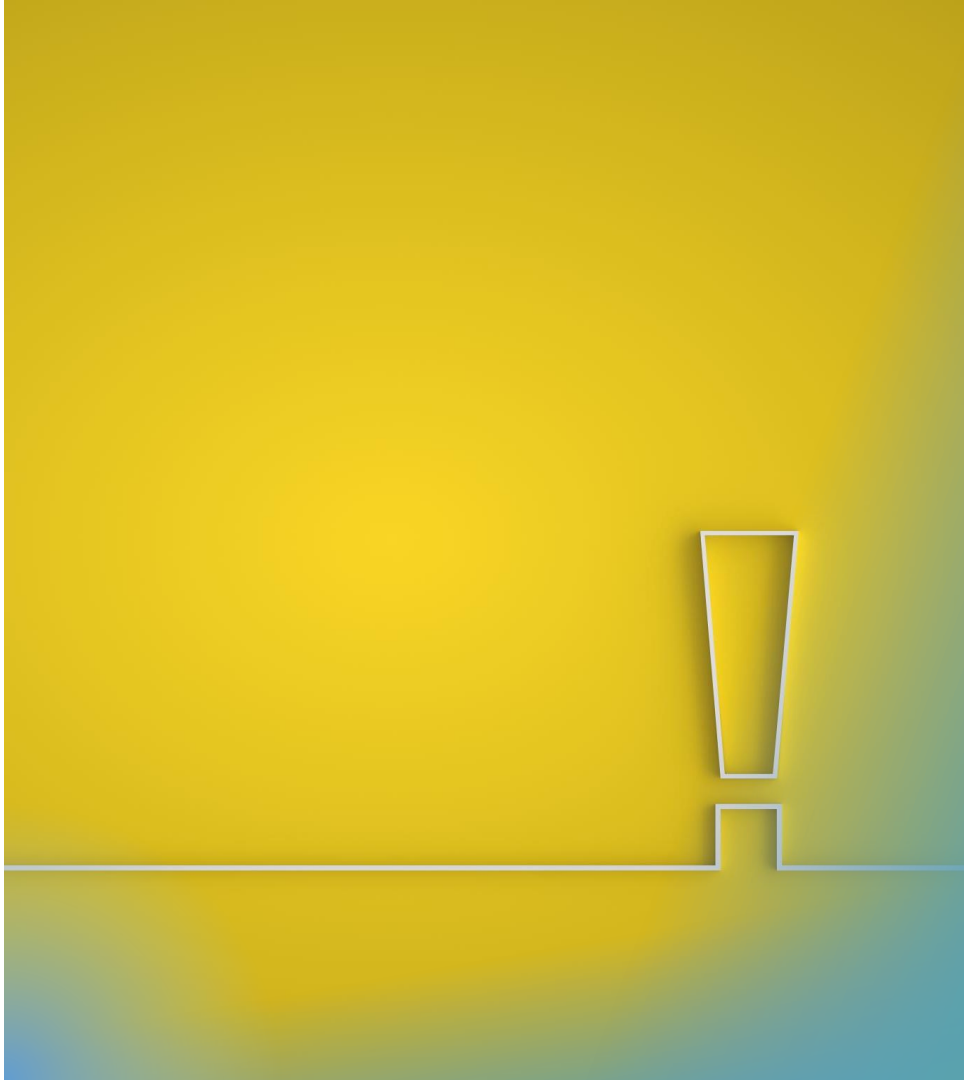
1. **WBC >30**: HR 1.85 (1.14–3.01)
2. **Ph-like**: HR 2.65 (1.51–4.66)
3. **CRLF2**: HR 3.27 (1.80–5.93)
4. **Intermediate-risk cytogenetics**: HR 0.47 (0.24–0.92)
5. **Undetectable MRD**: HR 0.25 (0.10–0.61)

MRD, measurable residual disease.

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

Identified problems/barriers in LATAM?

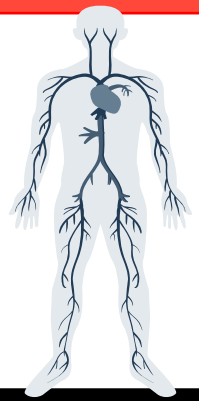
1. A lot of ALL in adults (some countries)
2. Lack of use of pediatric-inspired regimens
3. Treatment-related mortality
4. Poor access to transplant
5. Poor access to novel therapies
6. More high-risk groups



Multicenter retrospective study of adults with ALL in Mexico City (GTLA) 2009–2015

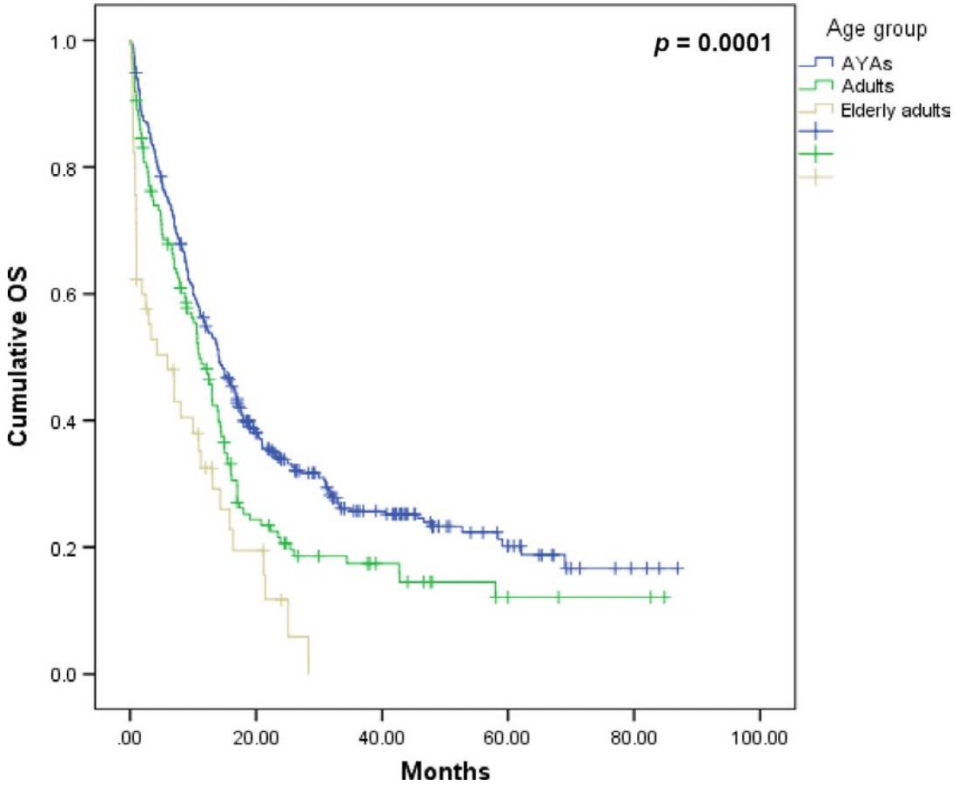
<10% pediatric-inspired regimens

67.3% AYA



3-year OS: 22.1%

AYA: 25.7%



Crespo-Solis E, et al. *Cancer Med.* 2018;7:2423-2433.

Strategy?

1 Identification of the problem

- Predominance of AYA
- Low rate of PIR use
- High infection-related mortality

2 Adaptation of CALGB 10403

3 Standardization of supportive care

Educational program with virtual sessions to discuss clinical cases

A modified CALGB 10403 in AYA with ALL: a multicenter experience in LATAM

1

Study population:

- 14-49 years
- Ph-neg B or T-cell ALL
- January 2017-December 2022

5 centers in Mexico
1 center in Guatemala

3

Safety and efficacy results

N = 95, 23 years (14-49)
45.3% high-risk

IRM: 7.4%

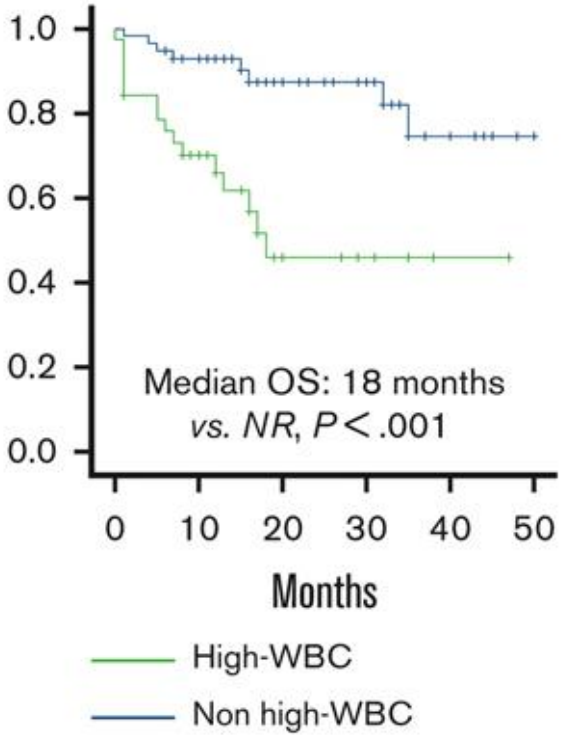
CR 87.8%

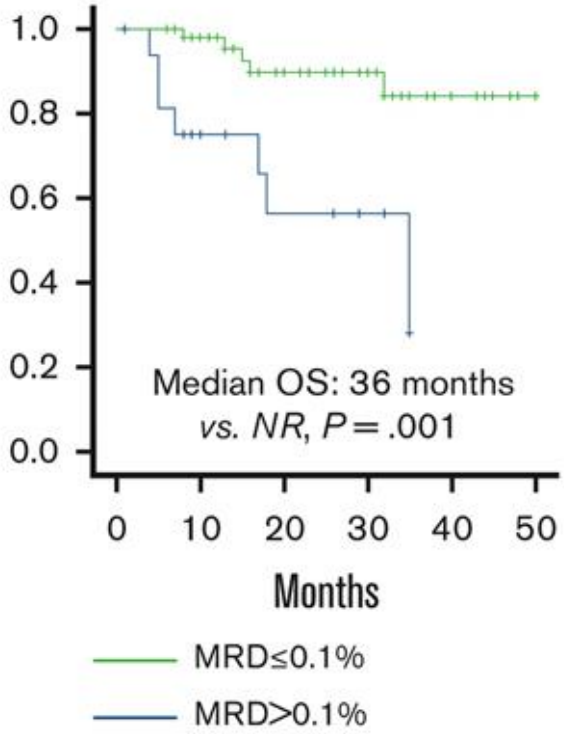
Relapse 28.3%

2-year OS 72.1%

Rangel-Patiño J, et al. *Blood Adv.* 2023;7:5202-5209.

A modified CALGB 10403 in AYA with ALL: a multicenter experience in LATAM





Rangel-Patiño J, et al. *Blood Adv.* 2023;7:5202-5209.

In our experience

Hyper-CVAD

Modified CALGB 10403

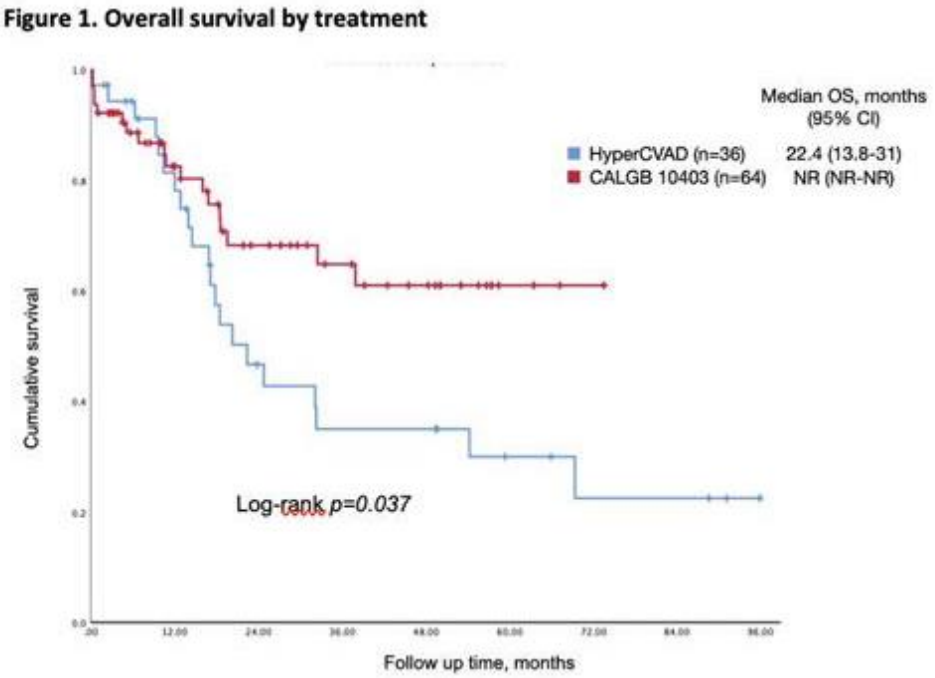
TRM

Relapses

Different toxicity profile

Less TRM

Better RFS and OS



Zalapa J, et al. *Blood*. 2023;142(suppl 1):2833.

Final messages

Email: roberta.demichelisg@incmnsz.mx
Twitter: @RobertaDemiche3

- ALL in AYAs is **common in Mexico and Central America**
  - Importance of local studies
- **AYA: population with special** biological and psychosocial **characteristics**
- Benefit of treatment with **pediatric-inspired regimens**
  - **Feasibility of implementation** in our region
- **Local challenges**
  - **Treatment-associated morbidity and mortality**
  - **Access** to transplantation and novel therapies

Global Leukemia Academy

ALL case-based panel discussion

Roberta Demichelis

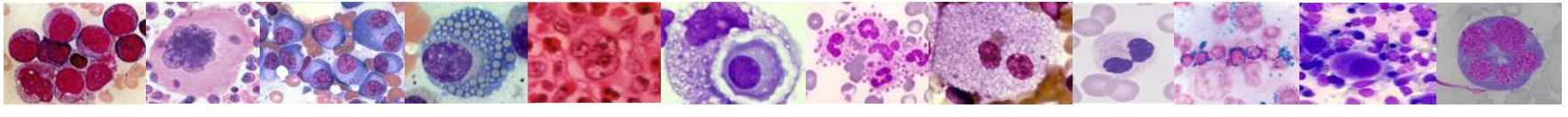
APTITUDE HEALTH®

ALL cases

Fausto A. Rios-Olais

Hematology Fellow

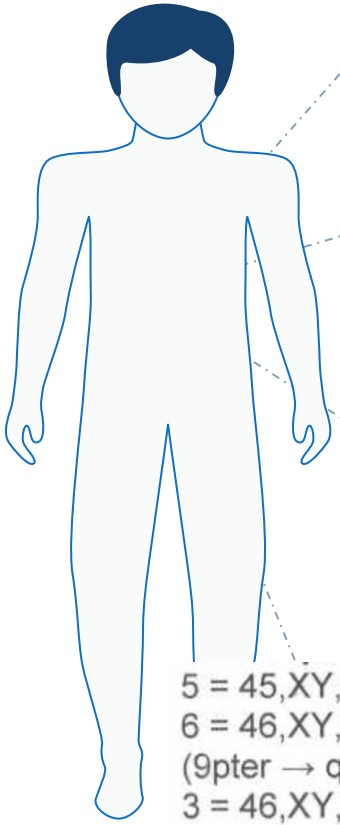
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán



Disclosures

Nothing to disclose

Case 1: Adult Ph-positive B-ALL



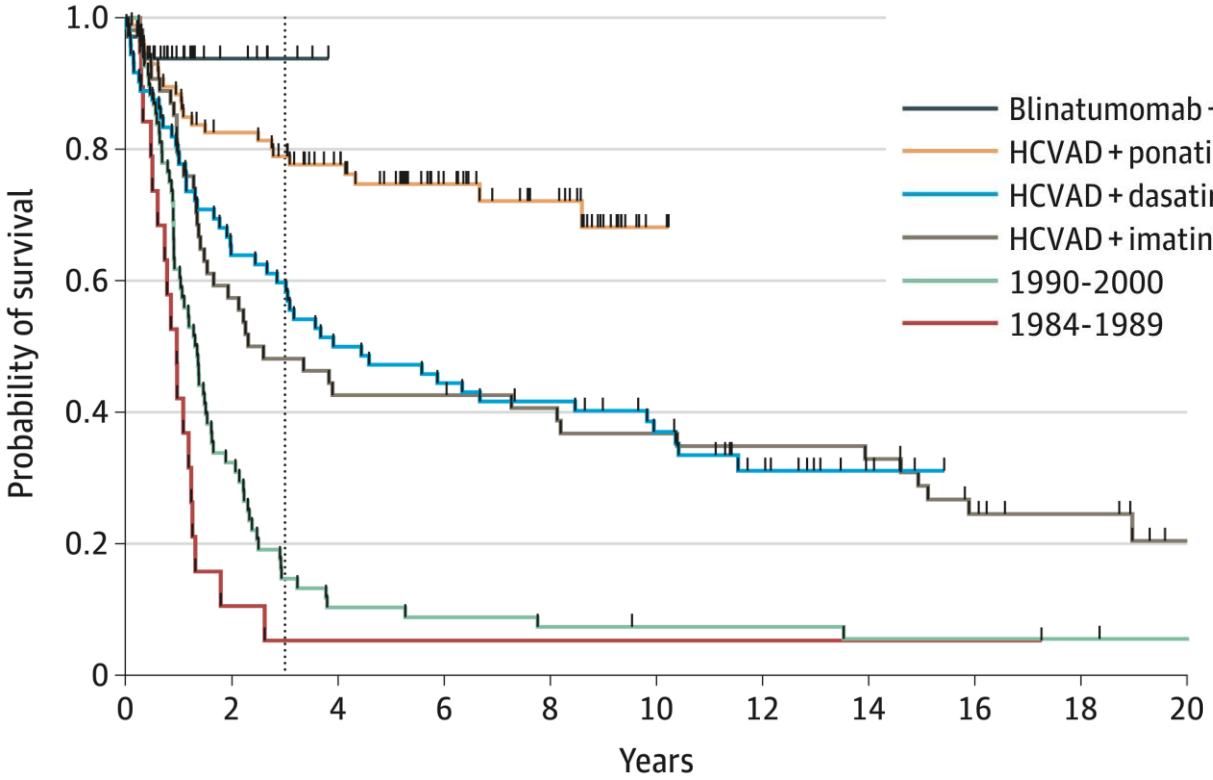
September 2023
60-year-old male
PMH: hypothyroidism
MFC 88% blasts
CD34, CD10, CD19, CD22
CD20 20%
RT-PCR *BCR::ABL* 100%
High-risk cytogenetics (complex karyotype)
ECOG 1

Parameter	Value
Hemoglobin	5.8 g/dL
WBC	32.0×10^9/L
Blasts	**56%**
Platelets	38×10^9/L

Ph-positive CD20-positive B-cell ALL Adult

5 = 45,XY,t(2;12)(p21;q21),del(5)(q13q15),del(6)(q21q23),-7,t(9;22)(q34;q11.2),del(19)(q13.33)
6 = 46,XY,der(1) t(9;22;1)(q34;q11.2;q23),t(2;12)(p21;q21),del(6)(q21q23),der(9)
(9pter → q22::?::1q23→1qter),der(16),del(19)(q13,33),add(20)(q13.1),add(22)(q13.1)
3 = 46,XY,t(2;12)(p21;q21),del(6)(q21q23),t(9;22)(q34;q11.2),del(19)(q13.33)
6 = 46,XY

Survival of Ph-positive B-ALL according to treatment



	3-y survival, %
Blinatumomab + ponatinib (Jun 2018-Jan 2022)	94
HCVAD + ponatinib (Nov 2011-May 2019)	79
HCVAD + dasatinib (Sep 2006-Mar 2012)	60
HCVAD + imatinib (Apr 2001-Sep 2006)	48
1990-2000	15
1984-1989	5

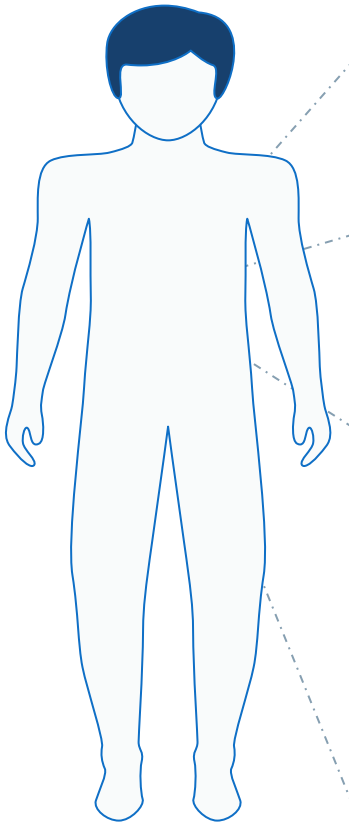
Jabbour E, et al. *JAMA Oncol.* 2022;8:1340-1348.

Problems identified in Latin America

- **Access to second- and third-generation TKIs**
  - Brazil: n = 123 Ph-positive B-ALL, imatinib as first-line TKI in 97%
  - Mexico: n = 119 Ph-positive B-ALL, imatinib as first-line TKI in 79%
- **Access to chemotherapy-free regimens**
- **Early mortality** (5.8%–14.6%)

Silva WF, et al. *Leuk Res.* 2021;110:106666; Rodriguez-Rodriguez S, et al. *Blood.* 2023;142(suppl 1):4204.

Case 1: Adult Ph-positive CD20-positive B-ALL



Treatment with Hyper-CVAD and imatinib

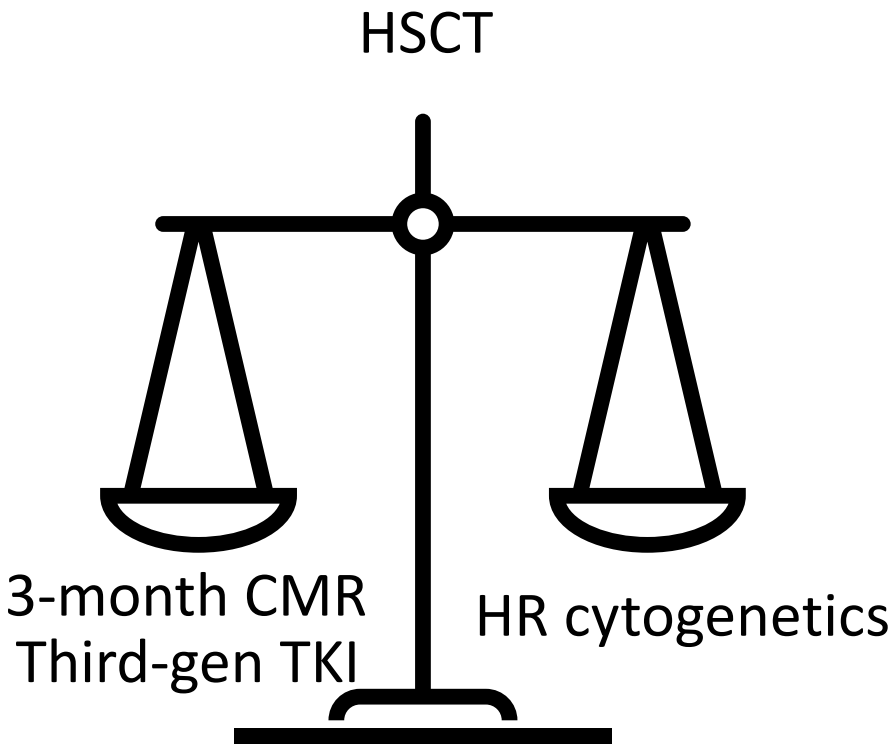
Febrile neutropenia
LP: CNS 0

Day 28 BMA: no blasts
MRD by MFC 1.6%
RT-PCR *BCR::ABL* 1.9%

- Completed 6 phases of intensive chemotherapy with Hyper-CVAD and imatinib
- 4 episodes of febrile neutropenia
- 3-month BM RT-PCR *BCR::ABL* 0% (MR4)
- No siblings; 3 haploidentical daughters

Transplant in 1 CR?

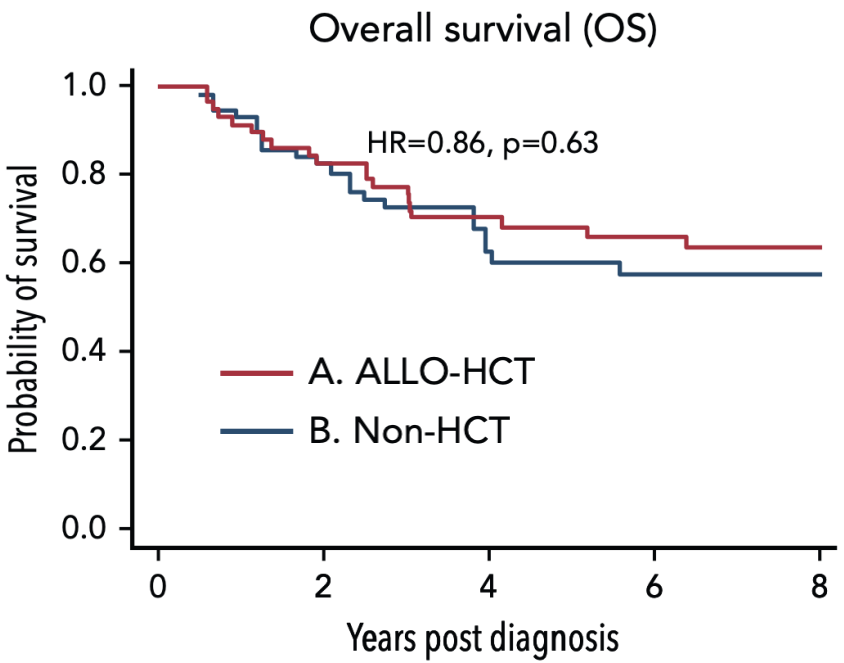
- **3-month CMR** is a strong independent prognostic factor for OS and RFS
- HSCT in 1 CR may not be beneficial in this subgroup of patients with deep responses
- High-risk subset? Ponatinib vs other TKI-treated patients?



Sasaki K, et al. *Cancer*. 2021;127:2648-2656; Ghobadi A, et al. *Blood*. 2022;140:2101-2112.

Transplant in 1 CR?

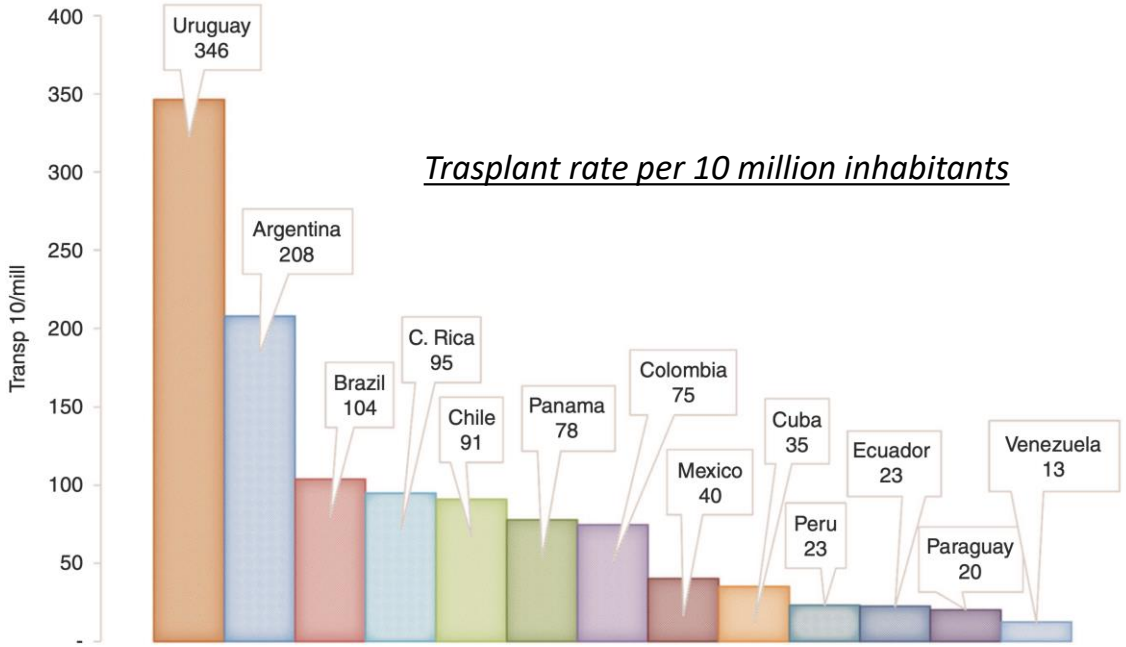
- **116 propensity score-matched patients with Ph-positive B-ALL with a 3-month CMR**
  - Number 1 TKI was dasatinib, followed by imatinib
  - 46% with additional cytogenetic changes
  - No difference between OS and RFS
  - Higher 5-year CIR in non-HCT (36% vs 16%)
  - Higher 5-year NRM in HCT (21% vs 11%)



Sasaki K, et al. *Cancer*. 2021;127:2648-2656; Ghobadi A, et al. *Blood*. 2022;140:2101-2112.

Challenges in Latin America

- **Low transplant rate across many countries**



Trasplant rate per 10 million inhabitants

Brazil: n = 123 Ph-positive B-ALL, HSCT in CR1 of 28.8%
Mexico: n = 119 Ph-positive B-ALL, HSCT in CR1 of 11.8%

Jaimovich G, et al. *Bone Marrow Transplant.* 2021;56:2382-2388; Silva WF, et al. *Leuk Res.* 2021;110:106666; Rodriguez-Rodriguez S, et al. *Blood* 2023;142(suppl 1):4204.

Discussion

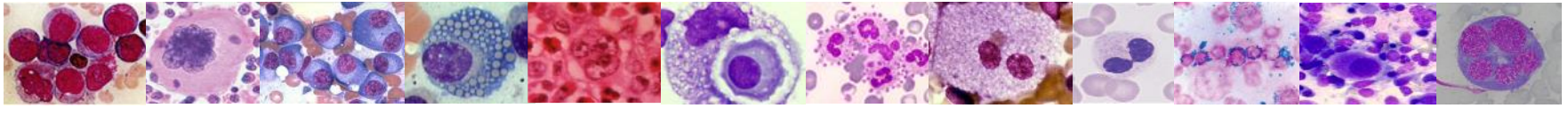
- Rituximab added to standard chemotherapy with a TKI in Ph-positive CD20-positive B-ALL
- Impact of additional chromosomal abnormalities and/or complex karyotype in prognosis and treatment decisions in Ph-positive B-ALL
- TKI treatment after SCT: how long is enough?


INSTITUTO NACIONAL DE

ALL cases

Jessica Zalapa

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

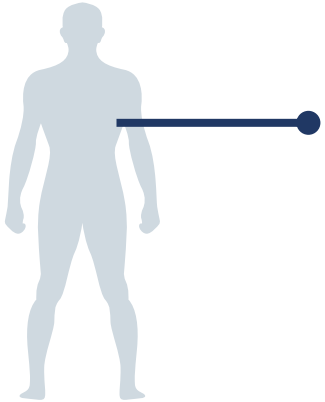


Disclosures

- Nothing to disclose

Clinical Case 2: AYA

Clinical case 2: AYA



35-year-old man

Comorbidities:
- Diabetes, diagnosed 3 months earlier

Fatigue and intermittent fever

August 2021

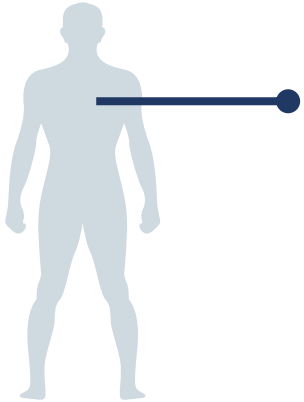
Weight loss of 4 kg, CBC: **19 × 10³** WBC

September 2021

Parameter	Value
Hemoglobin	11.7 g/dL
WBC	2.1 × 10^3
Blasts	2%
Platelets	309 × 10^3
LDH	99 UI
Triglycerides	681 mg/dL

Bone marrow aspirate + immunophenotype

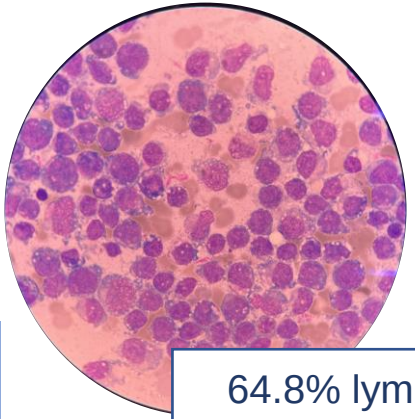
Clinical case 2: AYA



35-year-old man

Bone marrow aspirate + immunophenotype

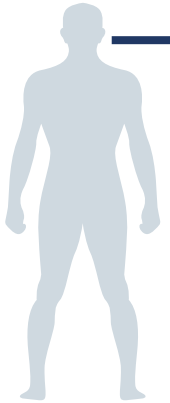
- **Karyotype:** 46, XY
- **FISH:** 11q23 and t(9;22) negative
- **PCR *BCR::ABL***: negative



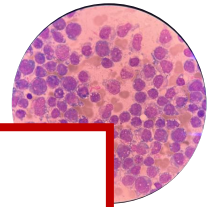
64.8% lymphoblasts
IF: CD45wk, CD34+, CD10+, CD19+, CD20+

B-cell acute lymphoblastic leukemia

Clinical case 2: AYA



AYA patient



Ph-negative, B-cell ALL

1. Best frontline treatment?

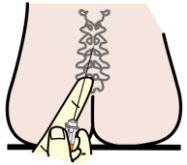
Clinical case 2: AYA

Pre-chemotherapy assessment:

- **TTE:** normal EF
- **FibroScan:** F0S3
- HIV and chronic hepatitis **viruses: negative**

Clinical case 2: AYA

m-CALGB 10403



+11 (Sep 18, 2021)
Headache and motor seizures of focal onset in the left pelvic limb, followed by bilateral clonic movements

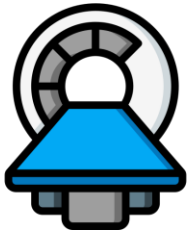
Sep 8, 2021

+9 (Sep 16, 2021)
Fibrinogen 91 mg/dL

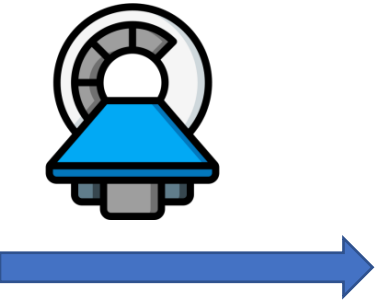
To prepare lumbar puncture:
- Cryoprecipitate transfusion
- Thromboprophylaxis was suspended

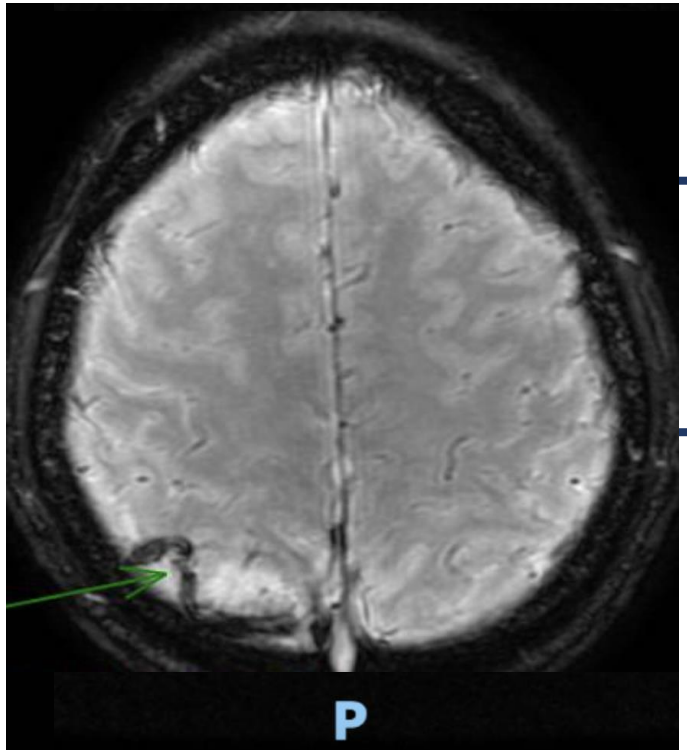
+10 (Sep 17, 2021)
Fibrinogen **170** mg/dL, platelets 124 × 10^3

Lumbar puncture; traumatic



Clinical case 2: AYA





Right cortical vein thrombosis

Anticoagulation with LMWH was started

- Testing for antiphospholipid antibody syndrome was negative
- Factor V Leiden, antithrombin III, and other causes of hereditary thrombophilia were ruled out

Clinical case 2: AYA

Anticoagulation with LMWH, with appropiate levels of heparin activity, no bleeding

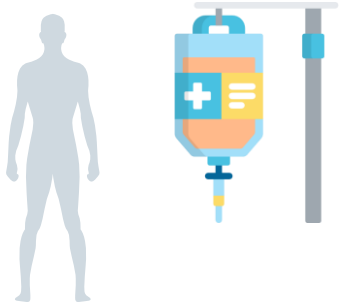
Remission of headache,
without new events of seizures

Questions for the audience

Would it be feasible for the patient to continue with an asparaginase-based regimen?

- Yes
- No

Clinical case 2: AYA



Modified-CALGB 10403

The remaining doses of L-aspar were administered at day 16

Remission consolidation

EMR <0.01%

Interim Maintenance

Asparaginase-related grade 2 adverse event

Day 28 BMA: no blasts; MRD by flow cytometry <0.01

Maintenance

#22 MRD <0.01%

Ended in April 2024

Last follow-up (Jun 4, 2024): no relapse; without neurologic symptoms.

Questions for the audience

- How to manage asparaginase-associated hypofibrinogenemia?
- Which are the main risk factors for asparaginase-associated thrombosis?
- When to restart asparaginase administration after associated thrombosis?
- Contraindications to resume asparaginase administration?
- Finally . . . what about thromboprophylaxis?

Global Leukemia Academy

BREAK

APTITUDE HEALTH®

Global Leukemia Academy

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

Naval Daver

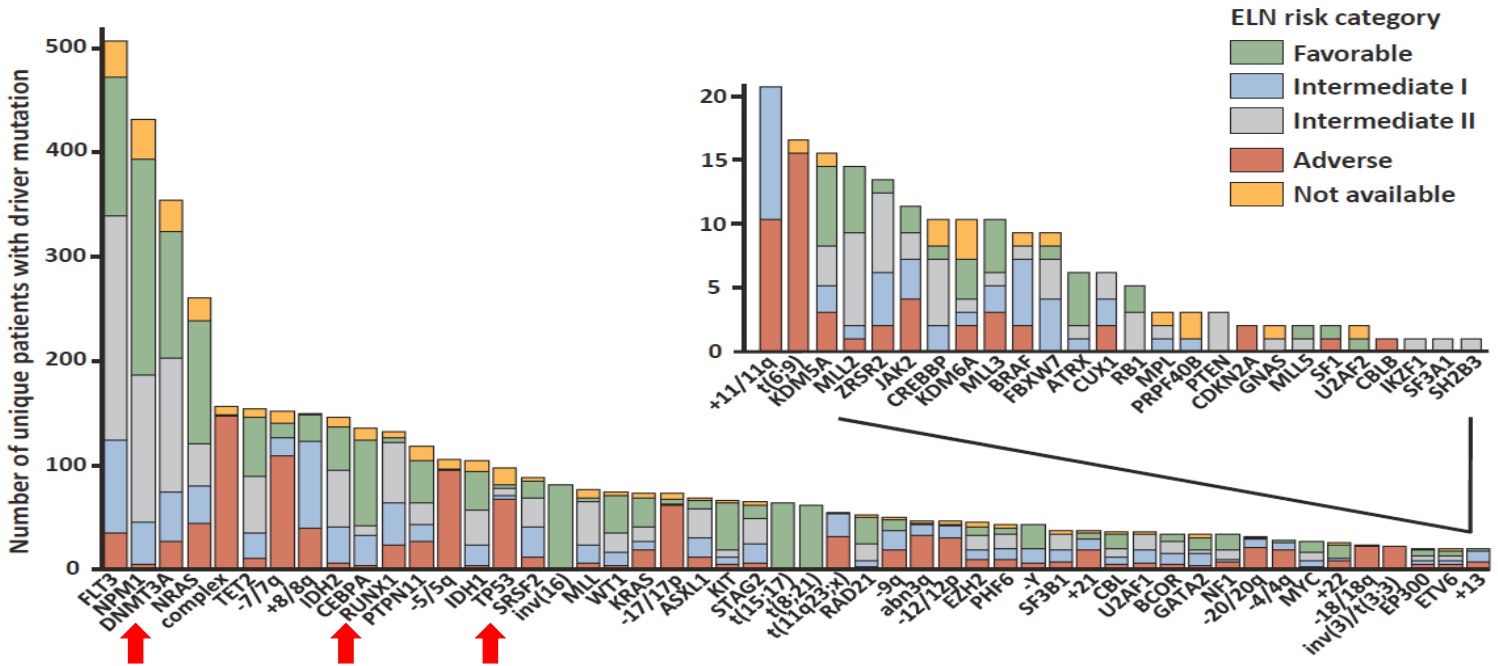
APTITUDE HEALTH®

Optimizing the Incorporation of Targeted Therapies in the Treatment of AML

GLA LATAM 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

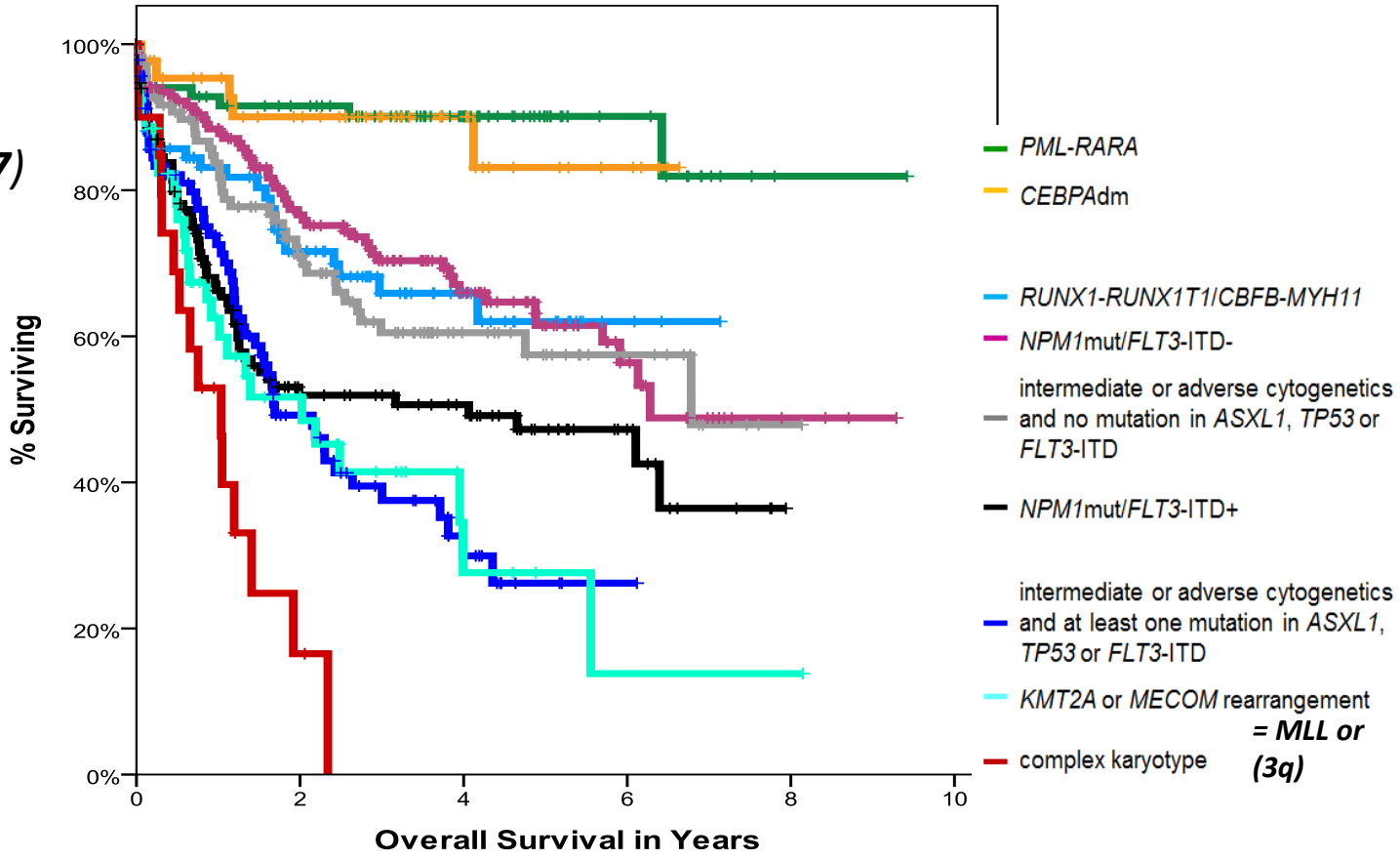
APL:

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.

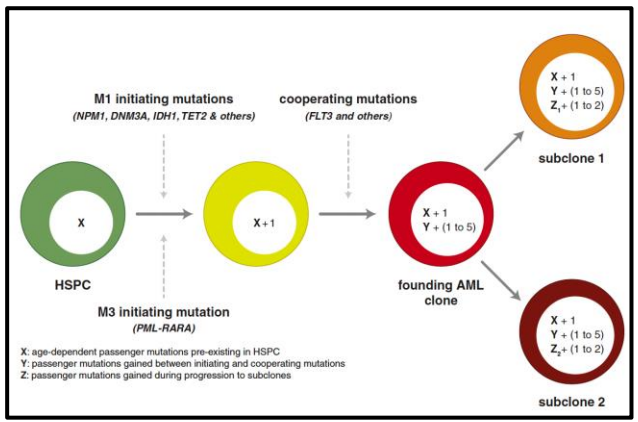
Using genomics to improve AML therapy

- ***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**

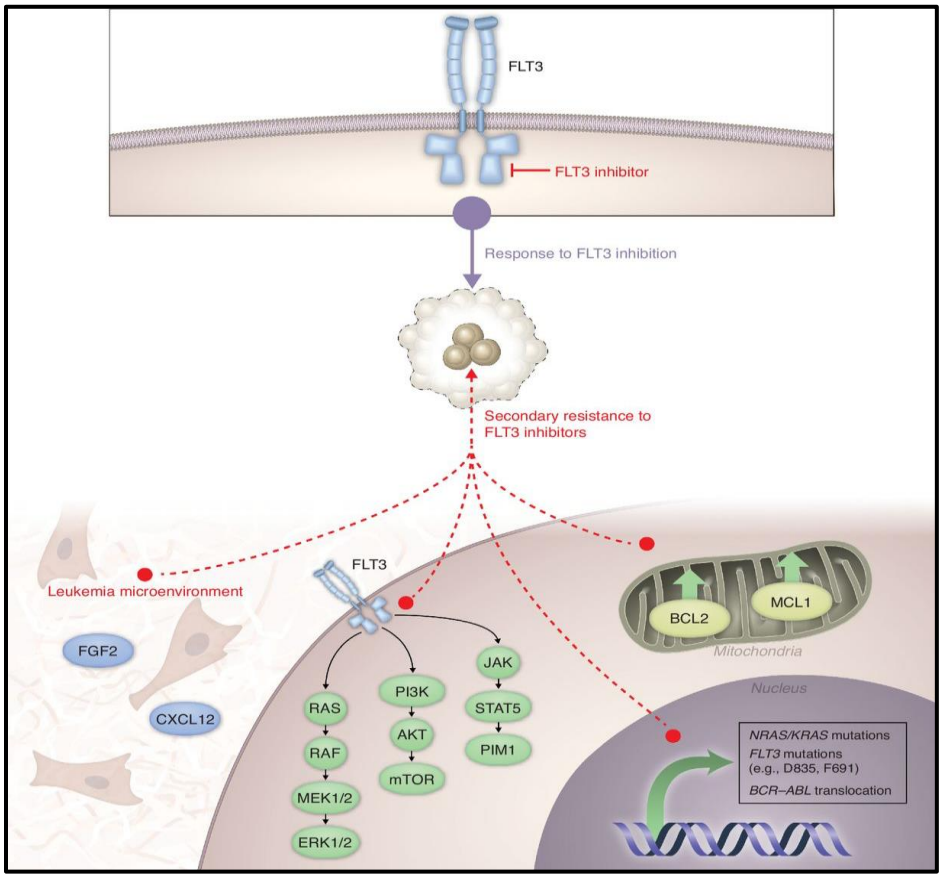
1. Targeting *FLT3* Mutations

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



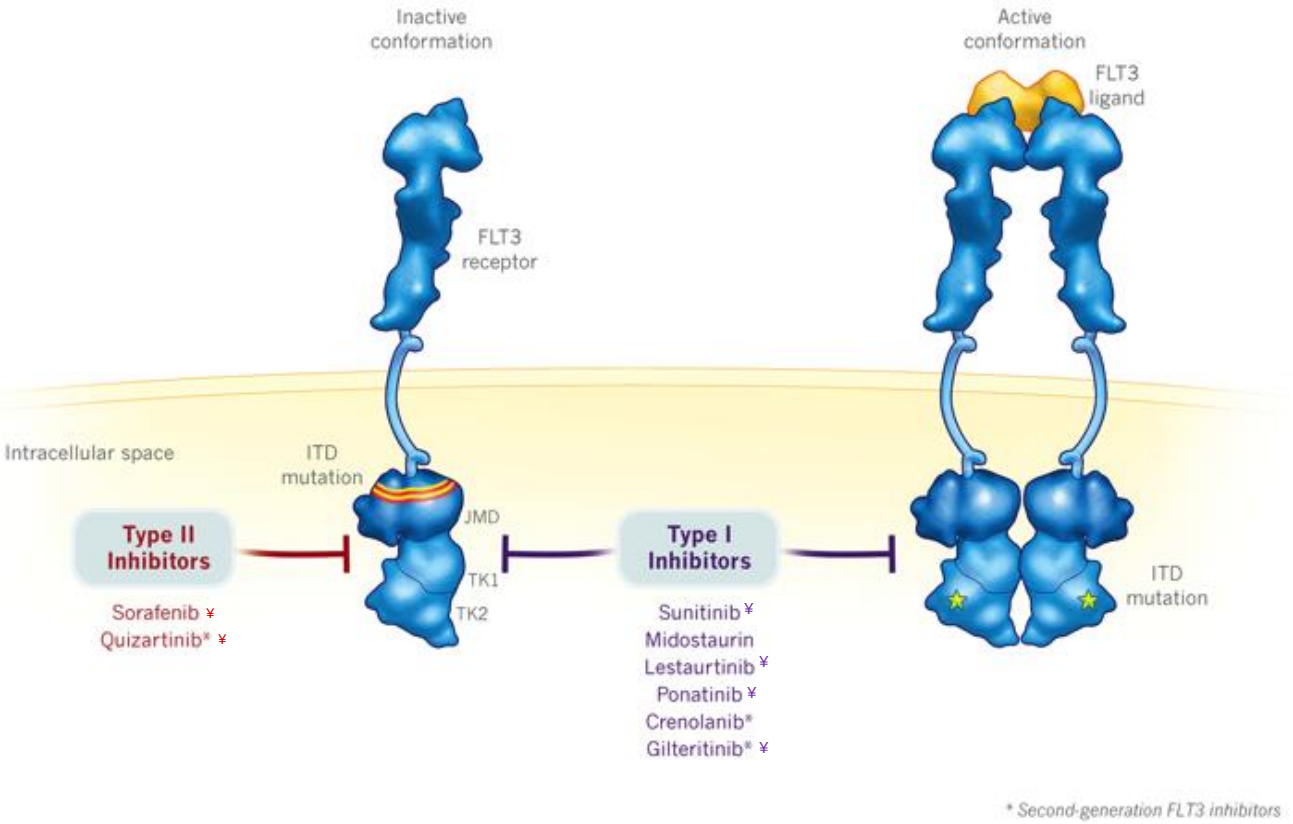
FLT3-ITD
NPM1
DNMT3A
WT1



- *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

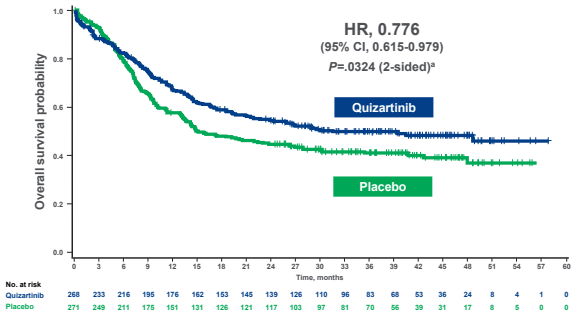
Type 1: Bind receptor "active" conformation near ATP pocket or activation loop: ITD and TKD
Type 2: Bind receptor "inactive" conformation near ATP pocket – ITD only

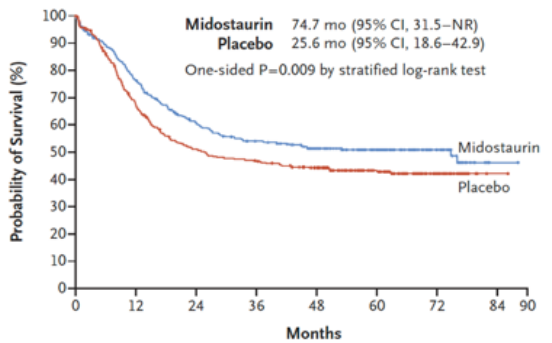


Daver N et al, Leukemia. 2019 Feb;33(2):299-312

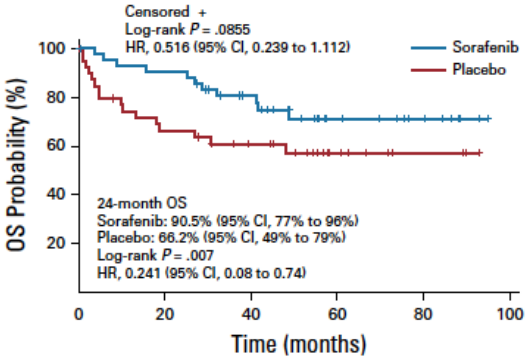
FLT3 inhibition improves survival in fit patients across the treatment spectrum

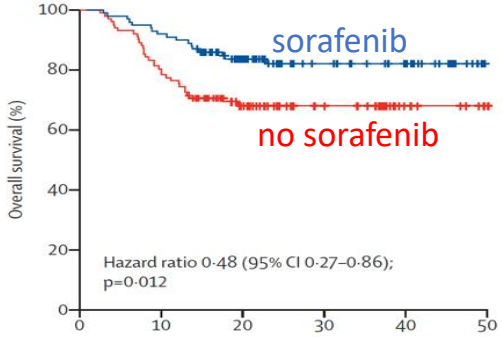
Newly diagnosed, intensive chemotherapy + TKI/placebo



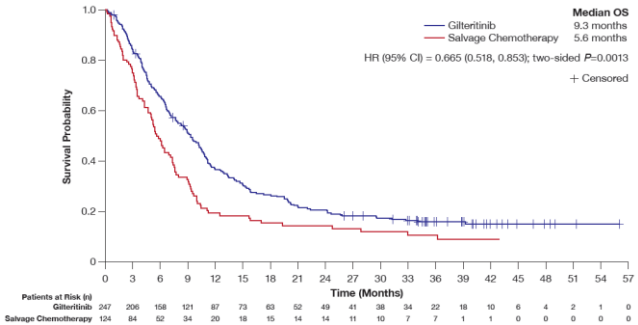


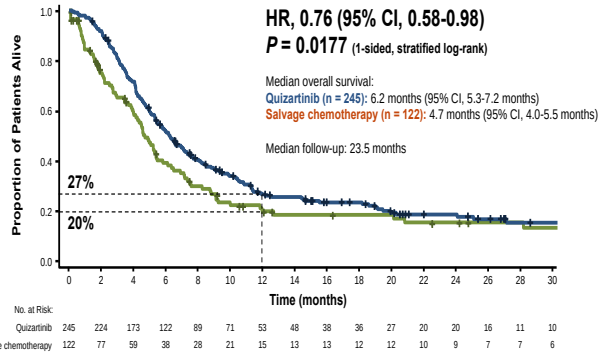
TKI maintenance after alloHSCT (sorafenib 2 studies)





Relapsed/Refractory single agent TKI vs chemotherapy

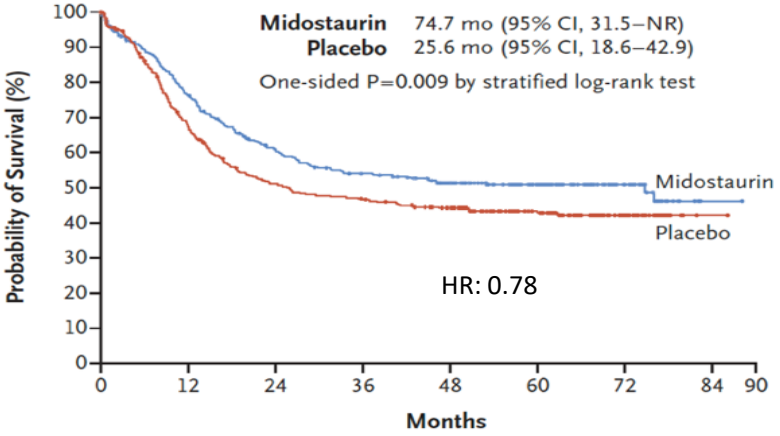




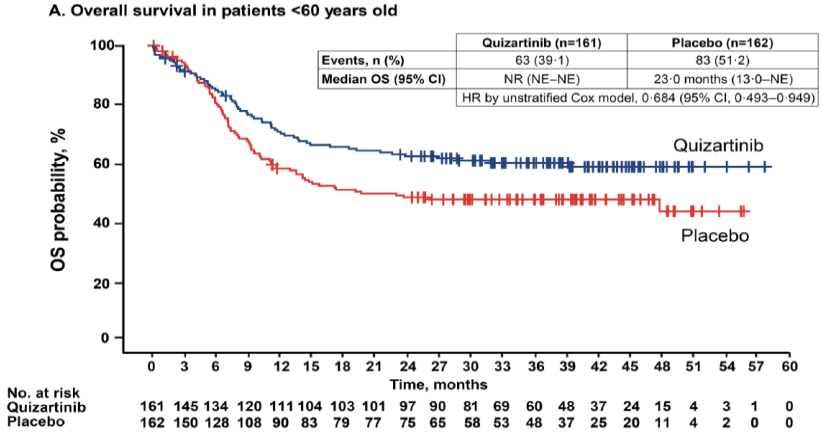
Erba HP, et al. EHA 2022, abstract S100;Stone RM, et al. N Engl J Med. 2017;377(5):454-464; Burchert A, et al. J Clin Oncol. 2020;38(26):2993-3002; Xuan Y, et al. Lancet Oncol. 2020;21(9):1201-1212; Perl AE, et al. Blood. 2022;139(23):3366-3375; Cortes JE, et al. Lancet Oncol. 2019;20(7):984-997.

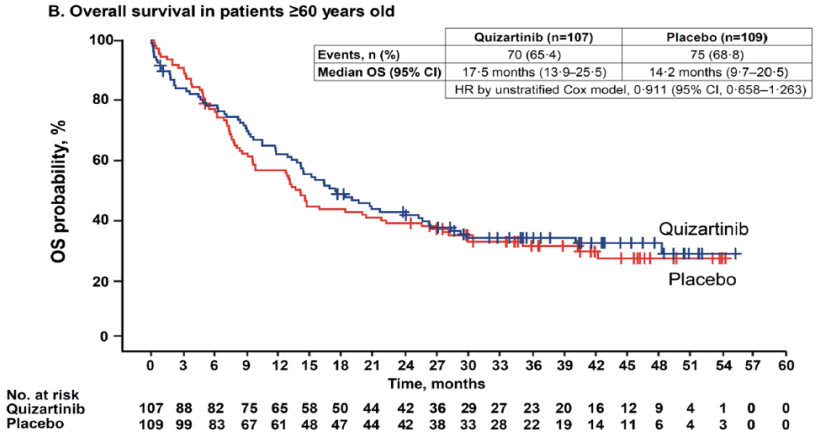
Younger patients (<60 years) particularly benefit from quizartinib

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%

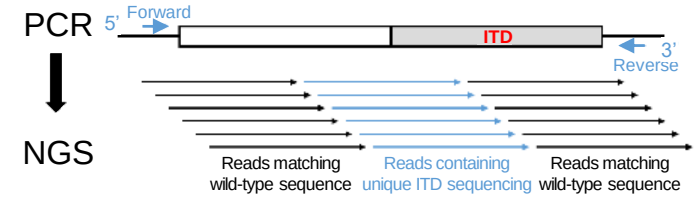


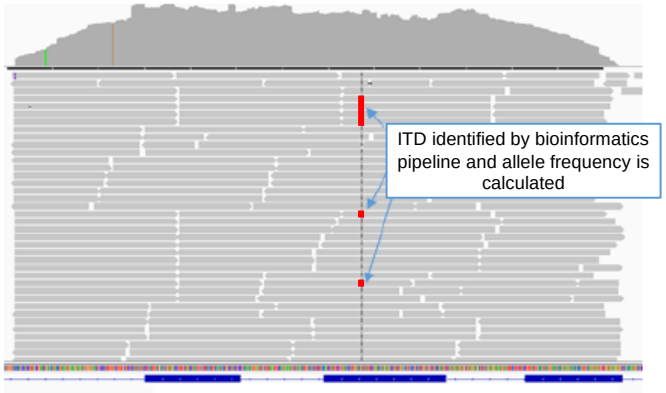


Measurable residual disease (MRD) and QuANTUM-First

- 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

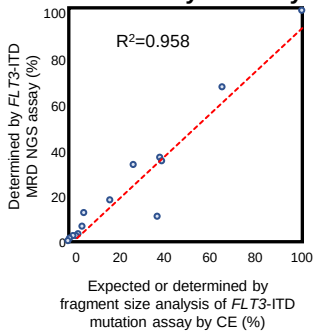
Schema for *FLT3*-ITD MRD Assay





Ultra-deep sequencing of the region (Illumina SBS)

MRD Assay Linearity

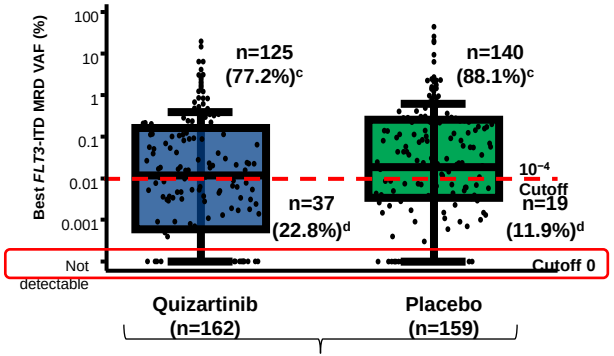


AML, acute myeloid leukemia; CE, capillary electrophoresis; CR, complete remission; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITD, internal tandem duplication; LLOD, lower limit of detection; LLOQ, lower limit of quantification; MRD, measurable 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.

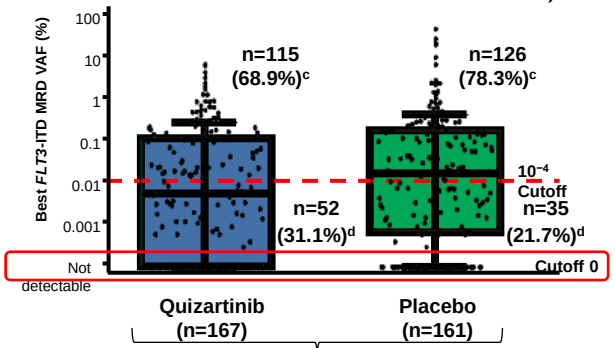
Across the treatment course, quizartinib leads to deeper responses and more frequently eliminates detectable MRD than placebo

CRc After Induction
(1 or 2 cycles)



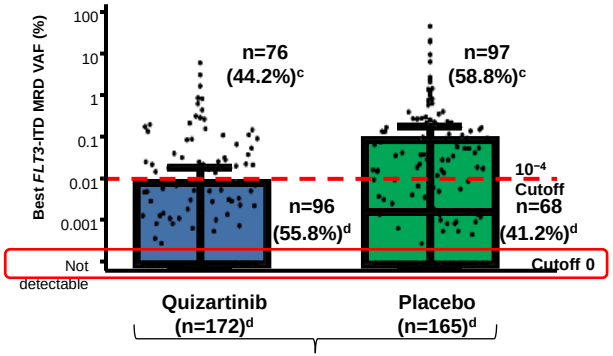
Median = 0.01% quizartinib vs 0.03% placebo
Nominal *P* value (2-sided) = 0.0251

After 2 Cycles of CTx[a]
(CRc after induction × 2 cycles or
CRc after induction #1 + consolidation #1)

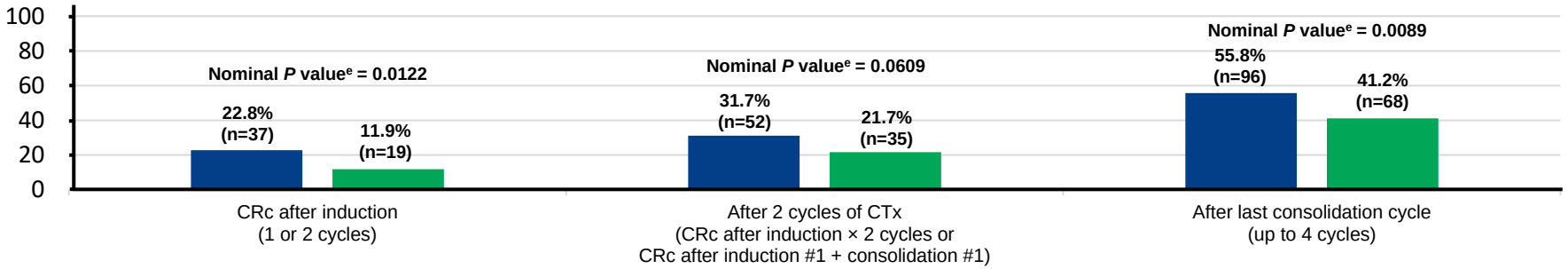


Median = 0.0054% quizartinib vs 0.0171% placebo
Nominal *P* value (2-sided) = 0.0540

After Last Consolidation Cycle[b]
(up to 4 cycles)



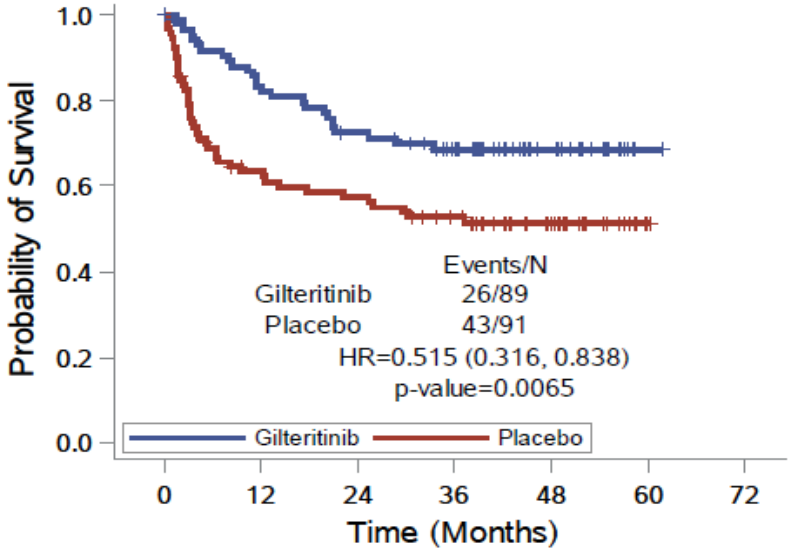
Median = 0% quizartinib vs 0.0017% placebo
Nominal *P* value (2-sided) = 0.0006



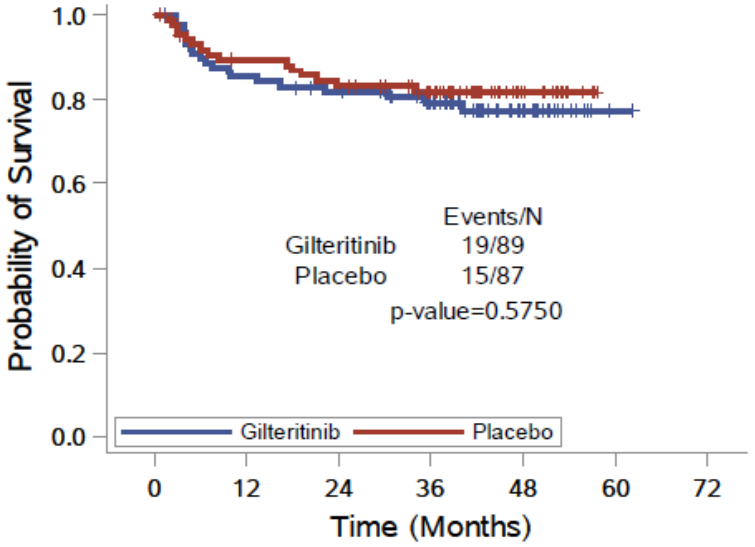
Post hoc analysis. [a]Defined as 2 cycles of induction CTx or 1 cycle of induction CTx + 1 cycle of consolidation CTx. [b]Include samples up to end of consolidation, including from induction. [c]Percentage of patients with *FLT3*-ITD MRD VAF>0 among CRc patients with MRD data. [d]Percentage of patients 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+



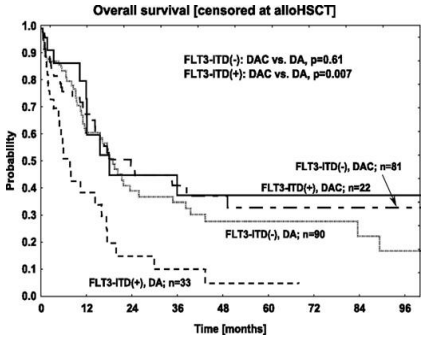
RFS
MRD-



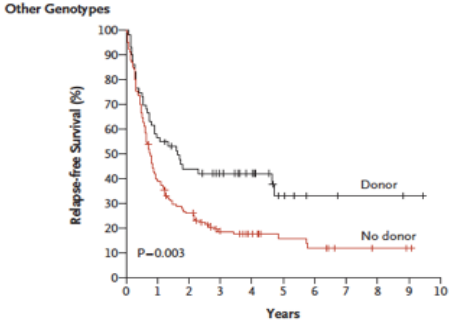
Levis M et al, LBA EHA 2023

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%

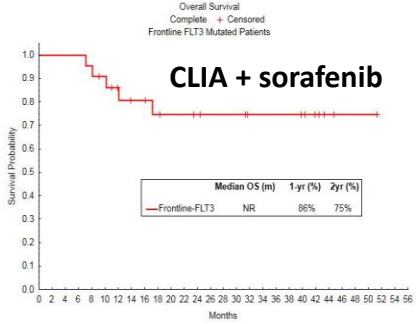
Adding purine analogue to DA (DAC)



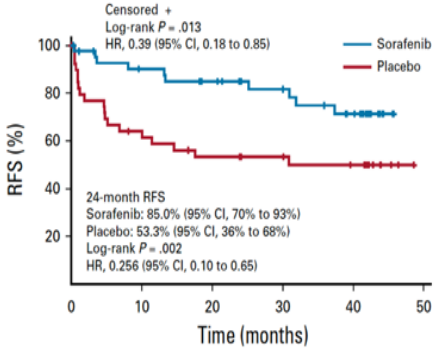
First remission AlloHSCT



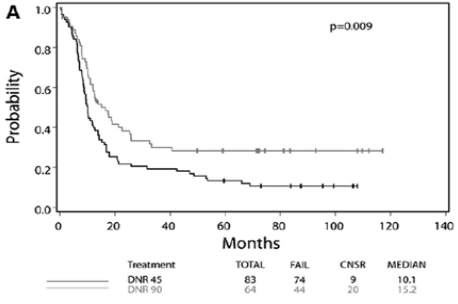
FLT3 inhibitors

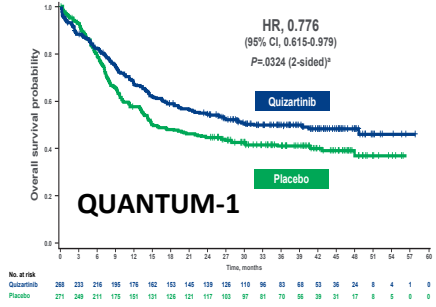


Post-AlloSCT sorafenib

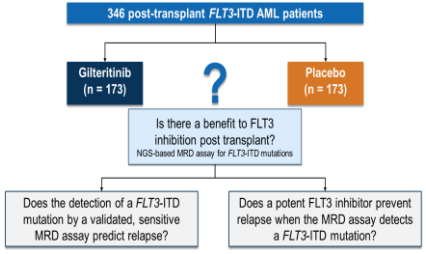


High-dose daunorubicin





GILT maintenance Ph III



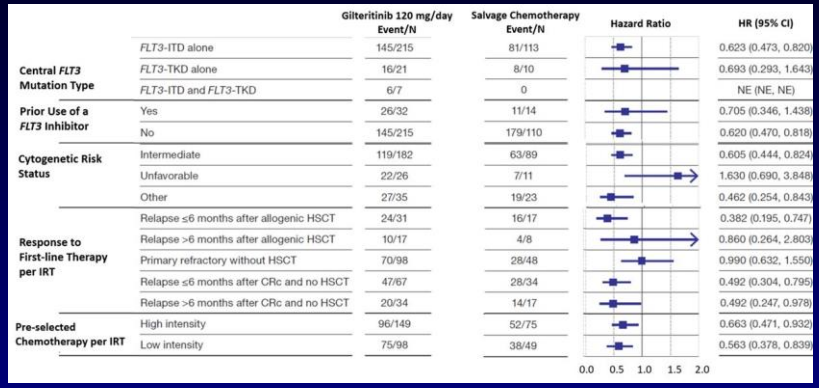
Would AZA+GILT be better?

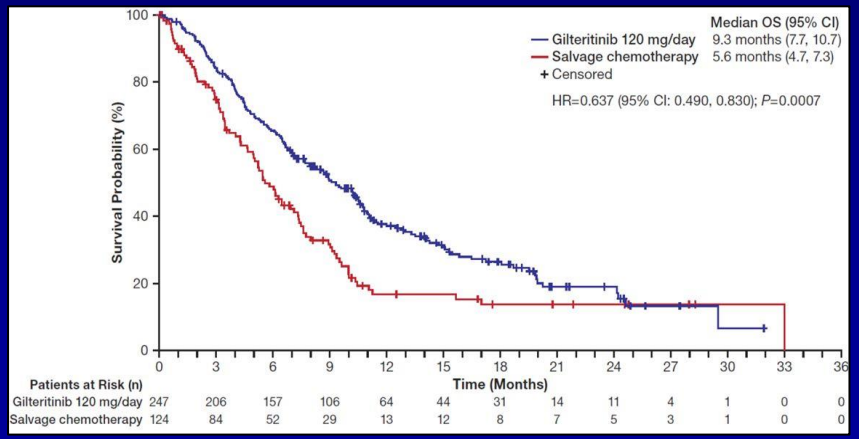
R/R AML

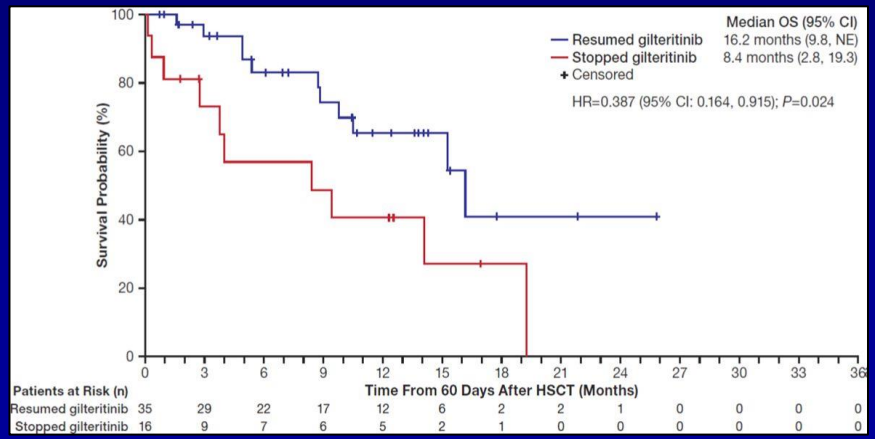
ADMIRAL trial: Gilteritinib vs salvage chemo in relapsed AML

- 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)	

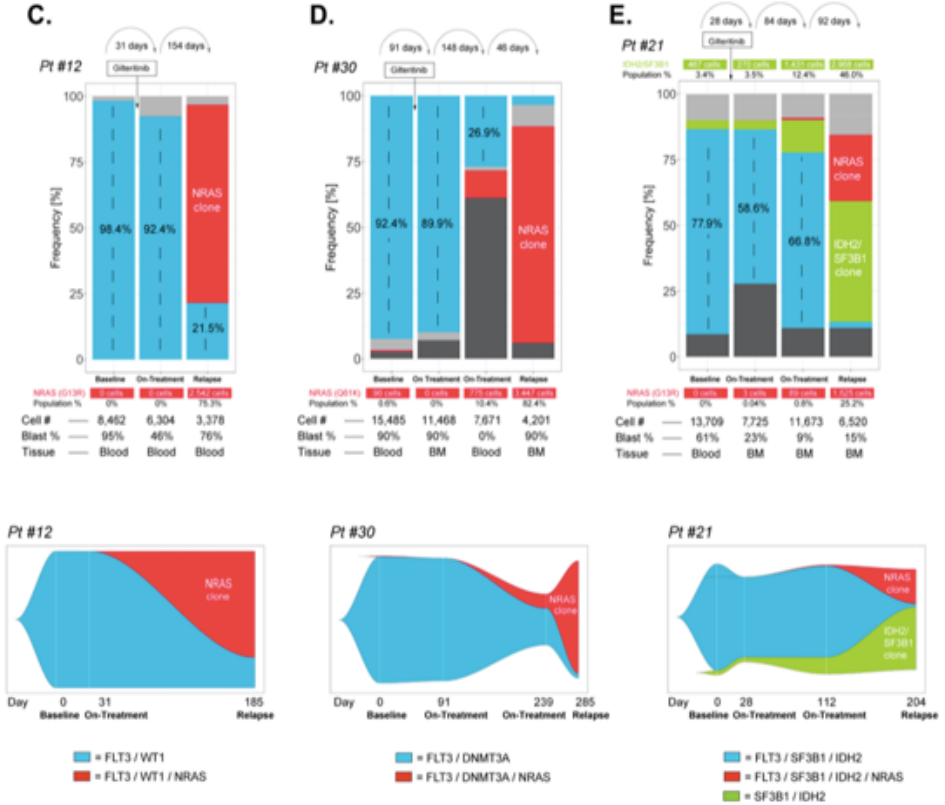
[a]Defined as the sum of the patients who achieved CR, Cri, and CRp

- 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.

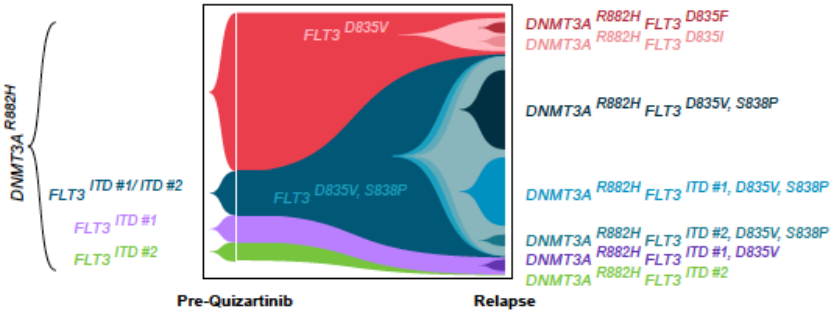
Resistance to second-generation FLT3 TKIs is highly polyclonal: Single-agent FLT3is, no matter how potent, are unlikely to be curative

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

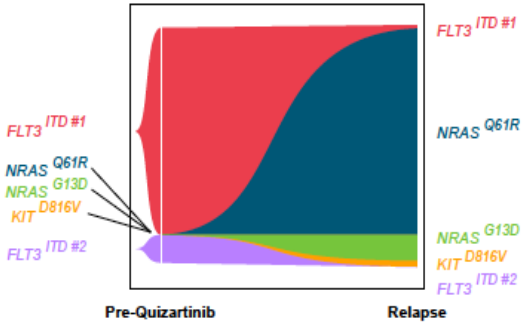


Quizartinib (Type II): On target resistance through acquisition of *FLT3*-TKD

Patient 15

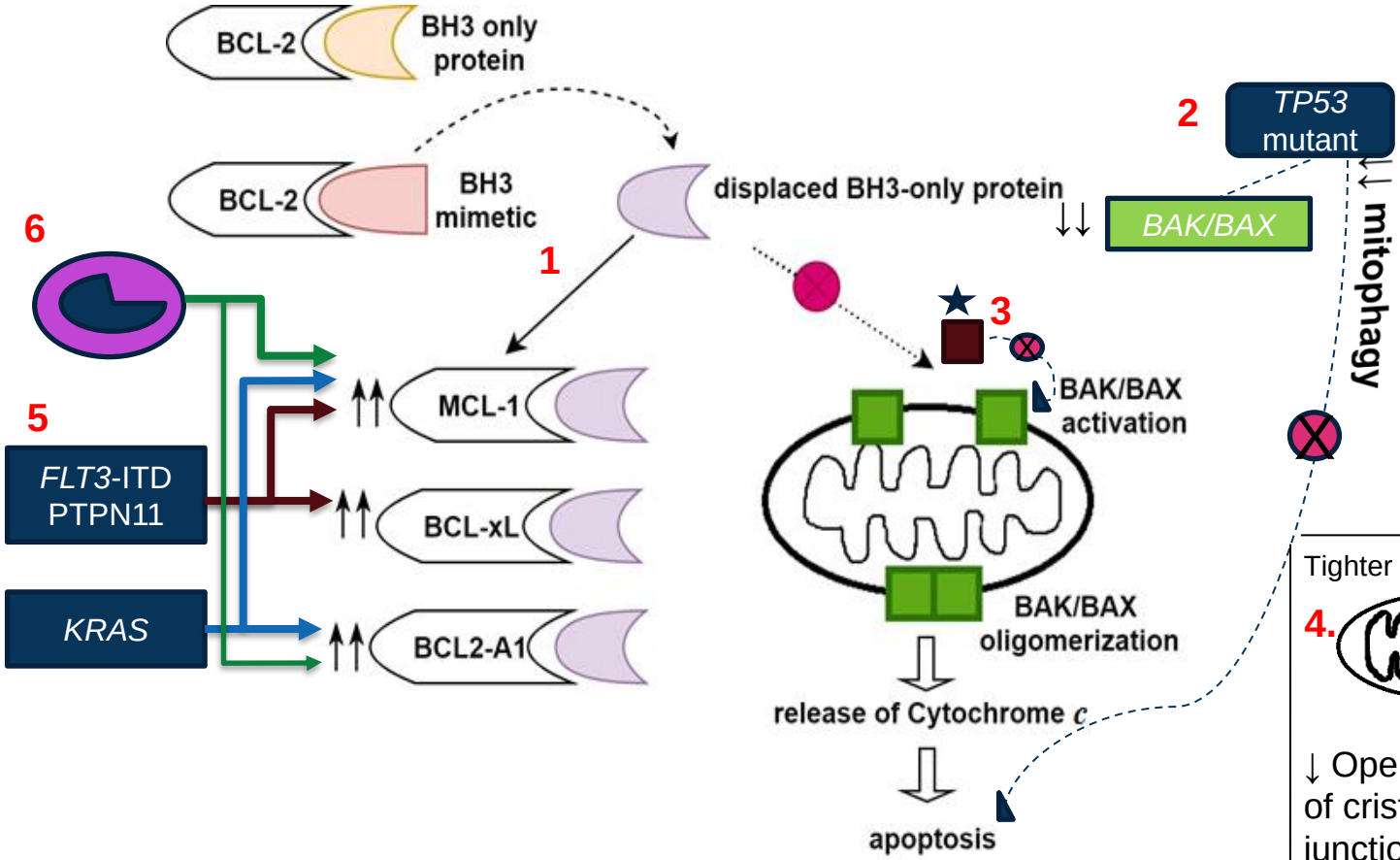


Patient 16

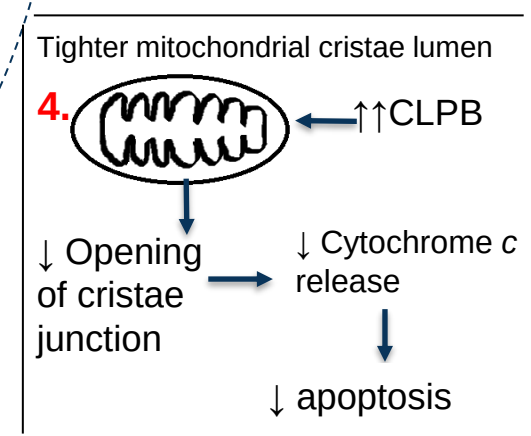


McMahon CM, et al. Cancer Discov. 2019 Aug;9(8):1050-1063; Peretz C, Catherine Smith, et al. Blood Adv. 2021 Mar 9;5(5):1437-1441

Venetoclax resistance: Road to “triplets”

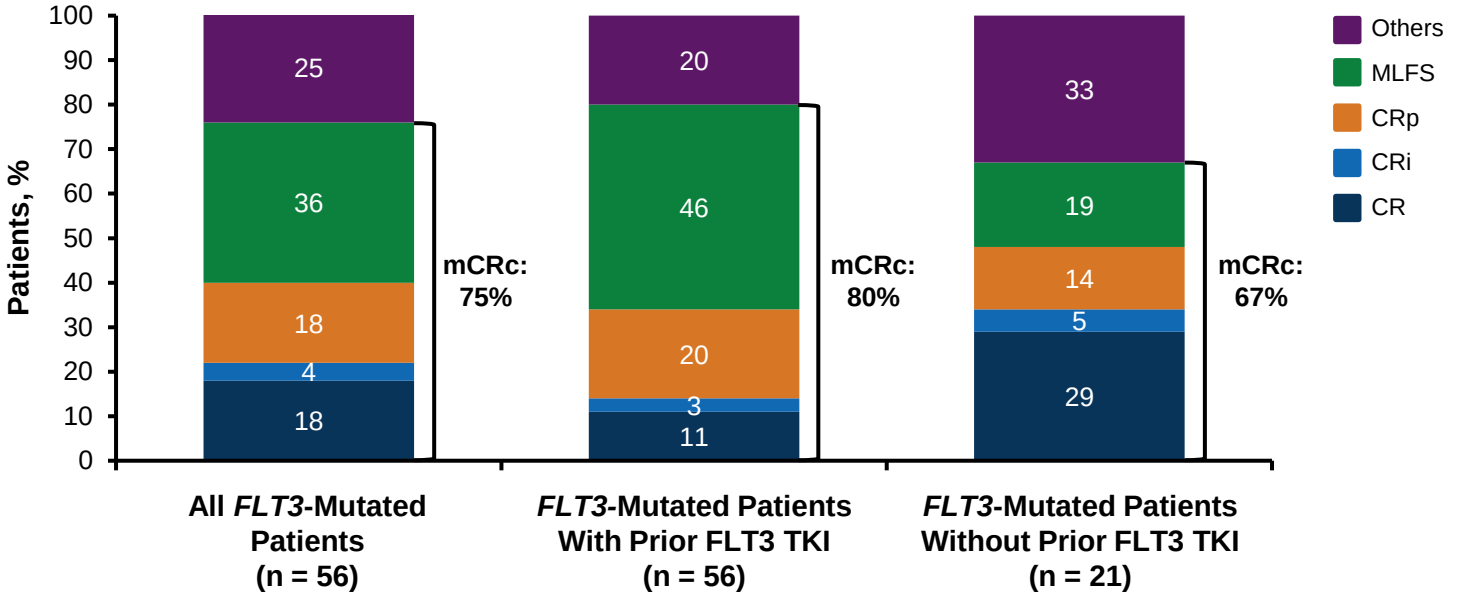


1. Other anti-apoptotic BCL-2 family proteins
2. *TP53* mutation?
3. *BAX* mutation?
4. Mitochondrial aberration?
5. Mutations in activating kinases
6. Monocytic differentiation



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.

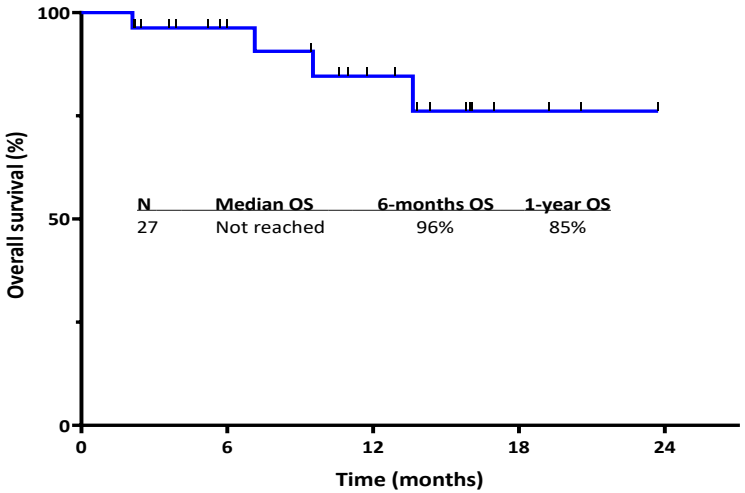
Aza + Ven + Gilteritinib in frontline *FLT3*-mutated AML: Healthier marrow, potentially more curative, and better tolerated

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

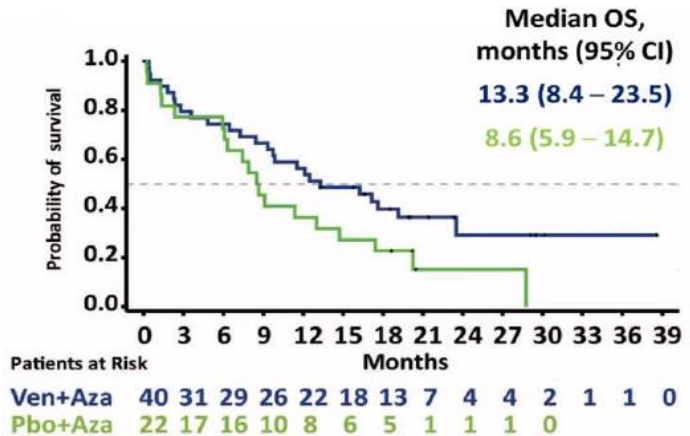


N=30

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

Recovery:
ANC ≥0.5 37d
Plt ≥50 25d

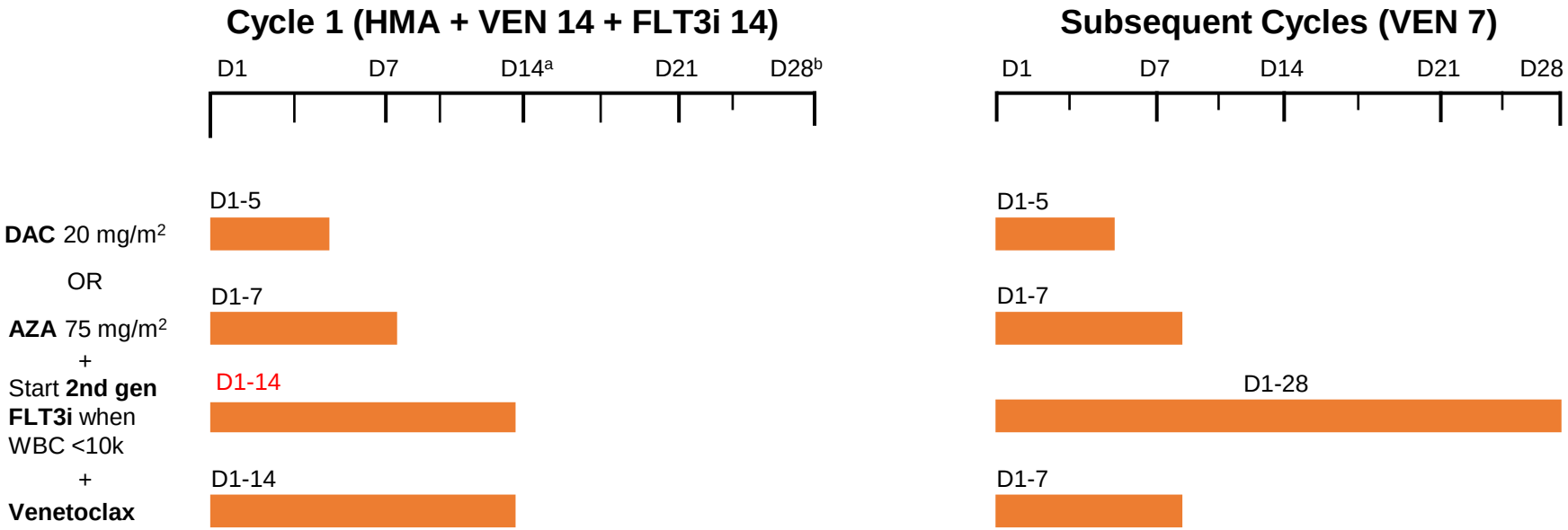
Historical perspective (Konopleva M et al CCR 2023)
AZA+VEN in FLT3m frontline AML (N=40)



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

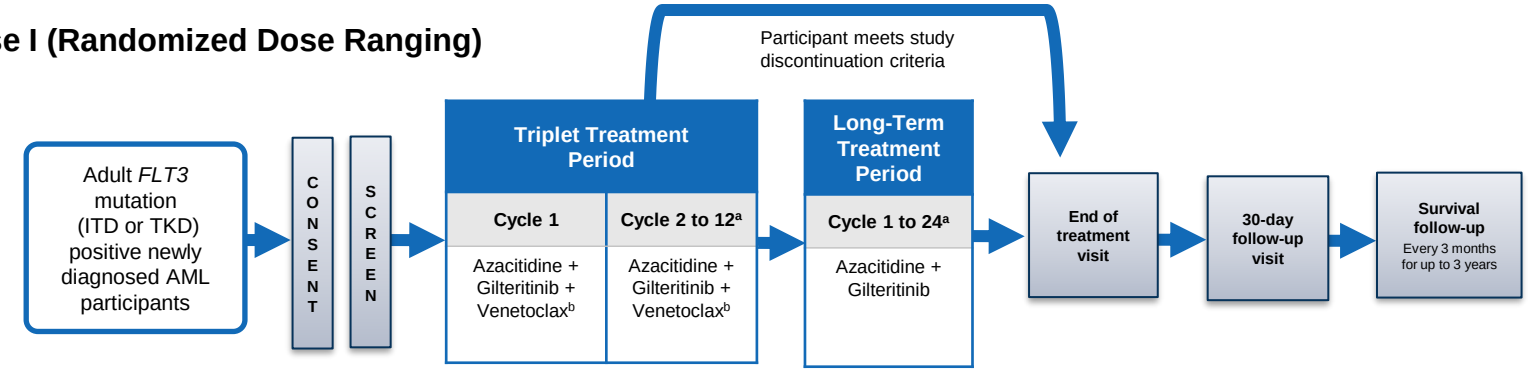


[a] C1 D14: Perform bone marrow biopsy; if bone marrow shows <5% blasts and/or <5% cellularity/insufficient sample → stop venetoclax on D14. [b] Repeat a C1 D28 bone marrow on all patients to confirm remission. If C1 D28 bone marrow confirms remission and ANC <0.5 and/or platelet <50K, consider interrupting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

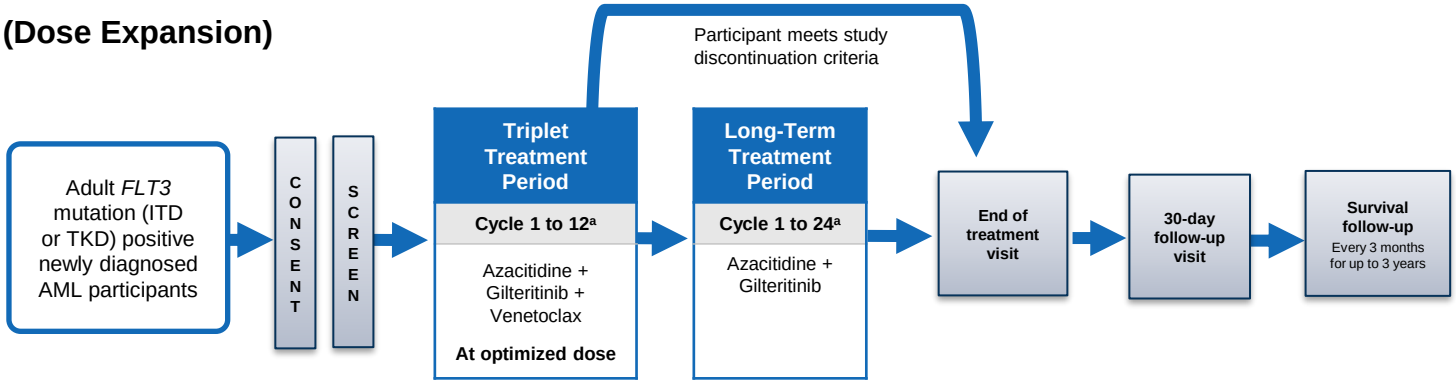
Daver N et al. Blood Cancer J. 2021;11:104.

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].

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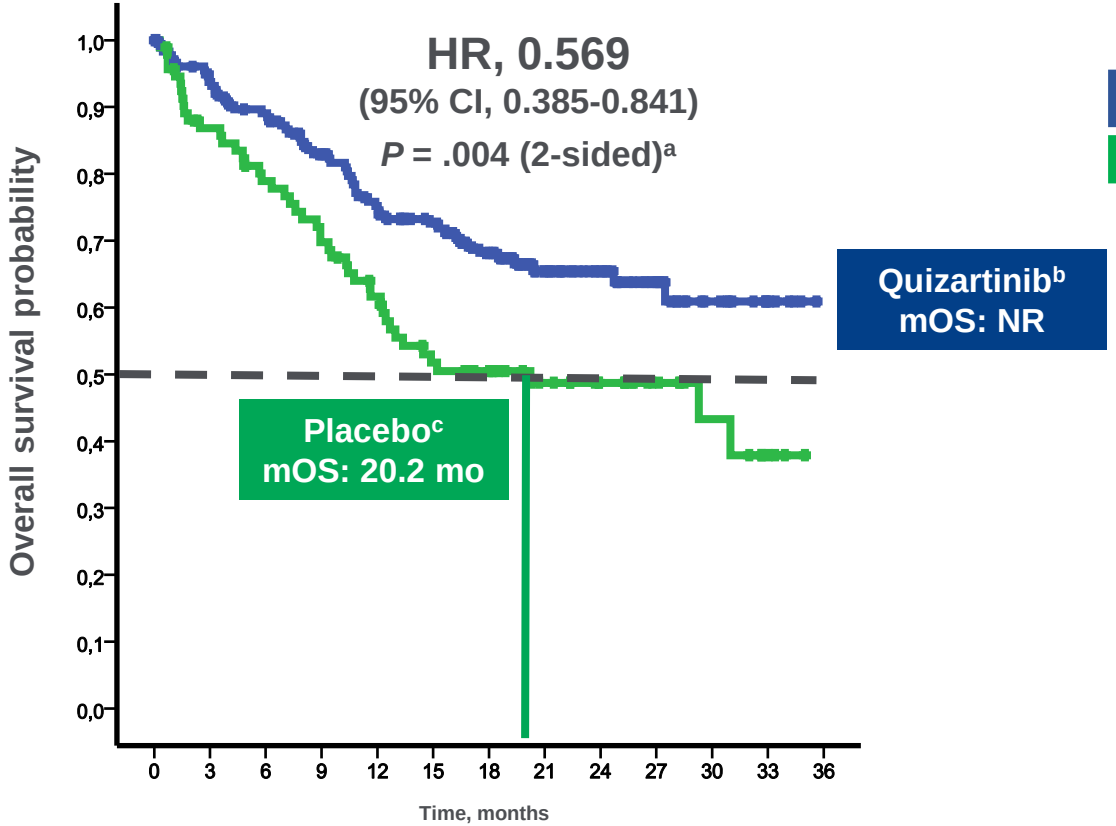
PETHEMA

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

Secondary endpoint (interim analysis): Overall survival



Number of Events

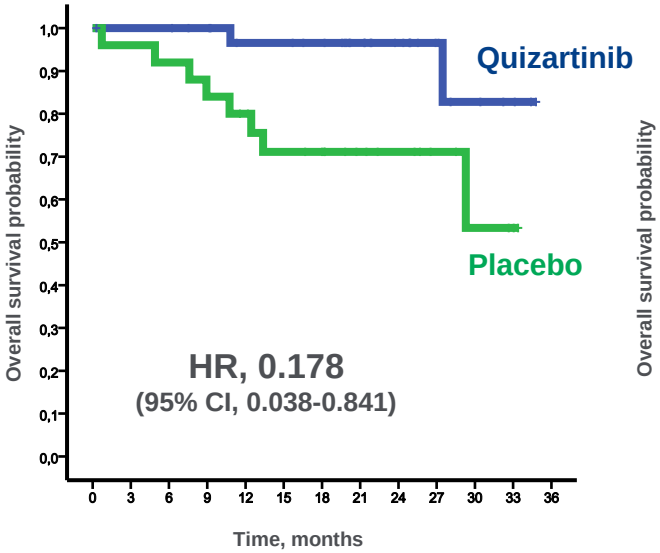
Quizartinib	56/180
Placebo	46/93

HR, hazard ratio; mOS, median overall survival; NR, not reached.

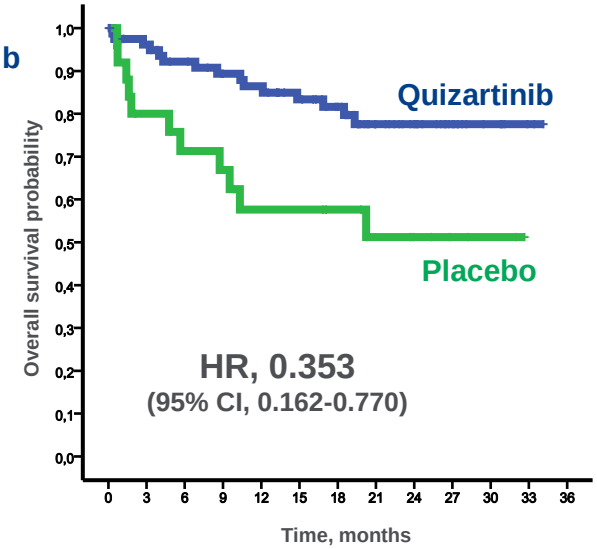
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 21.5 months. [c] Median follow-up time for placebo arm, 20.3 months.

Sensitivity analysis: Overall survival according to ELN2017 risk

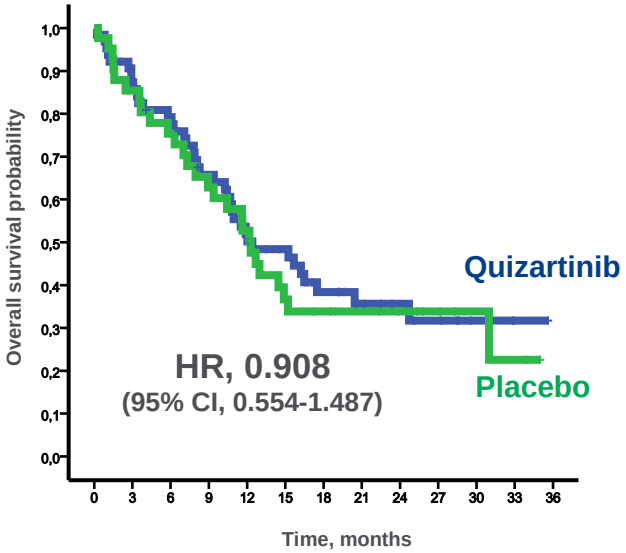
OS – ELN2017 Favorable



OS – ELN2017 Intermediate



OS – ELN2017 Adverse



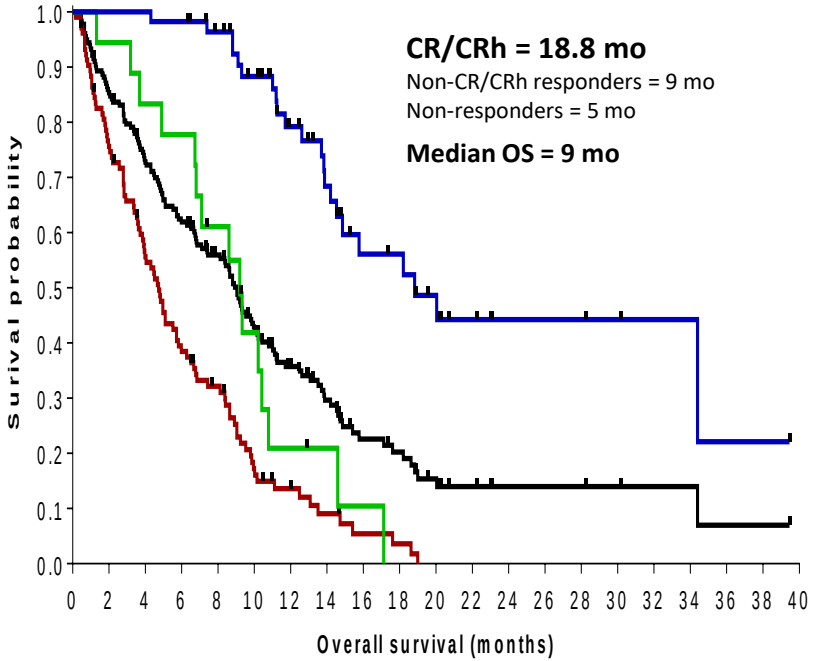
ELN, European LeukemiaNet; HR, hazard ratio

2. Targeting *IDH1* and *IDH2*

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

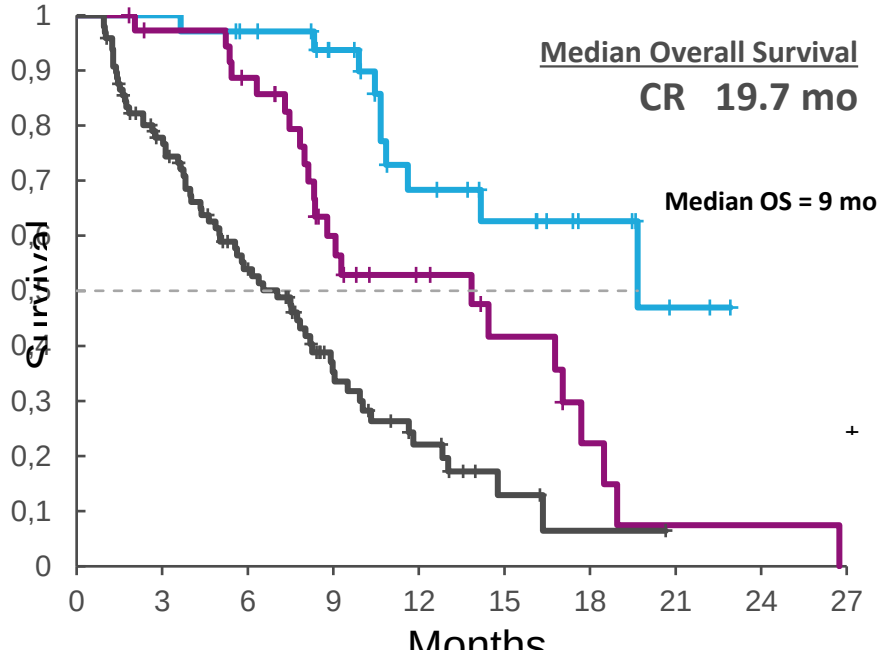
CR rate ~20%
CR/CRh rate ~30%
ORR ~40%

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)

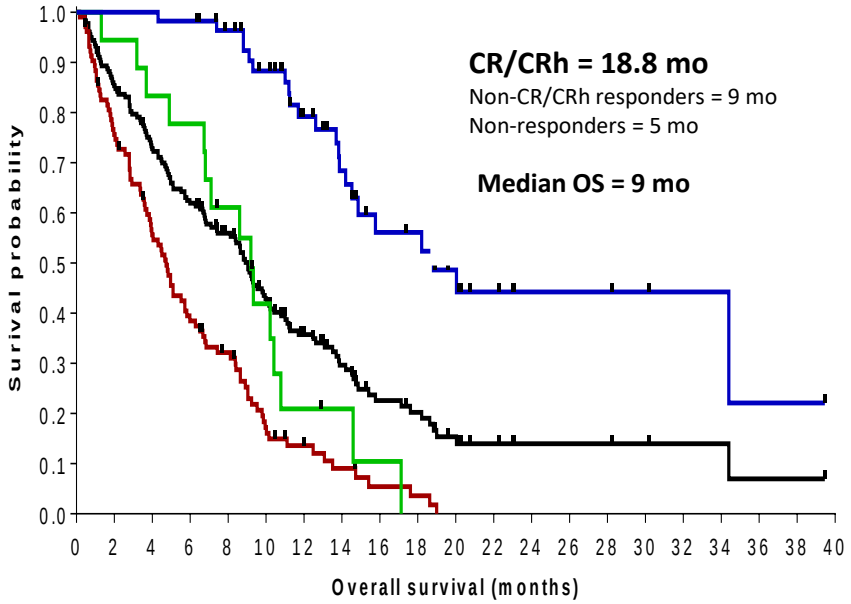
Median Duration of Response ~12 mo
(compared to ~6.5 mo w/ IVO)

***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

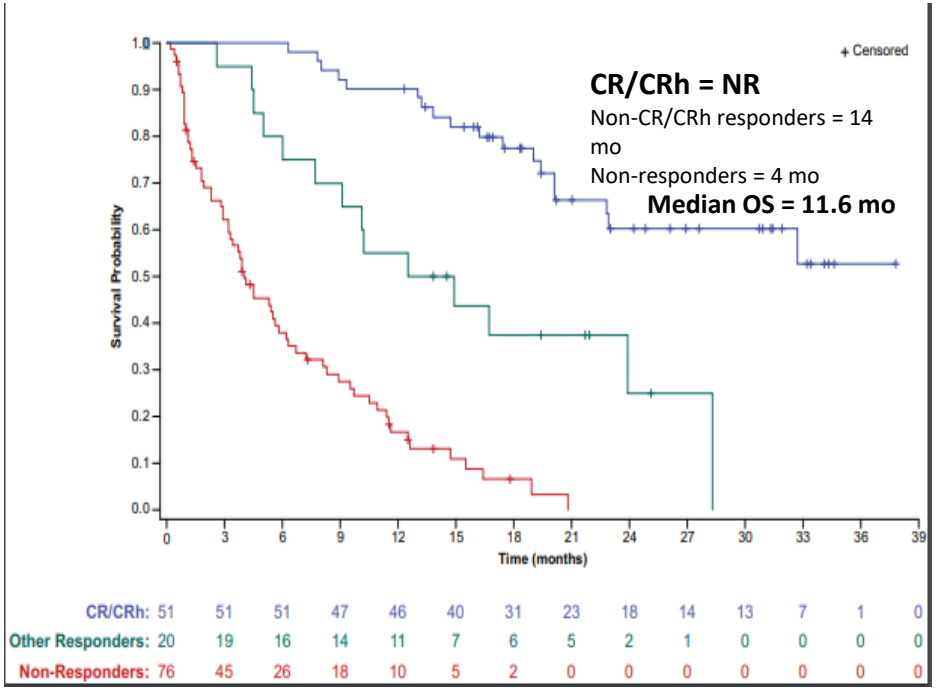
IDH1 OS with IVO and OLUTA from phase I study approval populations

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)**

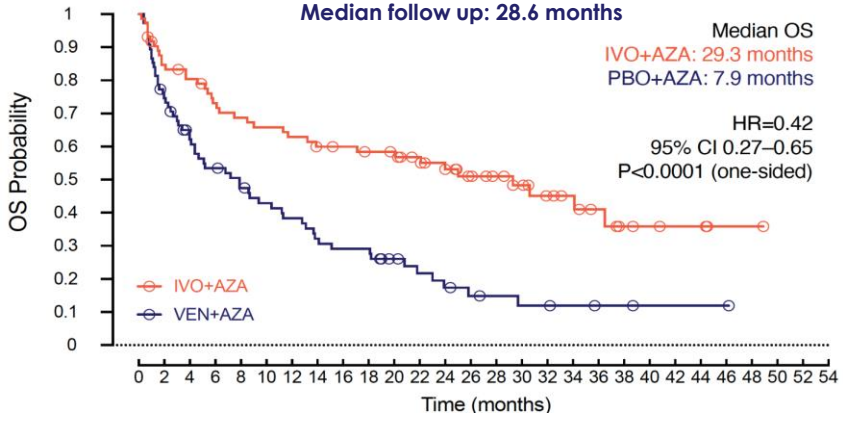
DS manifestations typically include

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

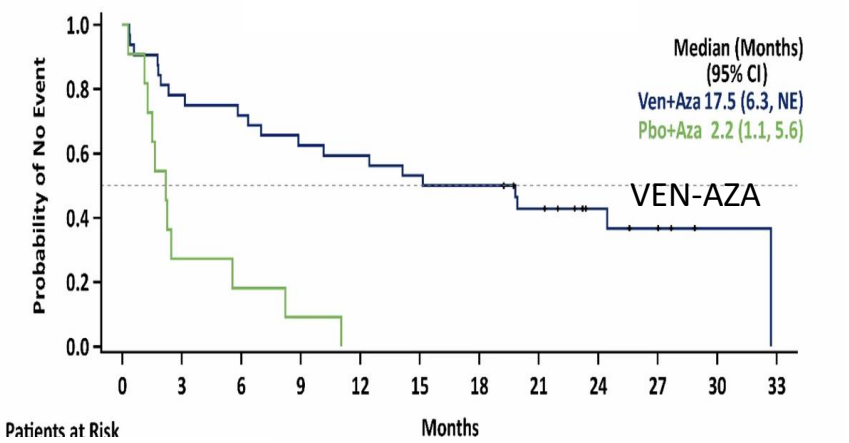
Stein EM, et al. *Blood*. 2017;130:722-731.
DiNardo CD, et al. *N Engl J Med*. 2018;378:2386-2398.
De Botton S et al, *Blood Adv.* 2023

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

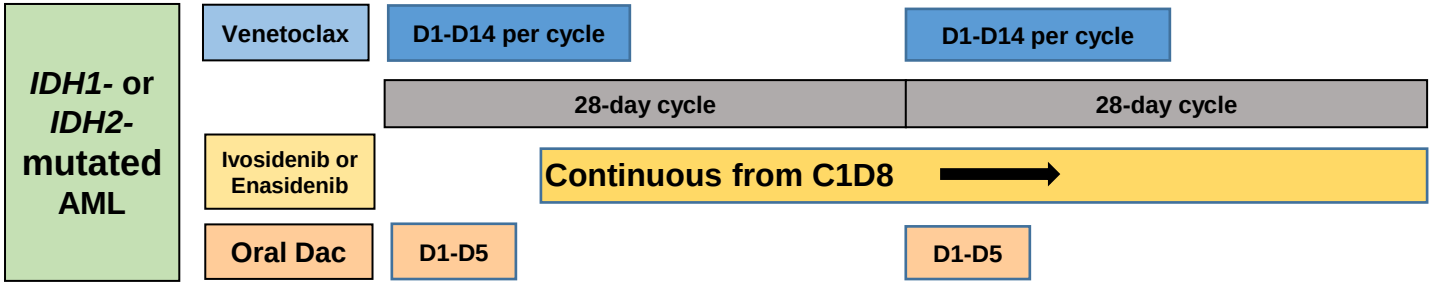


Pollyea, et al, *Clin Cancer Res 2022;28:2753–61*

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)



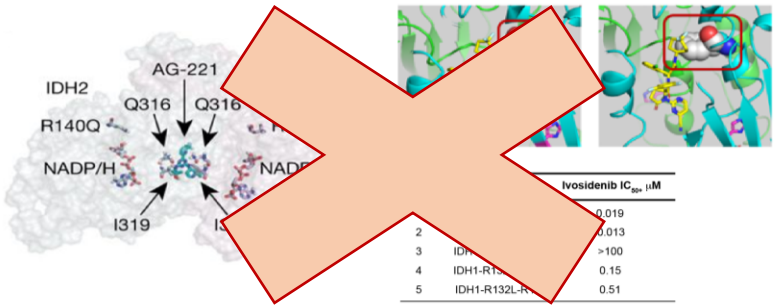
Response, %	Newly Dx *IDH1* (n = 10)	Newly Dx *IDH2* (n = 14)	R/R (n = 26) *IDH1*	R/R (n = 26) *IDH2*
CRc	90	100	50	44
MRD neg	80	93	50	19

***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.

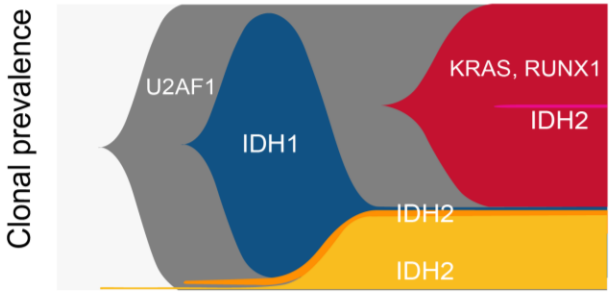
How does this compare with IDH inhibitor monotx resistance?

2HG Related



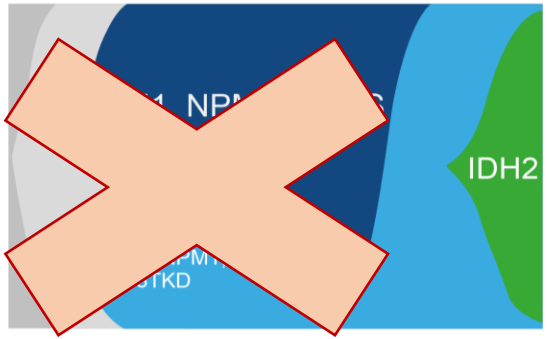
"Second Site Mutations"

Non-2HG Related

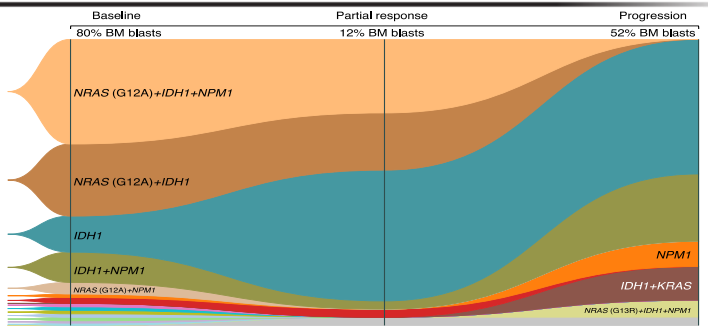


Reinstitution of Differentiation Block
(CEBPα, RUNX1, GATA2)

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



"Isoform Switching"

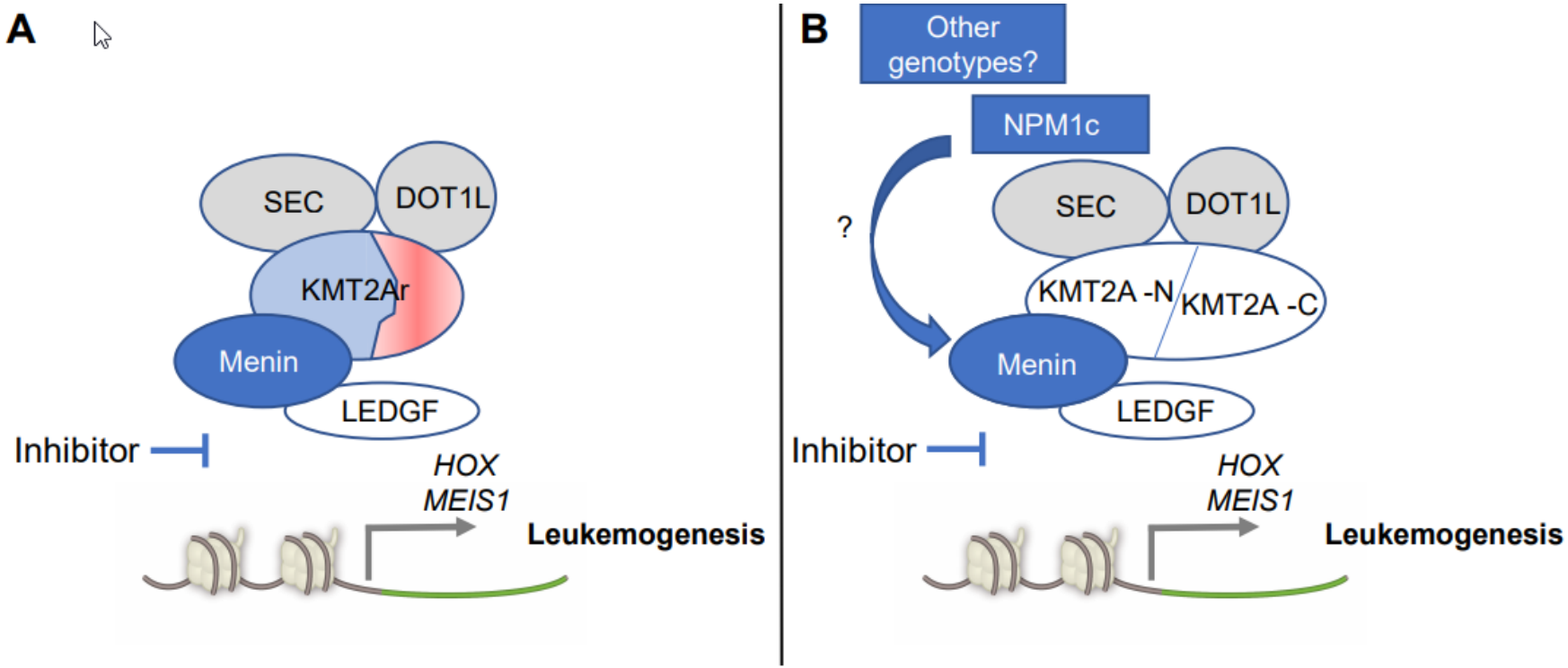


Activated Signaling / Proliferation Pathways
(FLT3-ITD, K/NRAS, PTPN11)

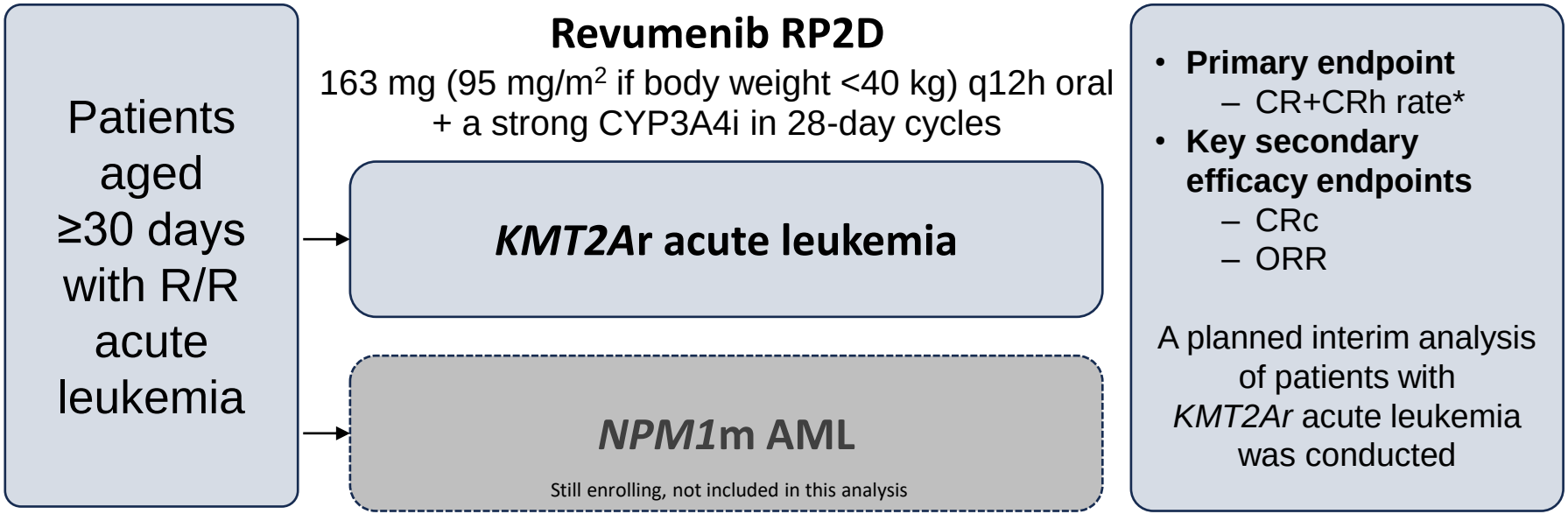
Quek L et al, Nature Med 2018, Intlekofer AM et al, Nature 2018, Harding JJ et al, Cancer Discov 2018, Choe S et al, Blood Adv 2020

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)

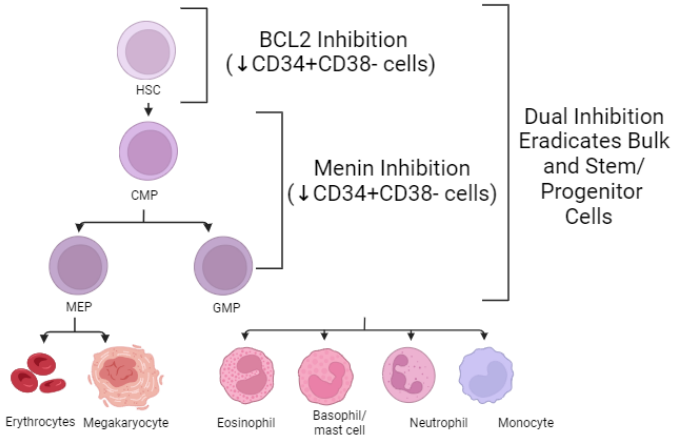
CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR);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

Rationale for SAVE combination

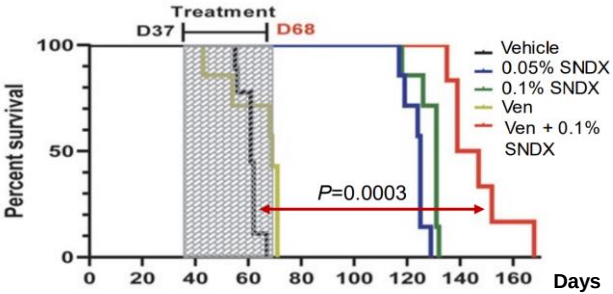
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

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

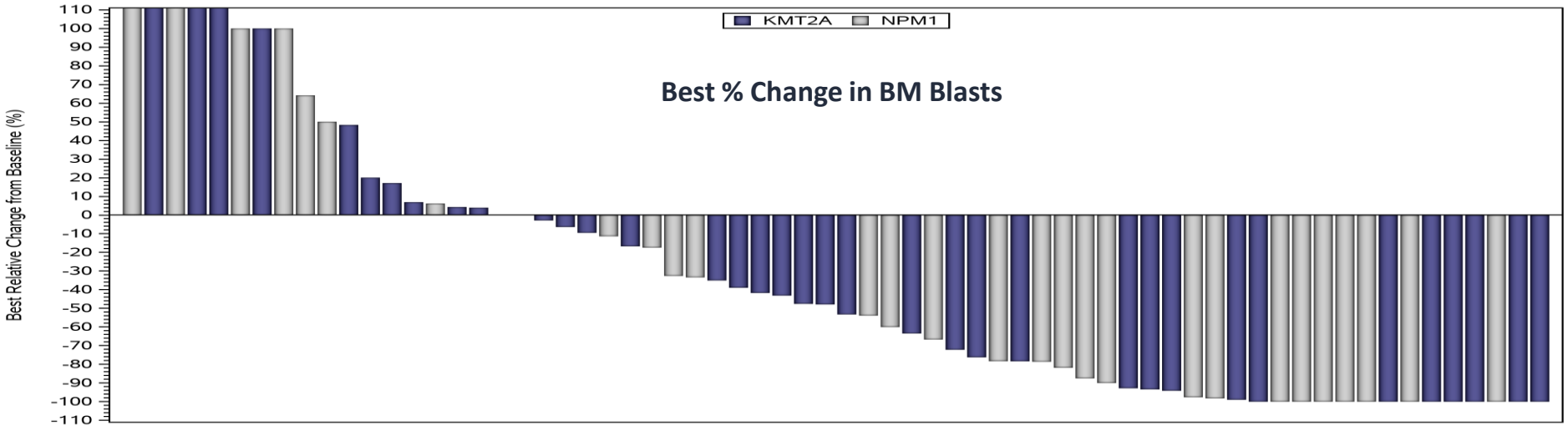
SAVE (SNDX-5613+ASTX727 +Ven) in R/R AML

- 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

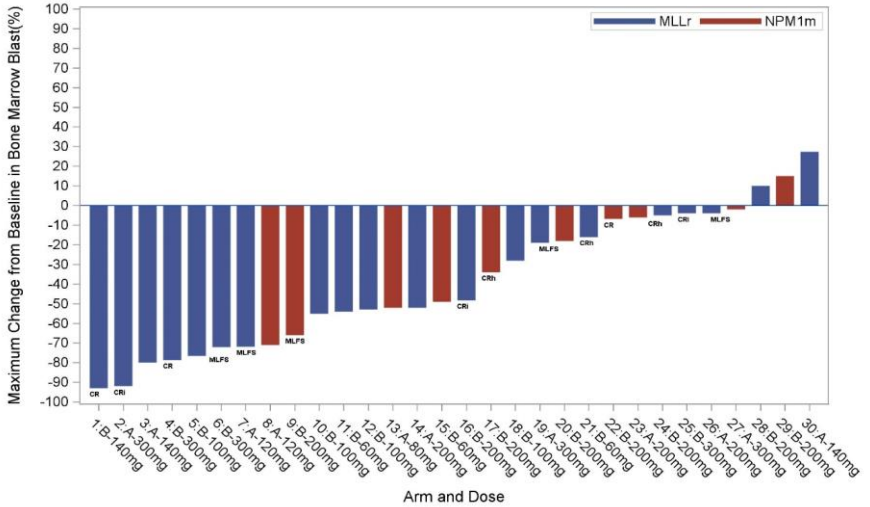


Jabbour. Blood 142: abst 57; 2023

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)

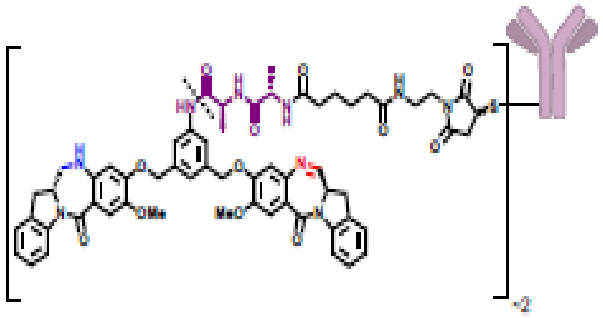
Daver N. EHA 2024 Abst S411

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%**

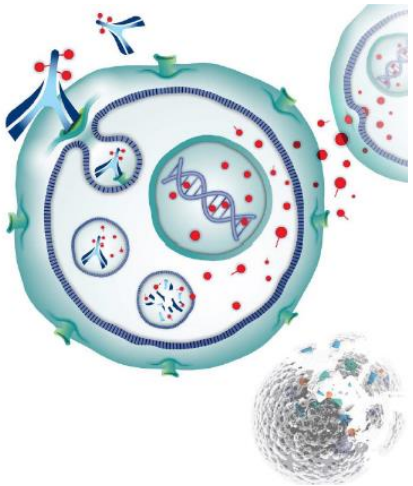


Red: imine (site of DNA alkylation)

Blue: amine (non-covalently binds DNA)

Purple: peptide linker

Dashed line: Site of catabolism

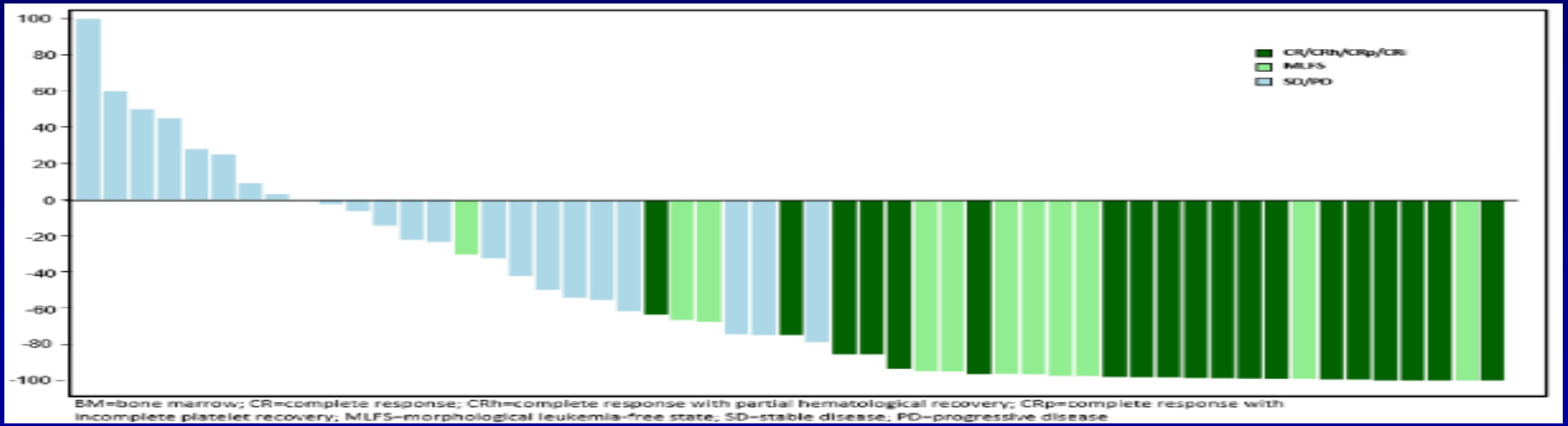


Daver N et al Lancet Oncology March 2024

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

Global Leukemia Academy

Therapeutic approaches in high-risk and frail patients with AML

Phillip Scheinberg

APTITUDE HEALTH®

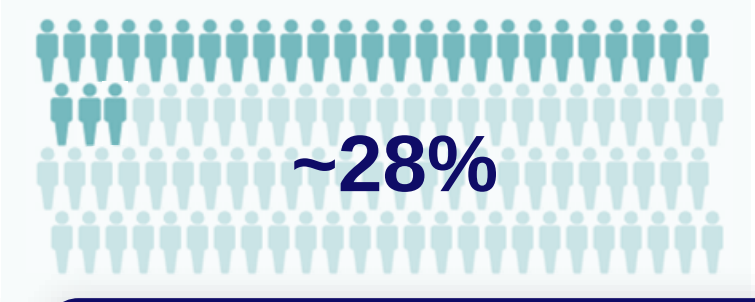
Disclosures

- **Clinical Research as Investigator:** Roche, Novartis, Viracta
- **Scientific Presentations:** Novartis, Amgen, Roche, Alexion, Janssen, AstraZeneca
- **Grants/Research Support**: Alnylam, Pfizer
- **Consultant/Advisory:** Roche, Alexion, Pfizer, BioCryst, Novartis, Astellas
- **Speaker:** Novartis, Pfizer, Alexion

- I declare **no** equity, stock options, patents, or royalties from any companies.

Patient survival and age at death

Percentage of patients who survive 5 years

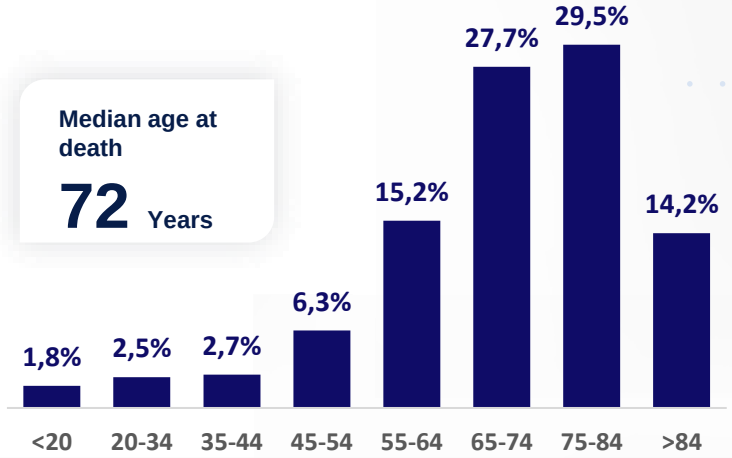


Worse outcomes in elderly patients, compared with those under 60 years of age, were associated with treatment tolerability problems and chromosomal abnormalities associated with poor prognosis.

Percentage of deaths due to AML by age group

Median age at death

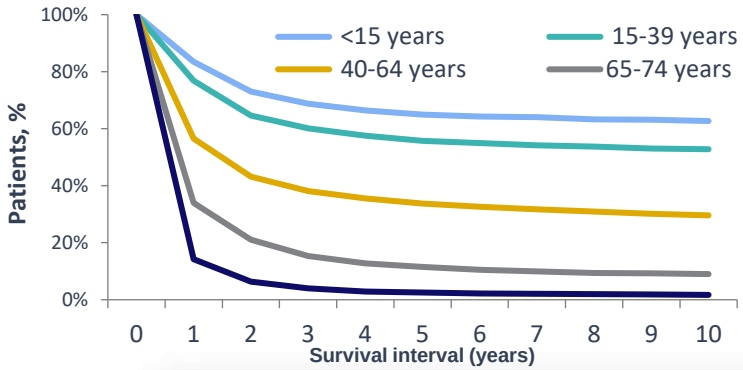
72 Years



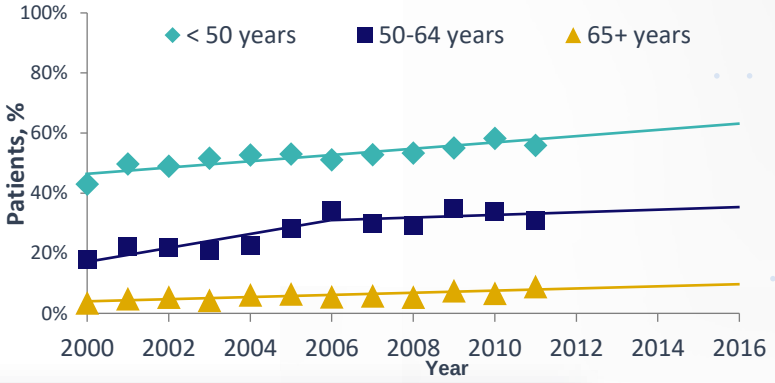
1. National Cancer Institute. Cancer Stat Facts: Acute Myeloid Leukemia (AML). https://seer.cancer.gov/statfacts/html/amyl.html. Acesso em julho de 2019.
2. Ma E, et al. Clin Lymphoma Myeloma Leuk. 2016;16:625-636. 3. Almeida AM et al. Leuk Res Rep. 2016;6:1-7.

Survival by age

Relative survival time from diagnosis to death in patients with AML, 2000-2015



5-year survival per year of diagnosis (2000-2016)



Although the survival of younger patients with AML has improved over the past decade, older patients continue to have a poor prognosis.

1. National Cancer Institute. SEER*Explorer: Acute Myeloid Leukemia. Sobrevivência. https://seer.cancer.gov/explorer/index.html. Acesso em julho de 2019.
2. Almeida AM et al. Leuk Res Rep. 2016;6:1-7.

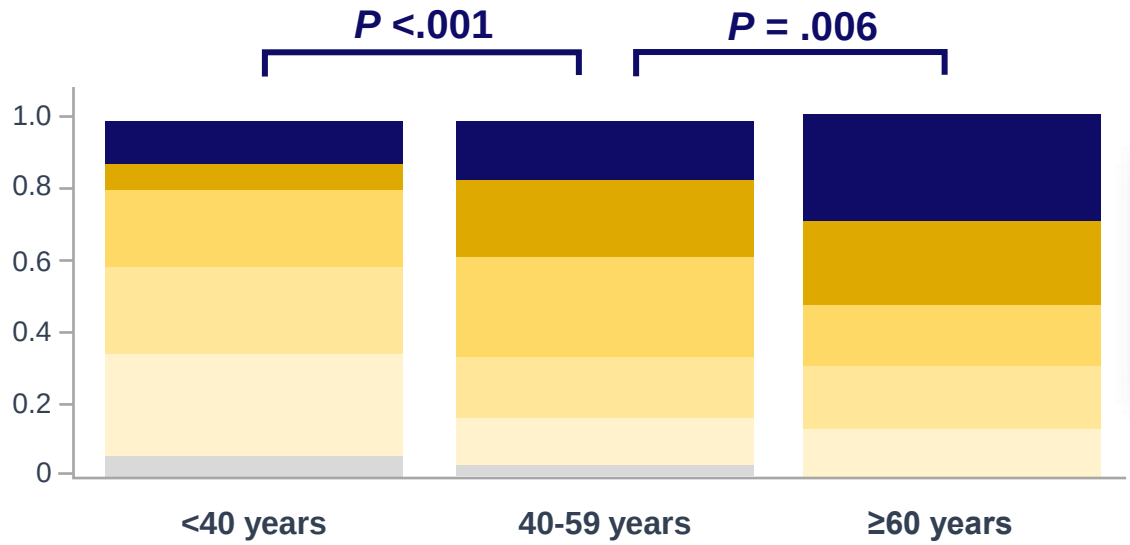
Clinical challenges of elderly patients with AML

- Poor performance status
- Higher incidence of comorbidities
- Low white blood cell count at diagnosis
- Low percentage of medullary blasts
- Increased likelihood of multi-drug resistance
- Lower incidence of "favorable" cytogenetics
- Less likely to achieve remission
- Increased likelihood of treatment-related morbidity/mortality
- Lower probability of survival
- Higher incidence of secondary (s-AML) and treatment-related (t-AML) AML

Craig et al. Blood Rev. 2008;22:221.

Number of mutations increases with age in patients with AML

Number of genes mutated by patient, by age group



Number of mutated genes

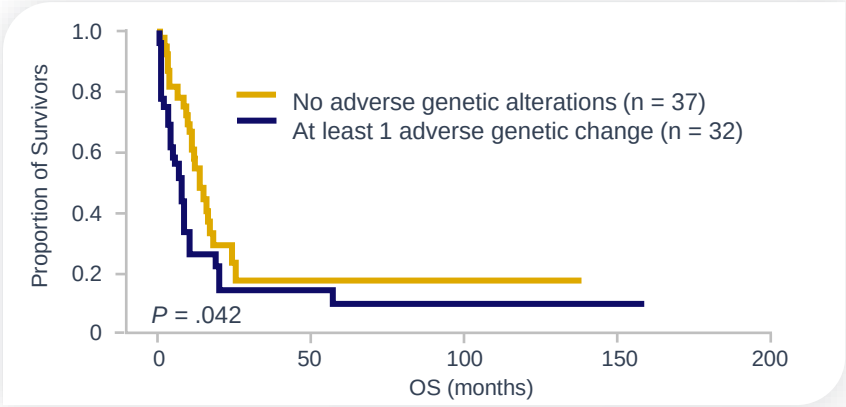
0 | 1 | 2 | 3 | 4 | ≥5

Metzeler KH, et al. Blood. 2016;128:686-698.

Worse prognostic mutations are more prevalent in elderly patients with AML

Variations*	Pts With Changes, %			*P* Value
	All	Elderly	Young	
FLT3/ITD	22.5	22.6	22.5	> .999
FLT3/TKD	6.5	6.8	6.3	.848
NRAS	12.1	13.0	11.6	.662
KRAS	3.2	2.3	3.9	.426
PTPN11	3.9	6.2	2.5	.050
KIT	3.2	2.3	3.9	.426
JAK2	0.6	0.6	0.7	> .999
WTI	6.9	3.4	9.1	.023
NPM1	22.3	28.2	18.6	.021
CEBPA	14.3	10.2	16.8	.055
RUNX1	13.4	19.8	9.5	.002
MLL/PTD	5.8	6.8	5.3	.543
ASXL1	10.9	17.6	6.7	< .001
IDH1	5.8	6.8	5.3	.543
IDH2	11.9	14.7	10.2	.183

Variations*	Pts With Changes, %			*P* Value
	All	Elderly	Young	
TET2	14.3	24.3	8.1	< .001
DNMT3A	15.2	20.9	11.6	.008
TP53	7.6	13.0	4.2	.001
Cohesin	10.0	9.6	10.2	> .999



*For all variables except *Cohesin*, n = 462; for *Cohesin*, n = 411.

Tsai CH, et al. Leukemia. 2016;30:1485-1492.

Ineligibility criteria – Ferrara

Criteria for defining non-eligibility for intensive chemotherapy in AML

Age >75 years

Congestive heart failure or cardiomyopathy documented with EF ≤50%

Documented lung disease with DLCO or FEV1 ≤65%, dyspnea, or any pleural neoplasm

On dialysis and age >60 years or uncontrolled renal carcinoma

Child B or C liver cirrhosis, or liver disease with marked transaminase elevation and >60 years, or any hepatic carcinoma or acute viral hepatitis

Active infection resistant to anti-infective therapy

Mental illness requiring hospitalization, institutionalization, or intensive outpatient treatment or addiction

Non-leukemia ECOG ≥3 performance status

Any other comorbidity that the physician deems incompatible with intensive chemotherapy

DLCO = Capacidade de Difusão Pulmonar para o Monóxido de Carbono. VEF=Volume Expiratório Forçado.

Ferrara F. et al. Leukemia. 2013;27:997-999.

Options for those ineligible for intensive CT by 2018

TREATMENT EXPECTATIONS:

CR, OS, and quality of life

UNTIL 2018

- BSC
- LDAC
- HMA monotherapy

RESULTS

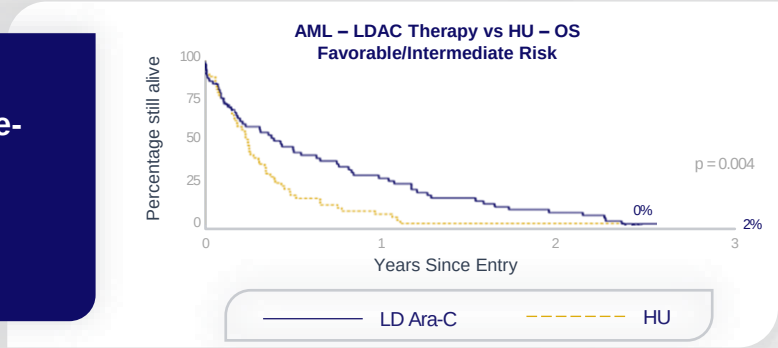
Burnett AK Cancer 2007;109:1114–24
Kantarjian HM. J Clin Oncol 2012;30:2670-7
Dombret H, et al. Blood. 2015/ 36126(3)?291-299

LDAC vs hydroxyurea

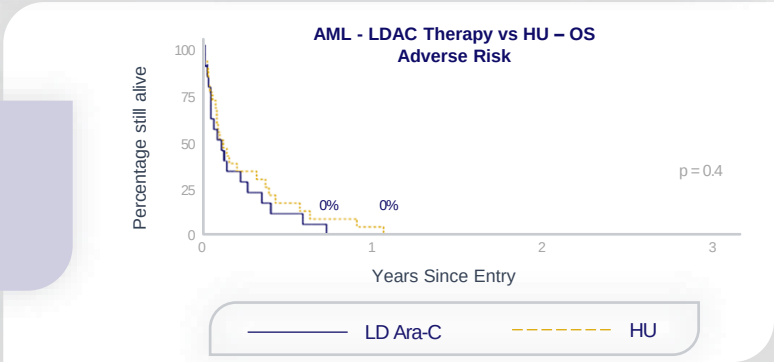
Study of 217 CT-Ineligible Patients Randomized to LDAC/HU (With and Without ATRA)

Modest benefit in the favorable- and intermediate-risk population

- CR 18% vs 1%
- OS 4m vs 3m



In the population of high risk, there was no benefit in OS

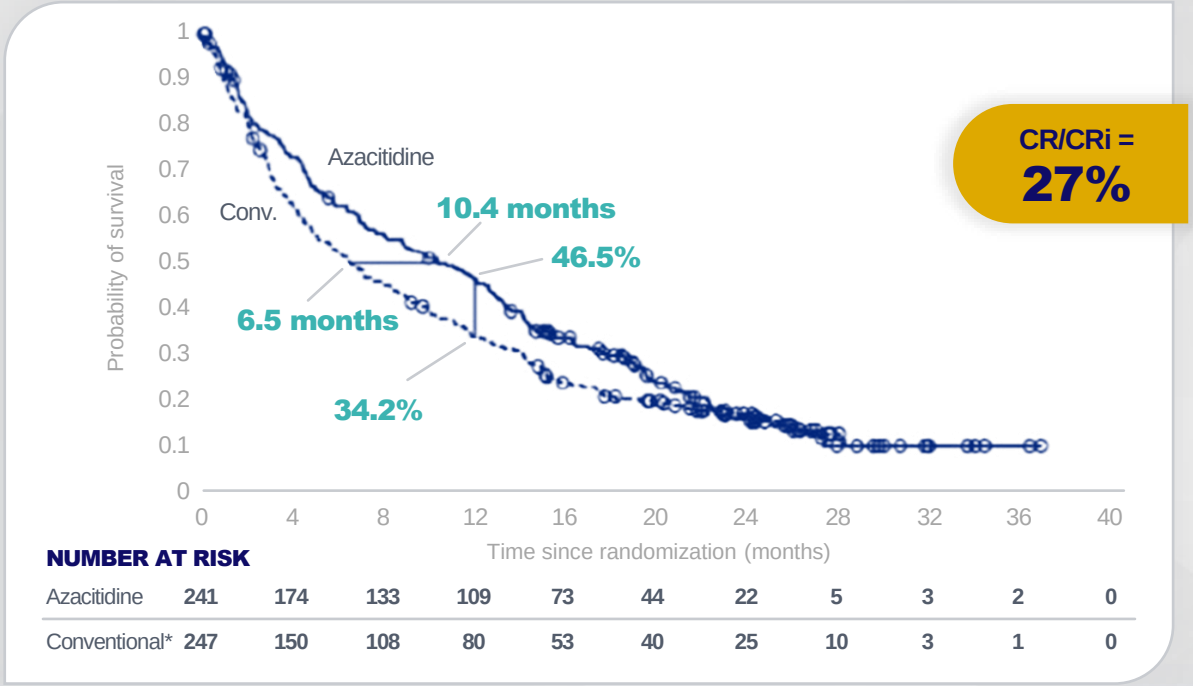


Burnett AK et al, Cancer 2007;109:1114–24

Dombret H, et al 2015

Azacitidine monotherapy for elderly patients with AML

Azacitidine monotherapy has modest CR/CRi rates when compared with conventional treatment (CT/LDAC/BSC)



NUMBER AT RISK

Azacitidine	241	174	133	109	73	44	22	5	3	2	0
Conventional*	247	150	108	80	53	40	25	10	3	1	0

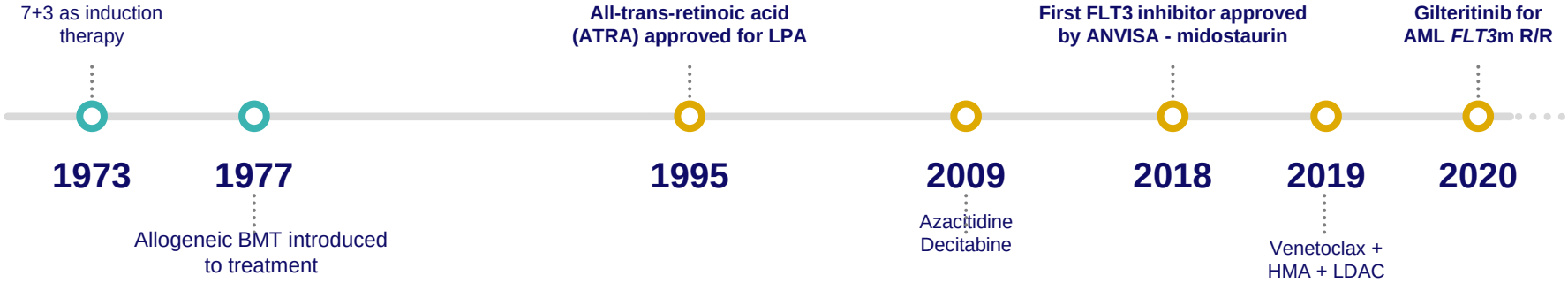
*Conventional: conventional support regimen (intensive induction CT, LDAC, or palliative support)

Dombret H, et al. Blood. 2015/ 36126(3)?291-299

Treatment of AML (accelerated progress 2018-2020): History

Since its introduction in the 1970s, 7+3 therapy has been the standard of care in AML

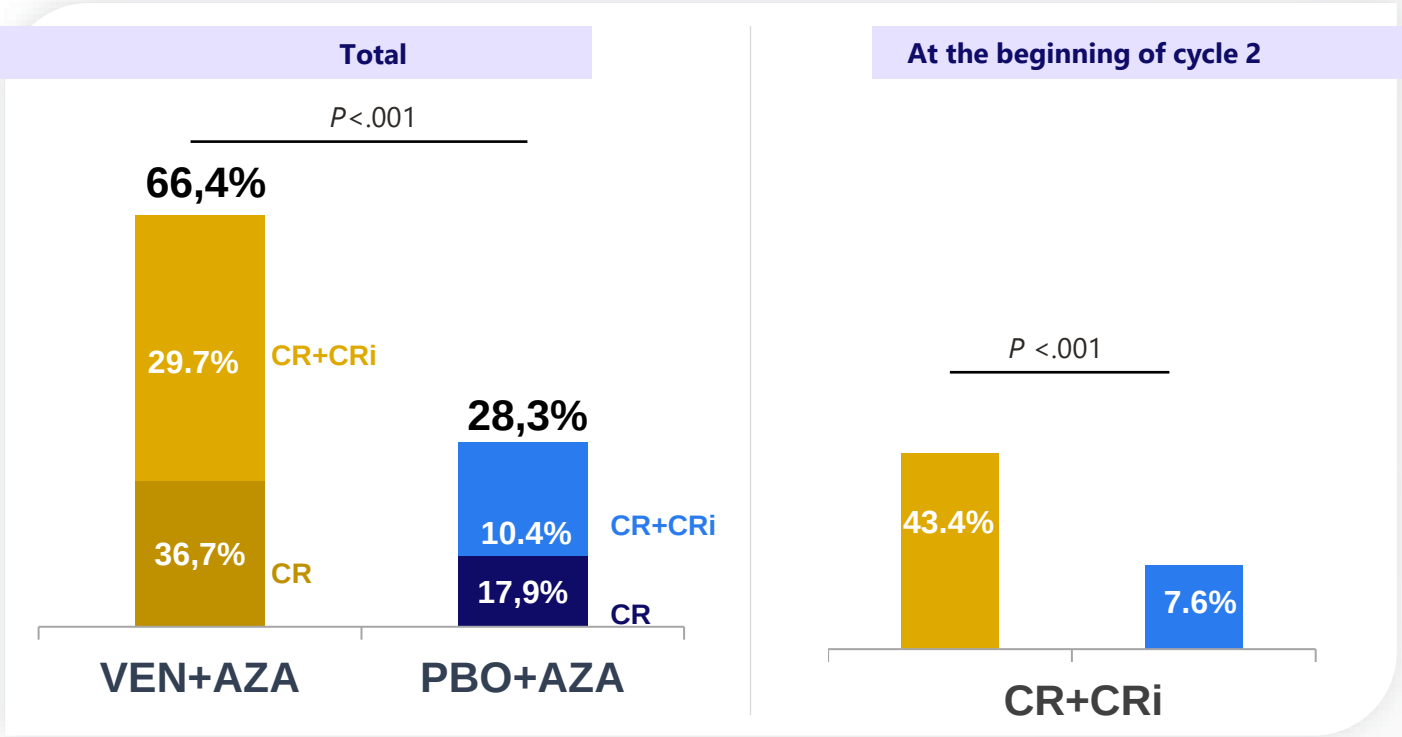
ANVISA Approvals



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

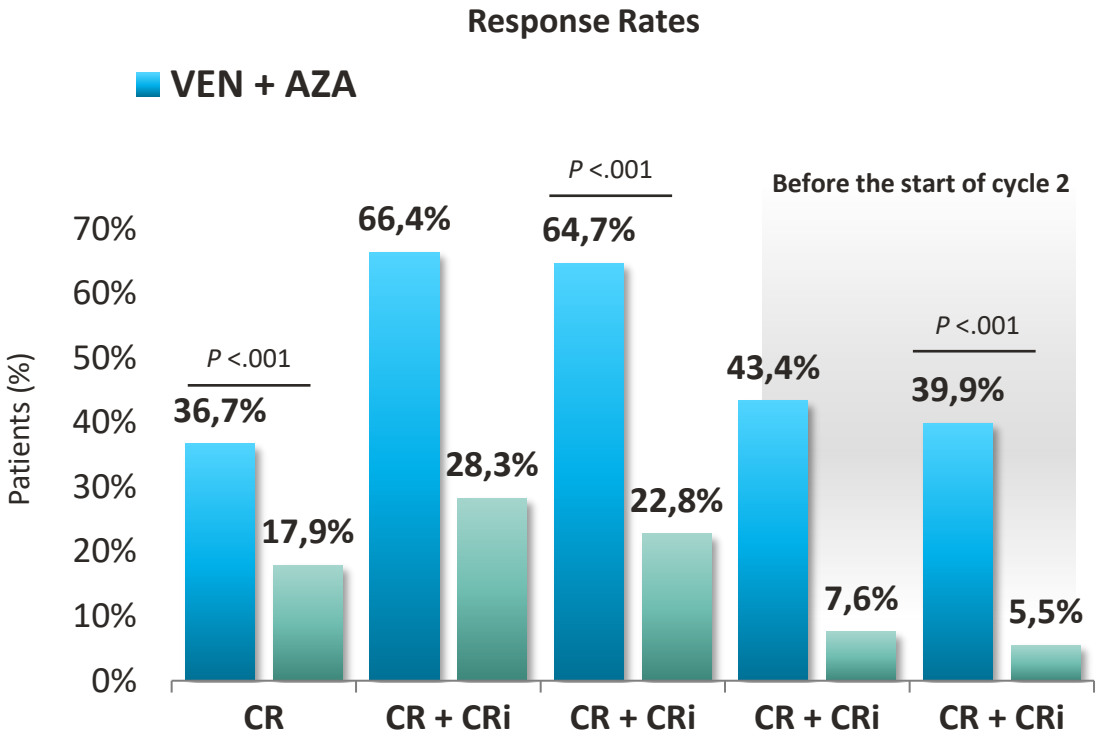
Portal ANVISA - https://consultas.anvisa.gov.br acessado em Abril 2021

VIALE-A: CR/CRi response rate



DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29

Response rates and response time



Median months (track)	VEN + AZA (N=286)	PBO + AZA (N=145)
Time to first response (CR or CRi)	**1.3** (0.6-9.9)	**2.8** (0.8-13.2)

In patients with CR+CRi, MRD negativity occurred in:

23.4% receiving VEN + AZA vs

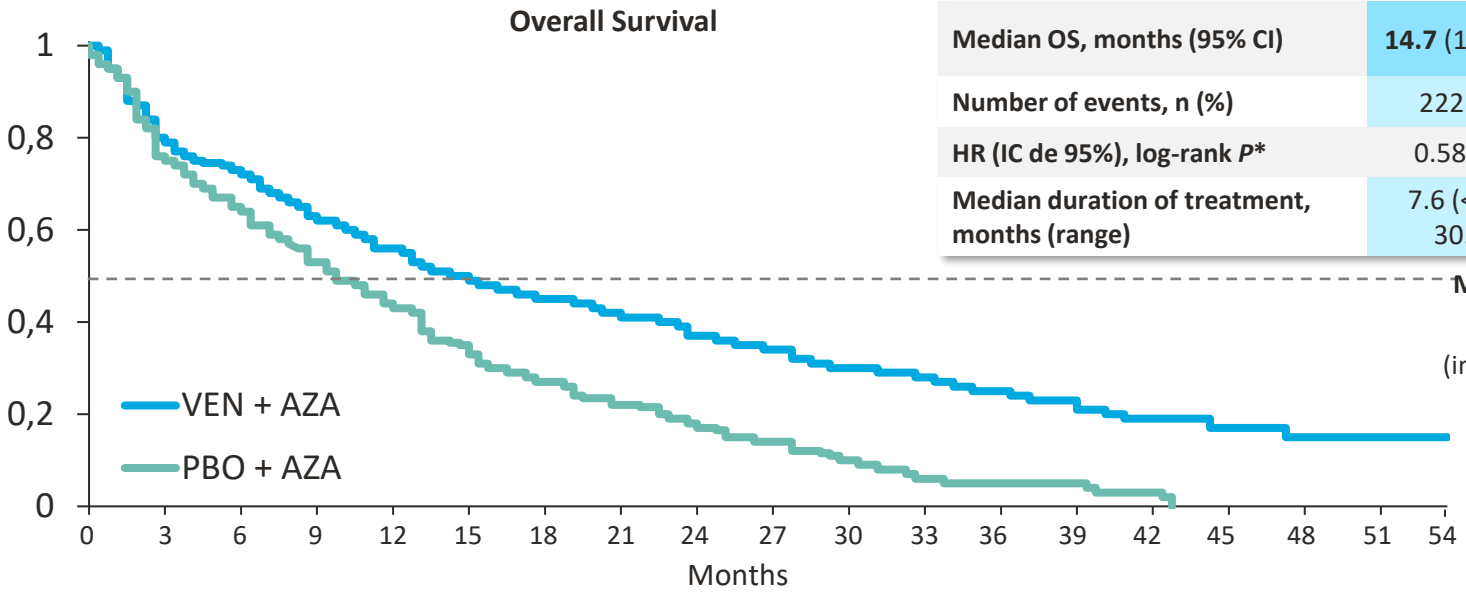
7.6% receiving PBO + AZA

AZA=Azacitidine. CI=Confidence Interval. CR=Complete remission. CRi=CR with Incomplete Recovery of Blood Count.
CRh=CR with Partial Hematologic Recovery. MRD=Measurable Residual Disease. NR=Not Reached. PBO=Placebo. VEN=Venetoclax.

Primary Outcome
Data cutoff: January 4, 2020.
DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29.

Long-term follow-up: Overall survival

	VEN + AZA (N=286)	PBO + AZA (N=145)
Median OS, months (95% CI)	**14.7** (12.1-18.7)	**9,6** (7.4-12.7)
Number of events, n (%)	222 (77.6)	138 (95,2)
HR (IC de 95%), log-rank *P**	0.58 (0.465-0.723), *P* <.001	
Median duration of treatment, months (range)	7.6 (<0.1-30.7)	4.3 (0.1-24.0)



VEN + AZA	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
PBO + AZA	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

Median follow-up:

43.2 months
(interval <0,1 – 53,4)

100% OS Analysis
360/431 survival events

*Distributions were estimated for each treatment arm using the Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, high risk). HR between treatment arms was estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test. AZA=Azacitidine. CI=Confidence Interval. HR=Risk Ratio. OS=Overall Survival. PBO=Placebo. VEN=Venetoclax.

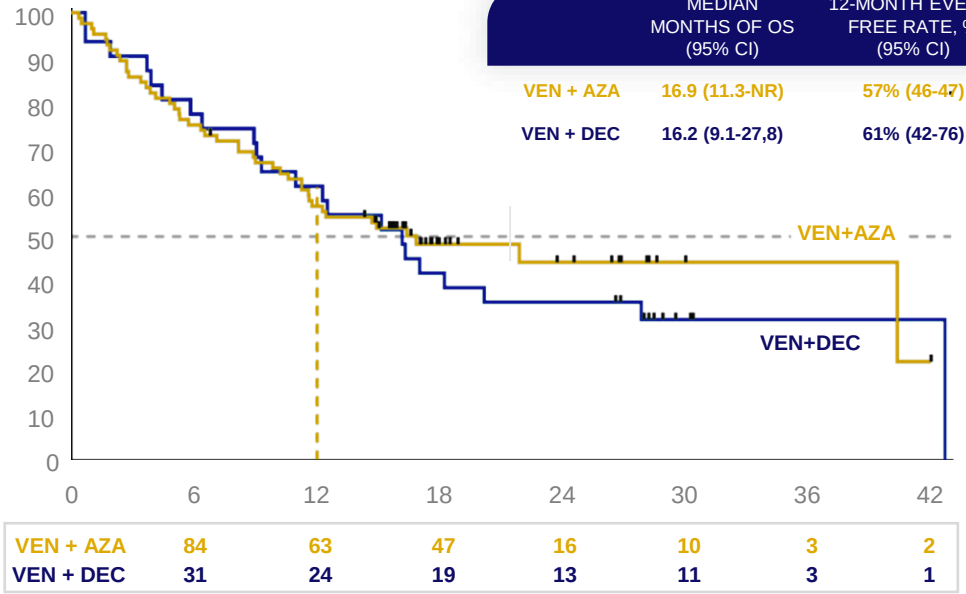
Primary Outcome
Data cutoff: December 1, 2021.
Pratz KW, et al. Oral 219. 64th ASH. Dec 10-13, 2022. New Orleans, LA.

M14-358: Overall survival – combined analysis

MEDIAN OS

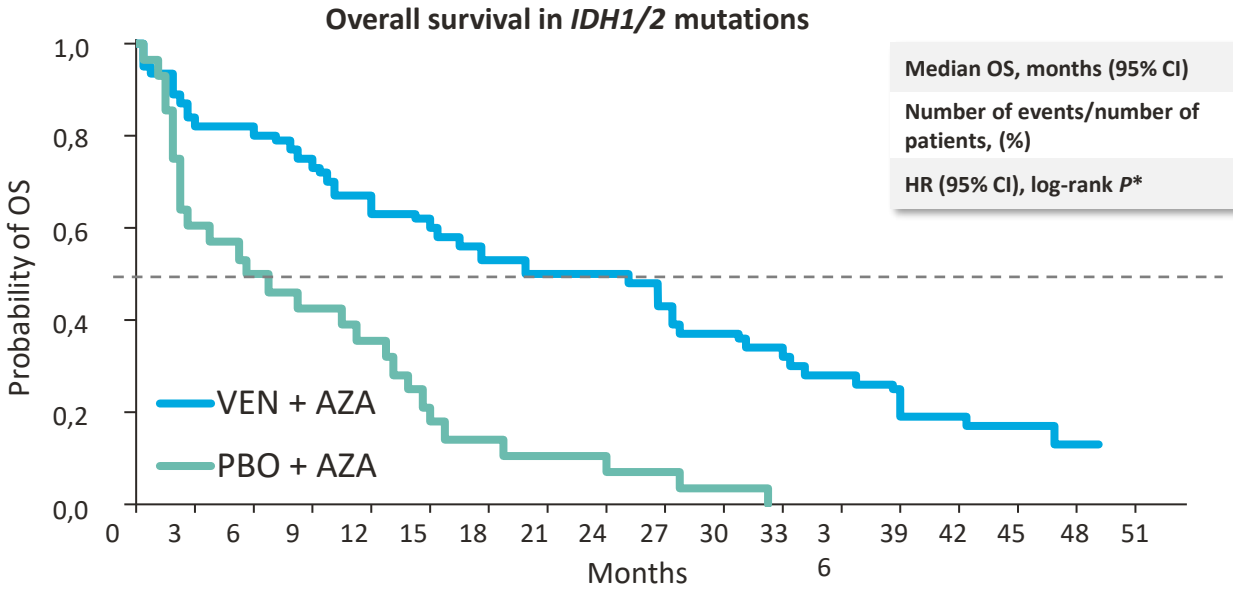
Venetoclax + azacitidine
14.9 months (0.4–42.0)

Venetoclax + Decitabine
16.2 months (0.7–42.7)



1. Pollyea DA, et al. ASH 2018. Abstract 285; 2. DiNardo CD, et al. Blood. 2018;133:7-17.

Long-term follow-up: Patients with *IDH1/2* mutations achieved median OS in the analysis of 100% OS



	VEN + AZA (N=286)	PBO + AZA (N=145)
Median OS, months (95% CI)	**19.9** (12.2-27.7)	**6.2** (2.3-12.7)
Number of events/number of patients, (%)	49/61 (80.3)	28/28 (100)
HR (95% CI), log-rank *P**	0.314 (0.189-0.522), *P* <.001	

VEN + AZA	61	51	48	44	39	35	31	29	29	24	21	19	15	11	9	8	3	0
PBO + AZA	28	17	14	12	10	5	4	3	2	2	1	0	0	0	0	0	0	0

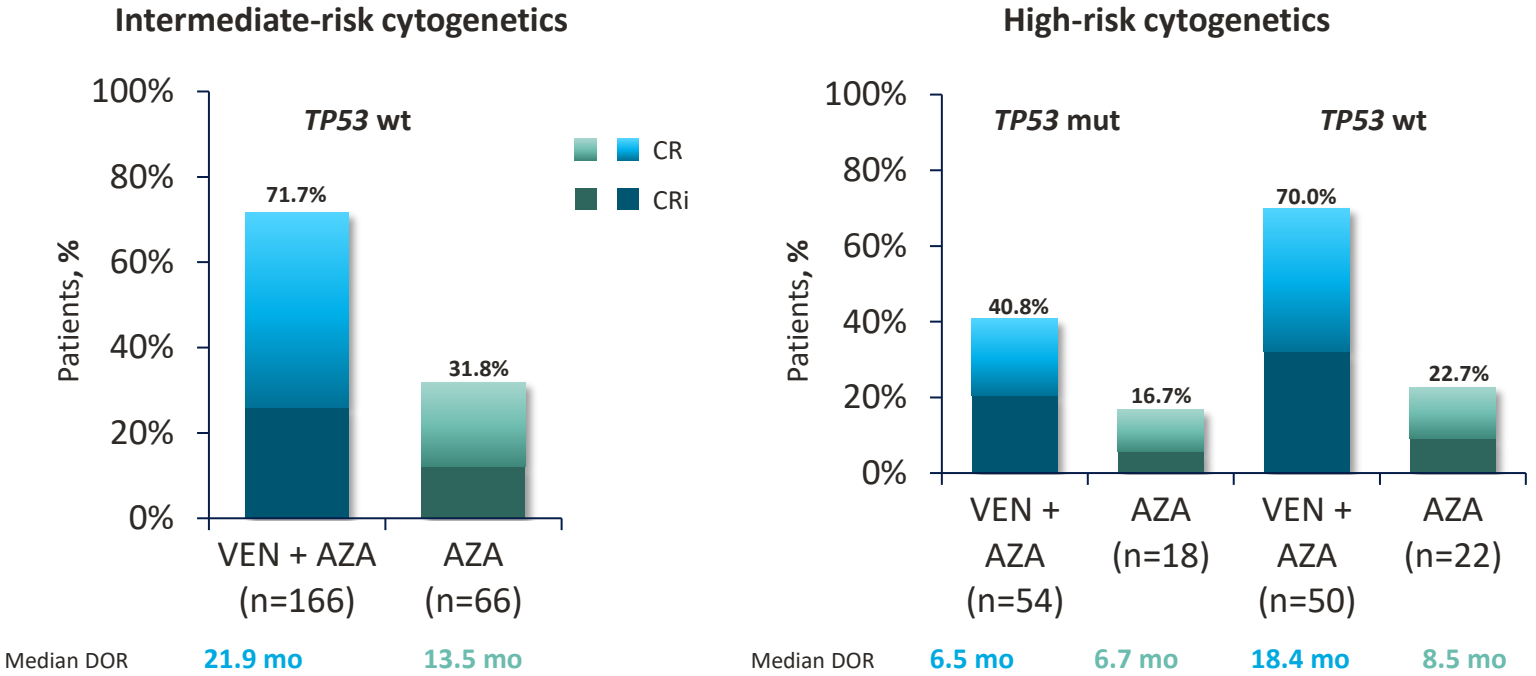
Post-hoc analysis

Subgroup analyses were not designed to demonstrate a statistically significant difference in OS or response rates.
Small numbers of patients in these subgroups may be a limitation of this analysis.
No conclusions of efficacy or safety can be drawn from these data.
Data cutoff: December 1, 2021.

*Distributions were estimated for each treatment arm using the Kaplan-Meier methodology.
The unstratified log-rank test and hazard ratio were estimated using the unstratified Cox model. The HDI1/2 data comes from the CDX method.
AZA=Azacitidine. CI=Confidence Interval. HR=Risk Ratio. OS=Overall Survival. PBO=Placebo. VEN=Venetoclax.

Pratz KW, et al. Oral 219. 64th ASH. December 10-13, 2022. New Orleans, LA.

In a pooled analysis of patients from VIALE-A and the phase Ib study, remission rates were high in intermediate- or high-risk cytogenetics and *TP53*wt patients treated with VEN+AZA



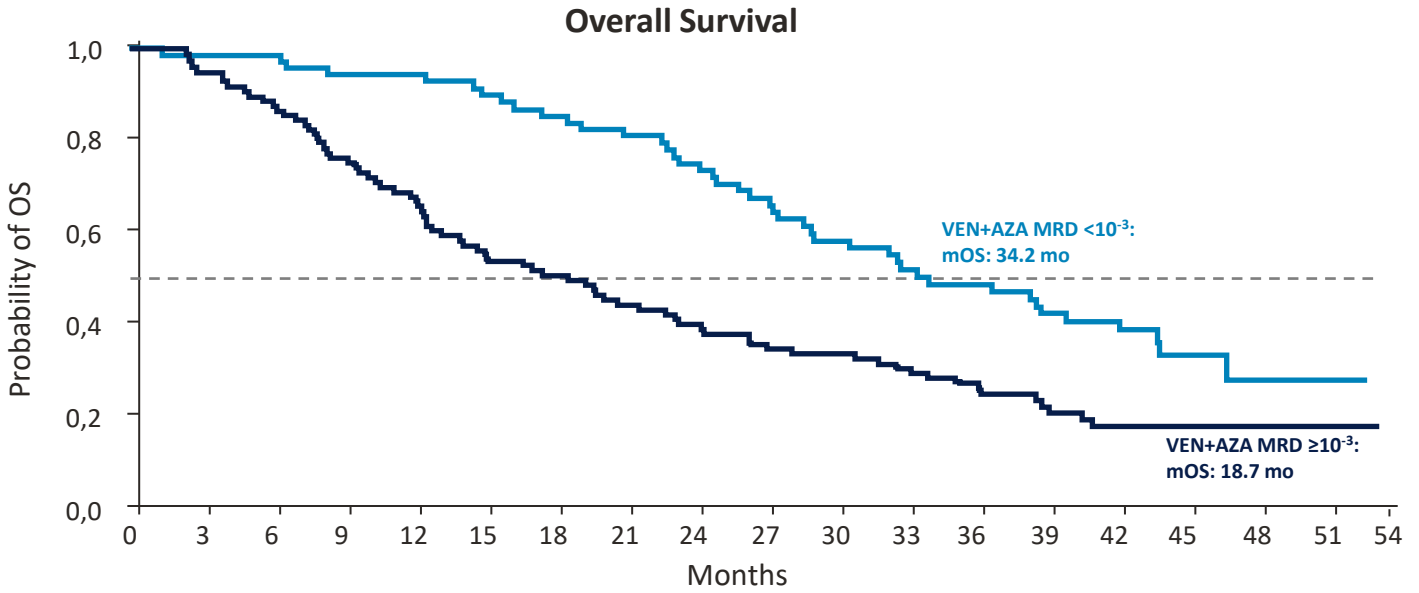
Post-hoc analysis

Subgroup analyses were not designed to demonstrate a statistically significant difference in OS or response rates.
Small numbers of patients in these subgroups may be a limitation of this analysis.
No conclusions of efficacy or safety can be drawn from these data.

Aza=Azacitidine. CR=Complete remission.
CRi=CR with Incomplete Hematologic Recovery. Mut=Mutation. Ven=Venetoclax. wt=Wild-type.

Pollyea DA, et al. Clin Cancer Res. 2022 Aug 25;CCR-22-1183. doi: 10.1158/1078-0432.CCR-22-1183. Online ahead of print.

Long-term follow-up: Overall survival by MRD response



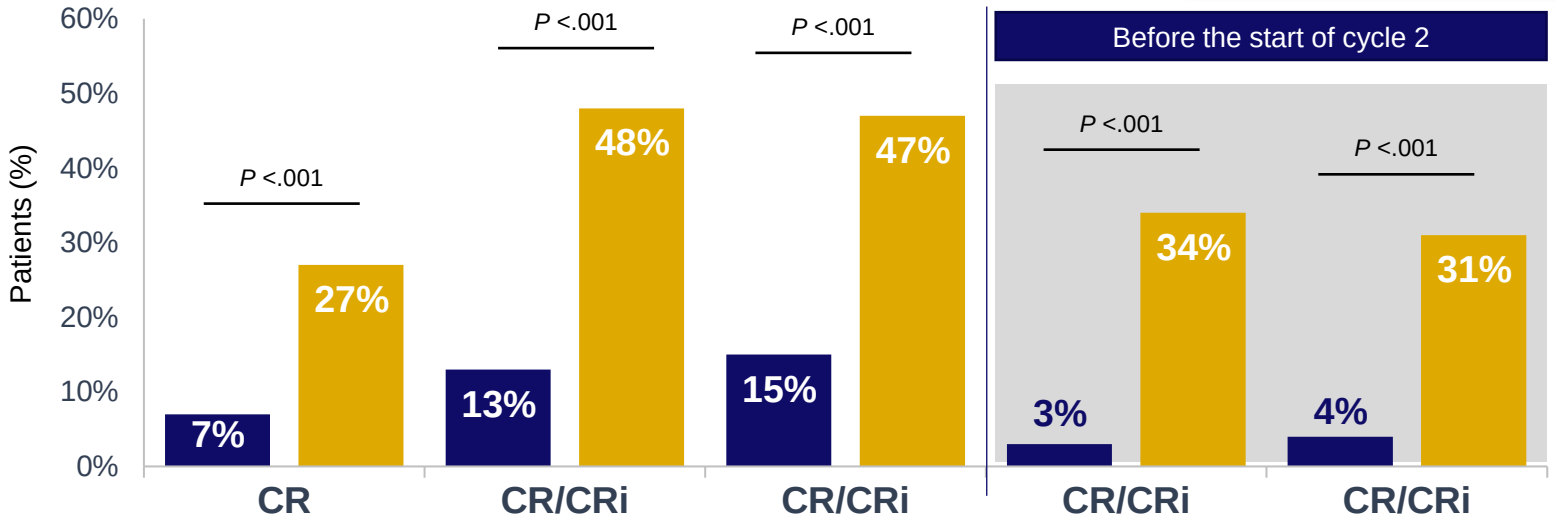
Patients at risk																			
<10⁻³ VEN	69	68	67	64	64	61	57	55	50	43	37	34	31	26	22	10	4	1	0
≥10⁻³ VEN	96	91	85	73	63	52	47	41	37	33	31	28	23	17	10	7	2	1	0

*Distributions were estimated for each treatment arm using the Kaplan-Meier methodology.
AZA=Azacitidine. CI=Confidence Interval. HR=Risk Ratio. OS=Overall Survival. PBO=Placebo. VEN=Venetoclax.

Data cutoff: December 1, 2021.
Pratz KW, et al. Oral 219. 64th ASH. December 10-13, 2022. New Orleans, LA.

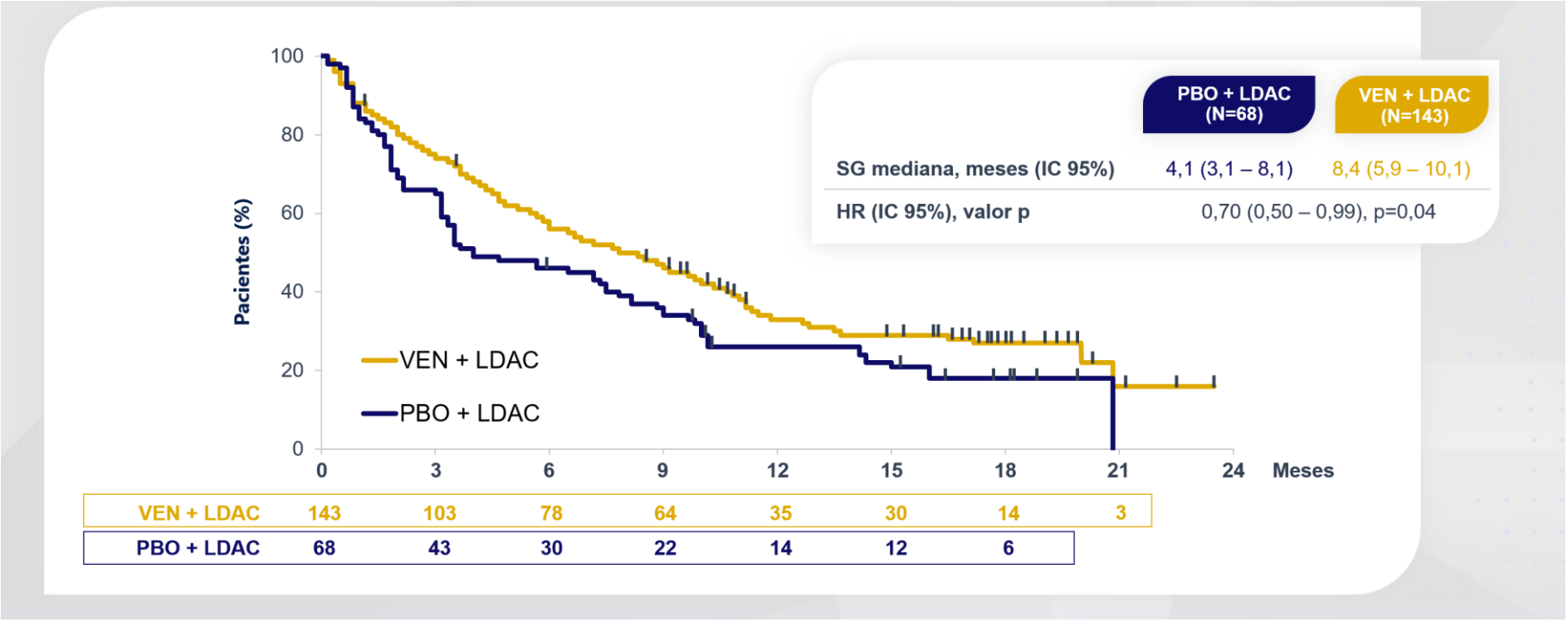
VIALE-C: Response rates

	PFS, median (95% CI) months
PBO + LDAC	2.0 (1.6-3.1)
VEN + LDAC	4.7 (3.7-6.4)*



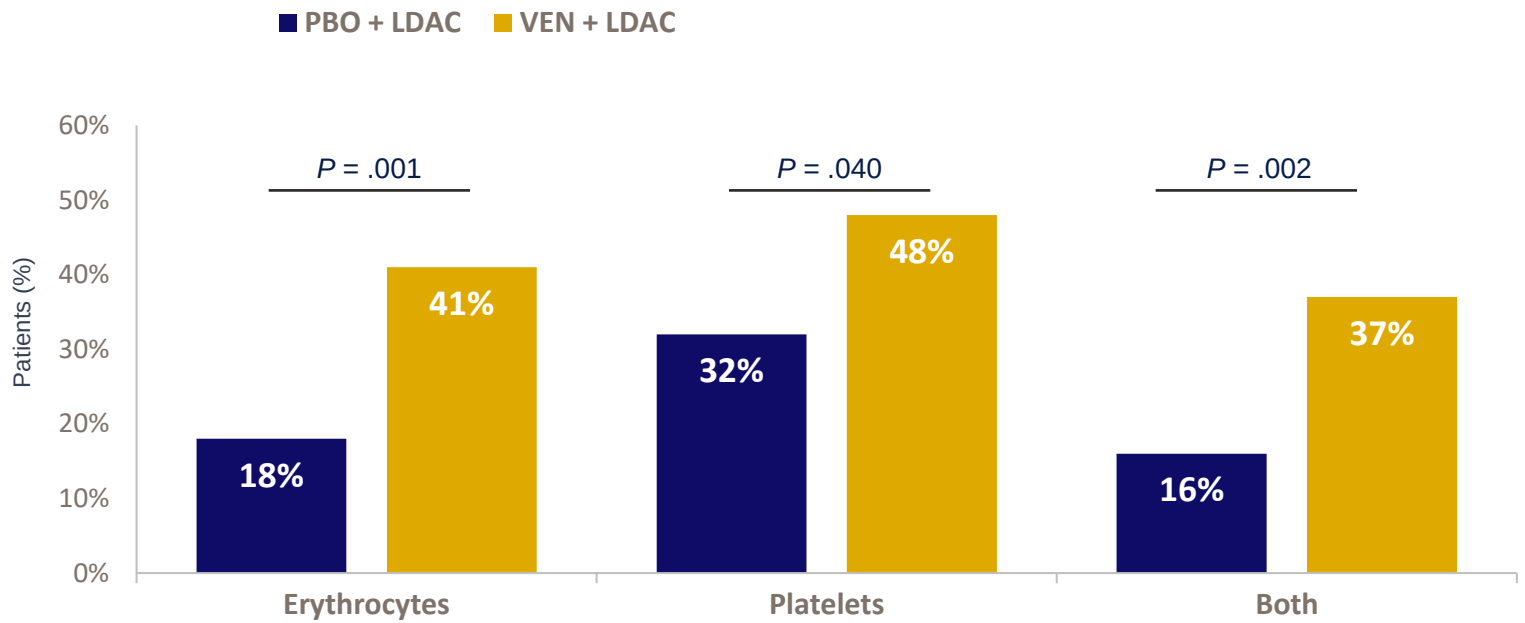
Wei AH et al, Blood 2020 Jun 11;135(24): 2137-2145. doi: 10.1182

VIALE-C: Overall survival in the preplanned primary analysis



Wei AH et al, Blood 2020 Jun 11;135(24): 2137-2145. doi: 10.1182

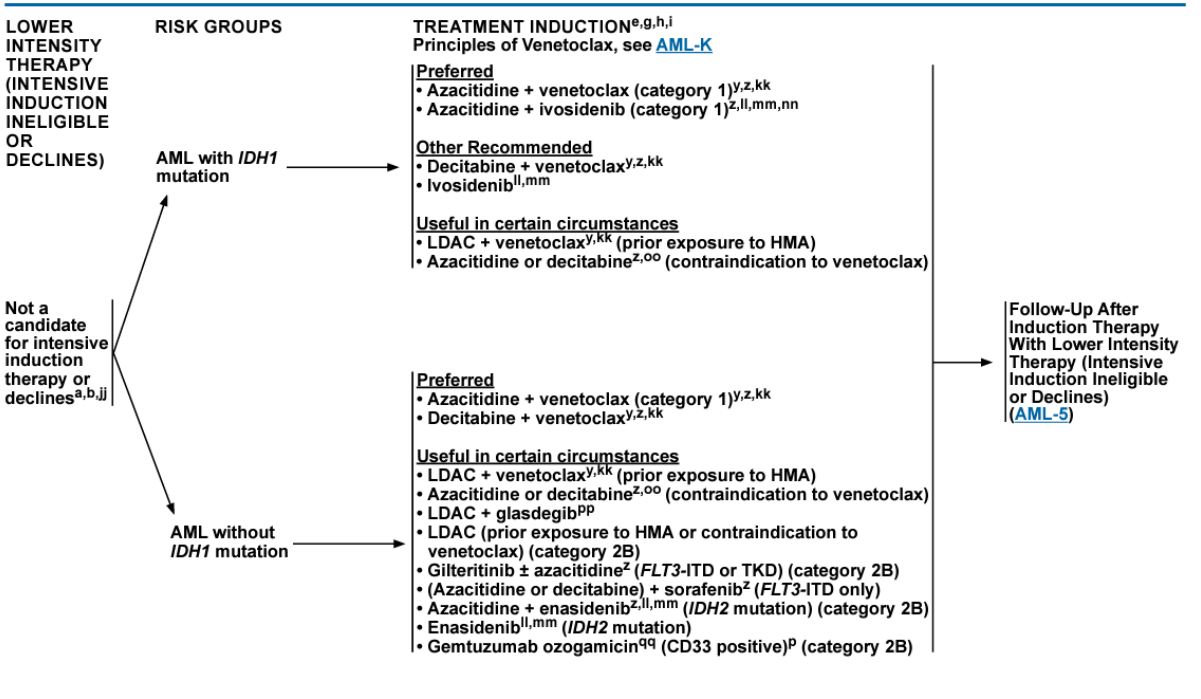
VIALE-C: Transfusion independence*



*Defined as ≥56 consecutive days without a complete blood count or platelet transfusion between the first and last day of treatment

Wei AH et al, Blood 2020 Jun 11;135(24): 2137-2145. doi: 10.1182

NCCN Guidelines prioritize venetoclax combinations as the first line of treatment for patients ineligible for CT

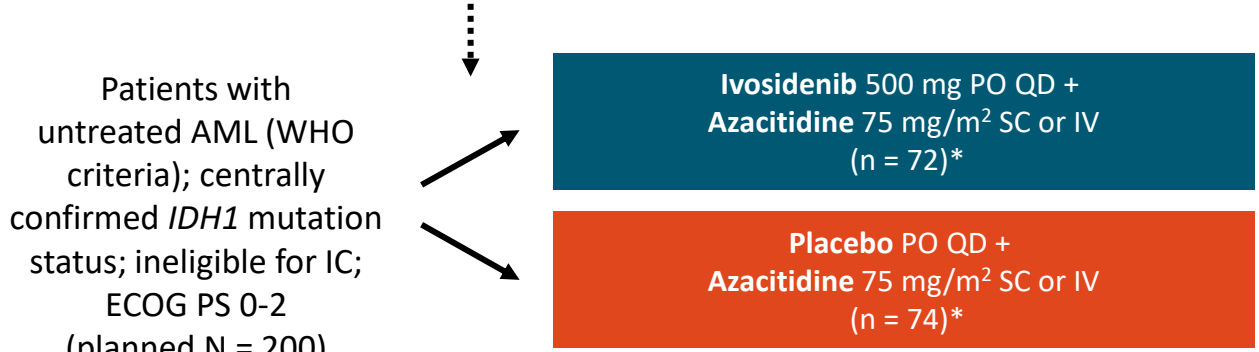


Note: Based on NCCN v3.2024 guidelines
NCCN: National Comprehensive Cancer Network; aHSCT: transplante alogênico de células-tronco hematopoiéticas;

AGILE: Study design

- Multicenter, double-blind, randomized phase III trial

  Stratified by region (US/Canada vs Western Europe, Israel, and Australia vs Japan vs rest of world) and disease history (de novo vs secondary AML)



*Enrollment at time of data cutoff (May 18, 2021).

- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

Montesinos. ASH 2021. Abstr 697.

AGILE: Baseline characteristics

Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median age, yr (range)	76.0 (58-84)	75.5 (45-94)
Sex, n (%)		
▪ Male	42 (58.3)	38 (51.4)
▪ Female	30 (41.7)	36 (48.6)
ECOG PS, n (%)		
▪ 0	14 (19.4)	10 (13.5)
▪ 1	32 (44.4)	40 (54.1)
▪ 2	26 (36.1)	24 (32.4)
Disease history, n (%)		
▪ De novo AML	54 (75.0)	53 (71.6)
▪ Secondary AML	18 (25.0)	21 (28.4)

Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median m*IDH1* VAF in BMA, % (range)	36.7 (3.1-50.5)	35.5 (3.0-48.6)
Cytogenetic risk, n (%)		
▪ Favorable	3 (4.2)	7 (9.5)
▪ Intermediate	48 (66.7)	44 (59.5)
▪ Poor	16 (22.2)	20 (27.0)
Median bone marrow blasts, % (range)	54.0 (20-95)	48.0 (17-100)

Montesinos. ASH 2021. Abstr 697.

AGILE: EFS and other efficacy outcomes

Survival Outcome	IVO + AZA	PBO + AZA	HR (95% CI)	*P* Value
Median EFS in ITT population	NR	NR	0.33 (0.16-0.69)	.0011
Median EFS in patients achieving CR by Wk 24, mo (95% CI)	NE (14.8-NE)	17.8 (9.3-NE)	NR	NR
Median OS, mo	24.0	7.9	0.44 (0.27-0.73)	.0005

- EFS benefit associated with IVO consistent across subgroups: de novo status, region, age, ECOG PS at BL, sex, race, BL cytogenetic risk, WHO AML classification, WBC at BL, percentage of BM blasts at BL
- OS benefit associated with IVO consistent against same subgroups
- Change in markers of health-related QOL favored IVO + AZA over PBO + AZA

Montesinos. ASH 2021. Abstr 697.

AGILE: TEAEs

TEAEs, n (%)	IVO + AZA (n = 71)		PBO + AZA (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAE	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs*				
▪ Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
▪ Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
▪ Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
▪ Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs*				
▪ Nausea	30 (42.3)	2 (3.8)	28 (38.4)	3 (4.1)
▪ Vomiting	29 (40.8)	0	19 (36.0)	1 (1.4)
▪ Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
▪ Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
▪ Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
▪ Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

*Occurring in >20% of patients.

Montesinos. ASH 2021. Abstr 697.

- AEs of special interest (IVO + AZA vs PBO + AZA):
  - Grade ≥2 differentiation syndrome: 14.1% vs 8.2%
  - Grade ≥3 QT prolongation: 9.9% vs 4.1%
- Fewer infections with IVO + AZA vs PBO + AZA (28.2% vs 49.3%)
- No treatment-related deaths

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Montesinos P et al. DOI: 10.1056/NEJMoa2117344

CLINICAL PROBLEM

Approximately 6 to 10% of patients with acute myeloid leukemia have somatic mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*). Ivosidenib, an inhibitor of mutant IDH1, showed promise when combined with azacitidine in a phase 1b trial involving patients with *IDH1*-mutated acute myeloid leukemia, but additional data are needed.

CLINICAL TRIAL

Design: A phase 3 global, double-blind, randomized trial examined the efficacy and safety of ivosidenib and azacitidine as compared with placebo and azacitidine in patients with previously untreated, *IDH1*-mutated acute myeloid leukemia who were ineligible for intensive induction chemotherapy.

Intervention: 146 adult patients were randomly assigned to receive oral ivosidenib (500 mg once daily) and intravenous or subcutaneous azacitidine (75 mg per square meter of body-surface area for 7 days in 28-day cycles) or to receive placebo and azacitidine, for at least six cycles. The primary end point was event-free survival, defined as the time from randomization to treatment failure, relapse from remission, or death from any cause.

RESULTS

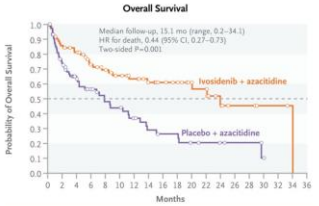
Efficacy: During a median follow-up of 12.4 months, event-free survival was significantly longer with ivosidenib and azacitidine than with placebo and azacitidine.

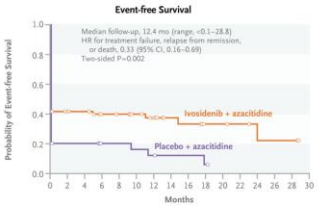
Safety: More than 90% of the patients in each group had adverse events of grade 3 or higher; common events included febrile neutropenia, anemia, thrombocytopenia, pneumonia, and infection.

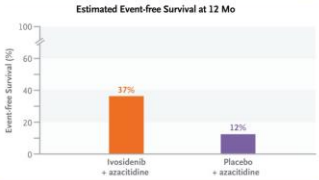
LIMITATIONS AND REMAINING QUESTIONS

- A data monitoring committee stopped enrollment early owing to an observed overall survival benefit with ivosidenib and azacitidine; accordingly, subgroup analyses were limited.
- How combination therapy with ivosidenib and azacitidine compares with current venetoclax-based regimens is unknown.

Links: Full Article | NEJM Quick Take

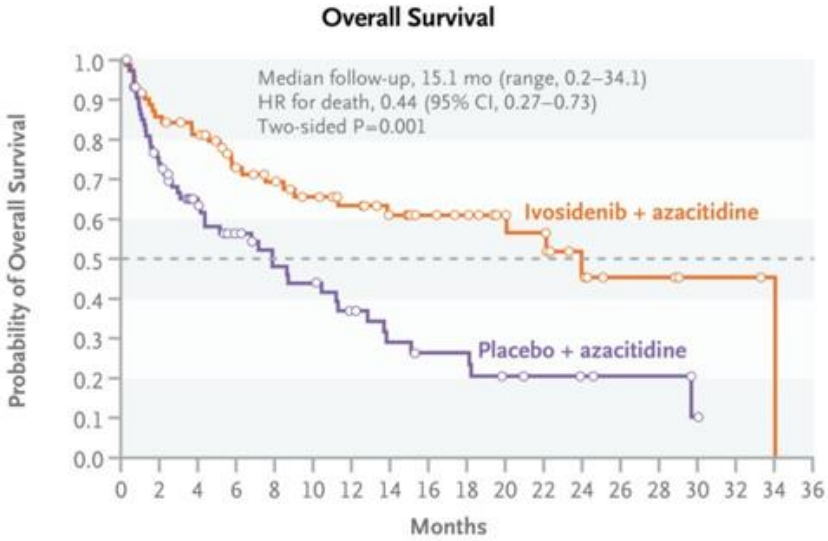






CONCLUSIONS

Among patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia, the combination of ivosidenib and azacitidine extended event-free survival as compared with placebo and azacitidine, without an increase in adverse events.



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

High-risk AML

- Highly unmet need
- HSCT may not be the answer for all patients
- Relapse post-HSCT still a problem – maintenance?
- High-dose decitabine [*N Engl J Med* 2016; 375:2023-2036]
- APR-246 (eprenetapopt) [*J Clin Oncol* 2021 May 10;39(14):1584-1594]
- Magrolimab (anti-CD 47) do not “eat me” signal [*J Clin Oncol* 2023 Sep 13]
- Sabatolimab (anti-TIM-3)
- IDH1/IDH2 inhibitors

Global Leukemia Academy

Panel discussion

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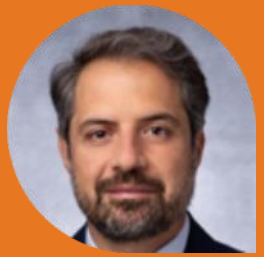
Session close

Elias Jabbour



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Question 3 [REPEATED]

If an elderly patient with Ph-negative ALL tests positive for MRD after dose-adjusted Hyper-CVAD induction chemotherapy, what would you advise?

Please assume that you have access to all of these options.

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

Question 4 [REPEATED]

Which of the following factors are important in assessing patients with AML at diagnosis?

Select all that apply.

A. Adverse genetic alterations
B. Age
C. Comorbidities
D. Performance status
E. Prior cytotoxic therapy
F. Prior myelodysplasia

Day 2: Virtual Plenary Sessions

Thursday, June 20, 2024
5.00 PM – 8.00 PM UTC -5 (Houston)
7.00 PM – 10.00 PM UTC -3 (Brasilia/Buenos Aires)

Time (UTC -3)	Title	Speaker
7.00 PM – 7.10 PM	Welcome to Day 2	Naval Daver
7.10 PM – 7.30 PM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
7.30 PM – 7.50 PM	Long-term safety considerations for leukemias (focus on ALL)	Jae Park
7.50 PM – 8.10 PM	Current and future role of transplantation in acute leukemias in LATAM	Phillip Scheinberg
8.10 PM – 8.20 PM	Break	
8.20 PM – 8.40 PM	Current treatment options for relapsed AML in adult and elderly patients	Fabio Santos
8.40 PM – 9.10 PM	AML case-based panel discussion • Case AML: young high-risk (8 min + 5-min discussion) • Case AML: elderly (10 min) (8 min + 5-min discussion)	Fabio Santos and TBD (case presenters) All faculty
9.10 PM – 9.50 PM	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 LATAM	Naval Daver and all faculty
9.50 PM – 10.00 PM	Session close	Naval Daver

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