Global Leukemia Academy

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

August 23 and 24, 2024 – Asia-Pacific

Meeting sponsors AMGEN rigel

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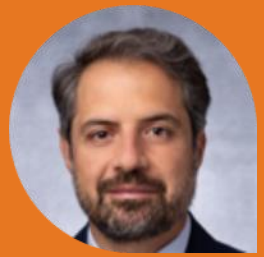
Global Leukemia Academy

Welcome and meeting overview

Elias Jabbour



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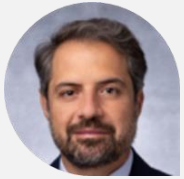
Meet the Faculty

CHAIR



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

CO-CHAIR

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

FACULTY

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

Junichiro Yuda, MD, PhD,
Department of Hematology and Experimental Therapeutics,
National Cancer Center Hospital East,
Kashiwanoha, Kashiwa, Japan

Shaun Fleming, MBBS(Hons), FRACP, FRCPA
Alfred Hospital, Melbourne, VIC, Australia

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 JAPAC

Agenda: Day 1

Time (UTC +8)	Title	Speaker
8.00 AM – 8.10 AM	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
8.10 AM – 8.25 AM	Latest achievements and developments in ALL and AML	Elias Jabbour
8.25 AM – 8.40 AM	Review of prognostic value of MRD in ALL and AML	Jae Park
8.40 AM – 8.50 AM	Best practices for first-line treatment in ALL	Elias Jabbour
8.50 AM – 9.05 AM	AYA patients with ALL: What is the current treatment approach for this diverse patient population?	Jae Park
9.05 AM – 9.35 AM	ALL case-based panel discussion • Case 1 ALL: Mridula Mokoonlall (Australia) • Case 2 ALL: Rithin Nedumannil (Australia)	Elias Jabbour Patient case presenters And all faculty
9.35 AM – 9.45 AM	Break	
9.45 AM – 10.10 AM	Genetic characterization and risk stratification of AML; role of *FLT3* and *IDH* in AML and special considerations for young and fit patients	Naval Daver
10.10 AM – 10.25 AM	Therapeutic approaches in high-risk and frail patients with AML	Shaun Fleming
10.25 AM – 10.50 AM	Panel discussion: Open questions in ALL and AML – regional challenges • How acute leukemia treatment is different in Asia-Pacific (guidelines, treatment availability)	Elias Jabbour, Junichiro Yuda and all faculty
10.50 AM – 11.00 AM	Session close	Elias Jabbour

Agenda: Day 2

Time (UTC +8)	Title	Speaker
8.00 AM – 8.10 AM	Welcome to Day 2	Naval Daver
8.10 AM – 8.30 AM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
8.30 AM – 8.50 AM	Long-term safety considerations for leukemias (focus on ALL)	Jae Park
8.50 AM – 9.10 AM	Current and future role of transplantation in acute leukemias in Asia-Pacific	Shaun Fleming
9.10 AM – 9.20 AM	Break	
9.20 AM – 9.40 AM	Current treatment options for relapsed AML in adult and elderly patients	Junichiro Yuda
9.40 AM – 10.10 AM	AML case-based panel discussion • Case 1 AML: Ane Veu (Fiji) • Case 2 AML: Feng-Ming Tien (Taiwan)	Naval Daver and Patient case presenters And all faculty
10.10 AM – 10.50 AM	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 Asia-Pacific	Naval Daver and all faculty
10.50 AM – 11.00 AM	Session close	Naval Daver

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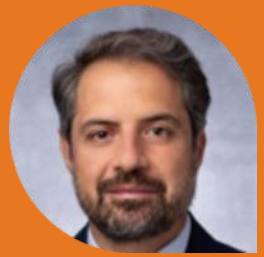
Introduction to the voting system

Elias Jabbour



APTITUDE HEALTH®

Question 1

In which country do you currently practice?

A. Australia
B. China
C. Hong Kong
D. Japan
E. Malaysia
F. Singapore
G. South Korea
H. Taiwan
I. Other country in Asia-Pacific
J. Other country outside Asia-Pacific

Question 2

Which leukemias do you primarily treat?

A. AML

B. ALL

C. Both

Question 3

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

A. After induction/consolidation

B. Prior to allogeneic hematopoietic cell transplant

C. After transplant

D. All of the above

Question 4

Which of the following is NOT true for treating ALL?

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

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

C. MRD– CR does not correlate strongly with outcome

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

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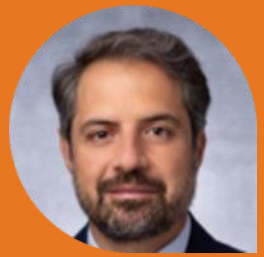
Latest achievements and developments in ALL and AML

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)

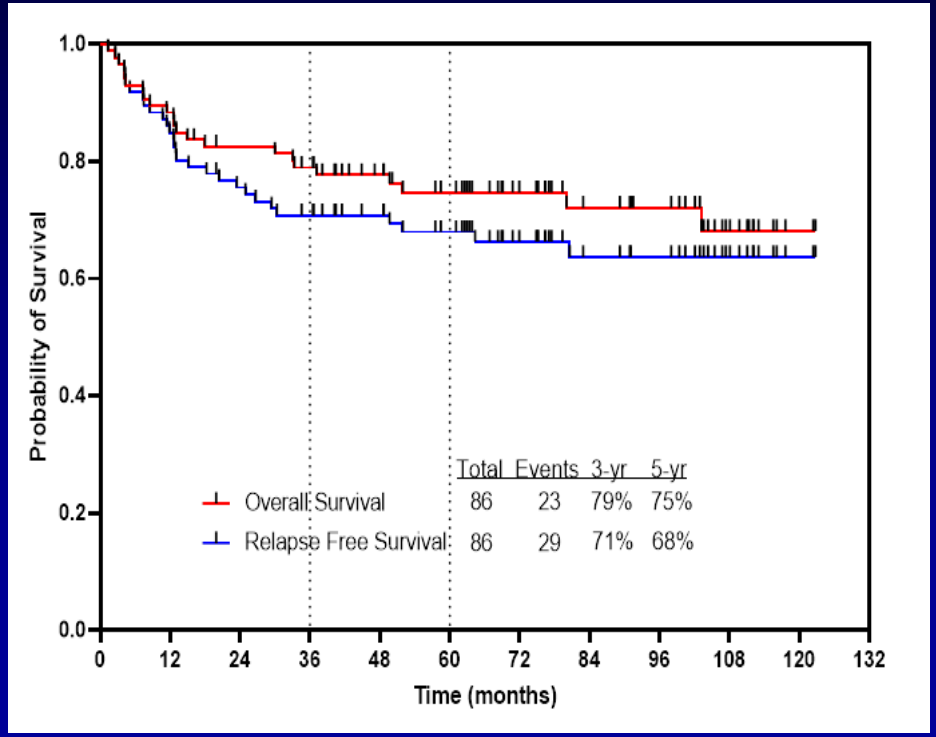
Garciaz. HemaSphere 8: S146; 2024

What Is New in ALL

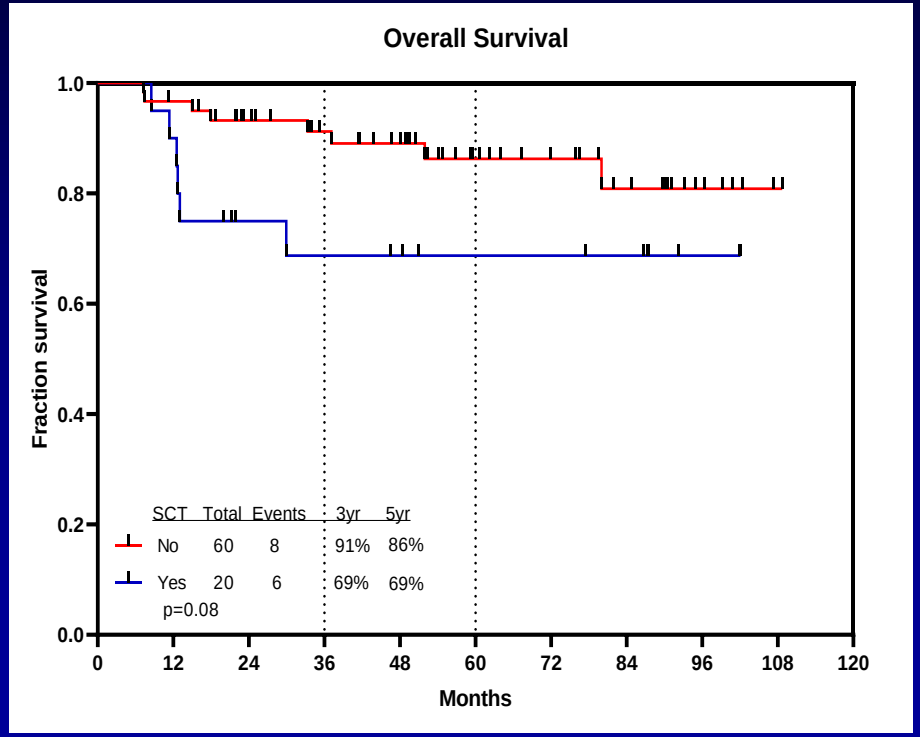
HyperCVAD + Ponatinib in Ph+ ALL

- 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



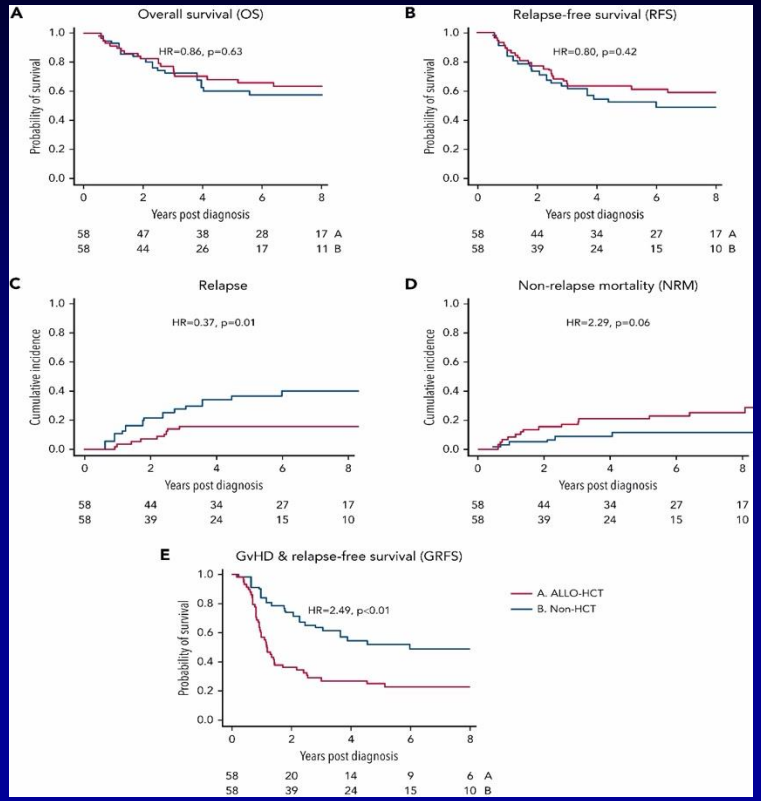
6-month Landmark



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

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

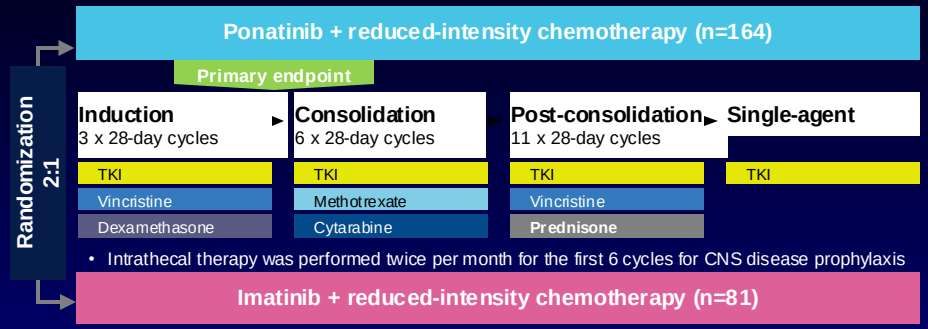
- Propensity score analysis of patients who achieved CMR within 3 months
- Allogeneic SCT → lower risk of relapse but higher NRM
- No impact of SCT on OS or RFS



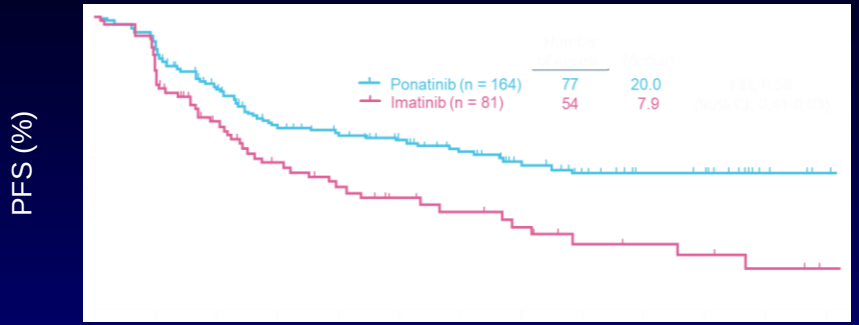
Ghobadi A et al. *Blood* 2022;140(20):2101-12

Ponatinib vs Imatinib With Rx in Ph+ ALL: PhALLCON

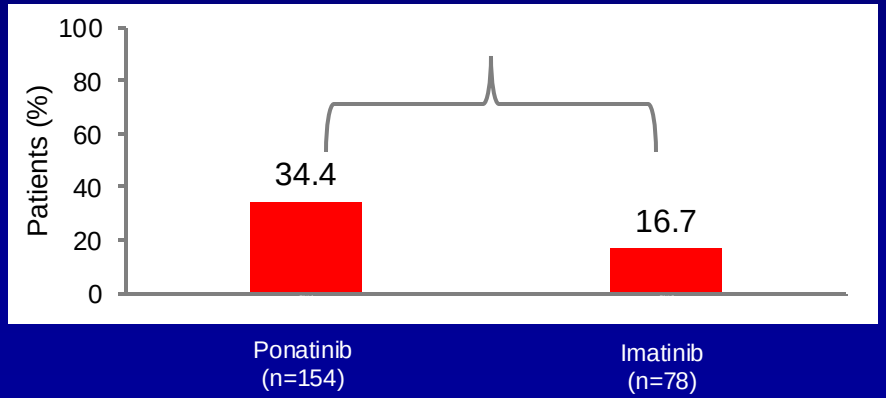
Study design



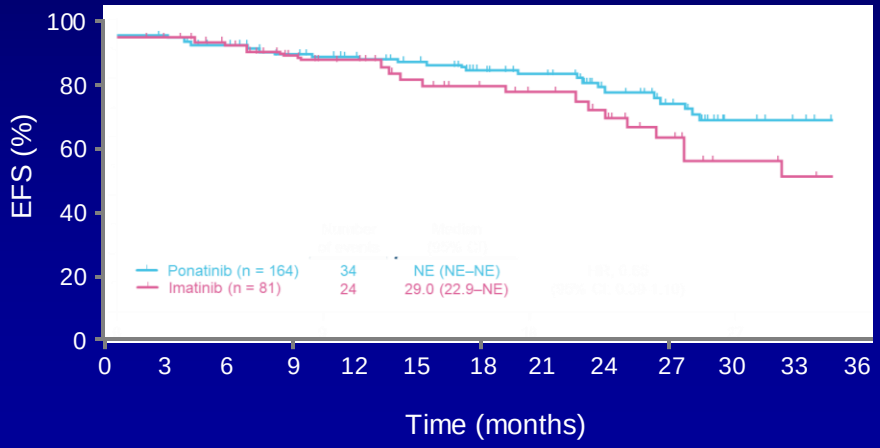
PFS



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



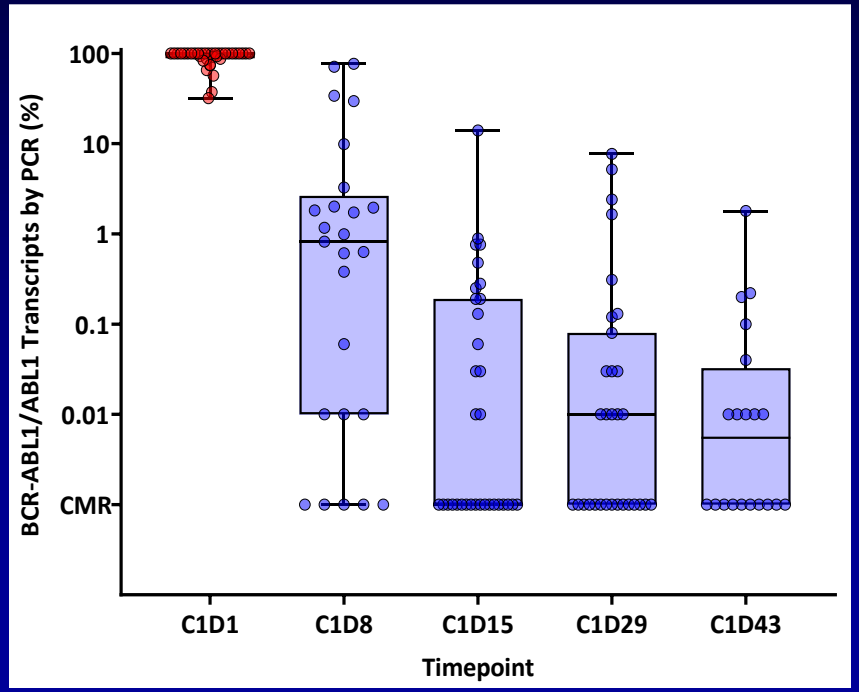
EFS

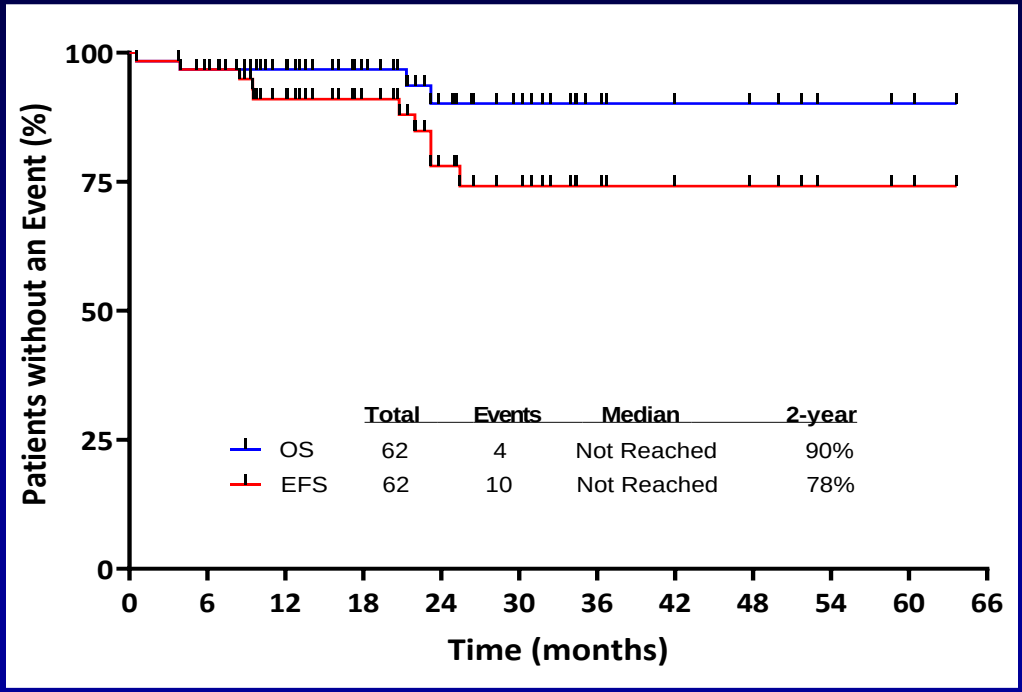


Jabbour. JAMA. 2024 May 9:e244783.

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.

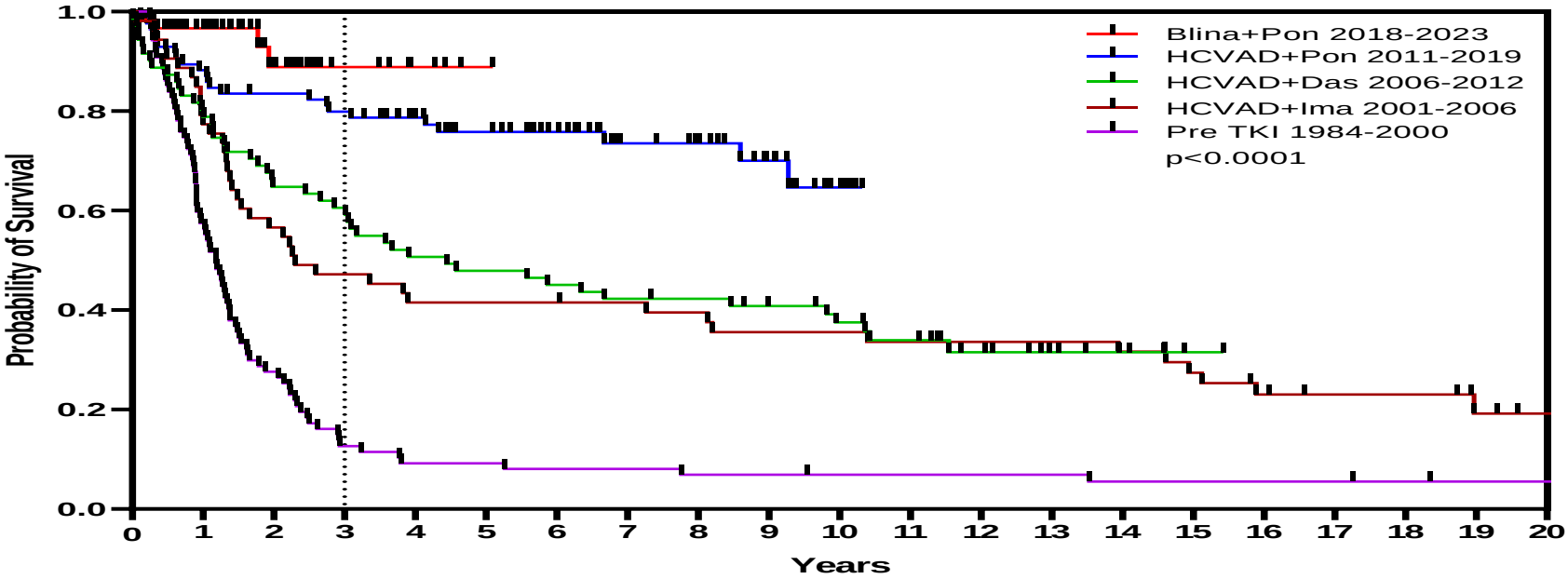
Haddad. Blood 142: abstr 2827;2023

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

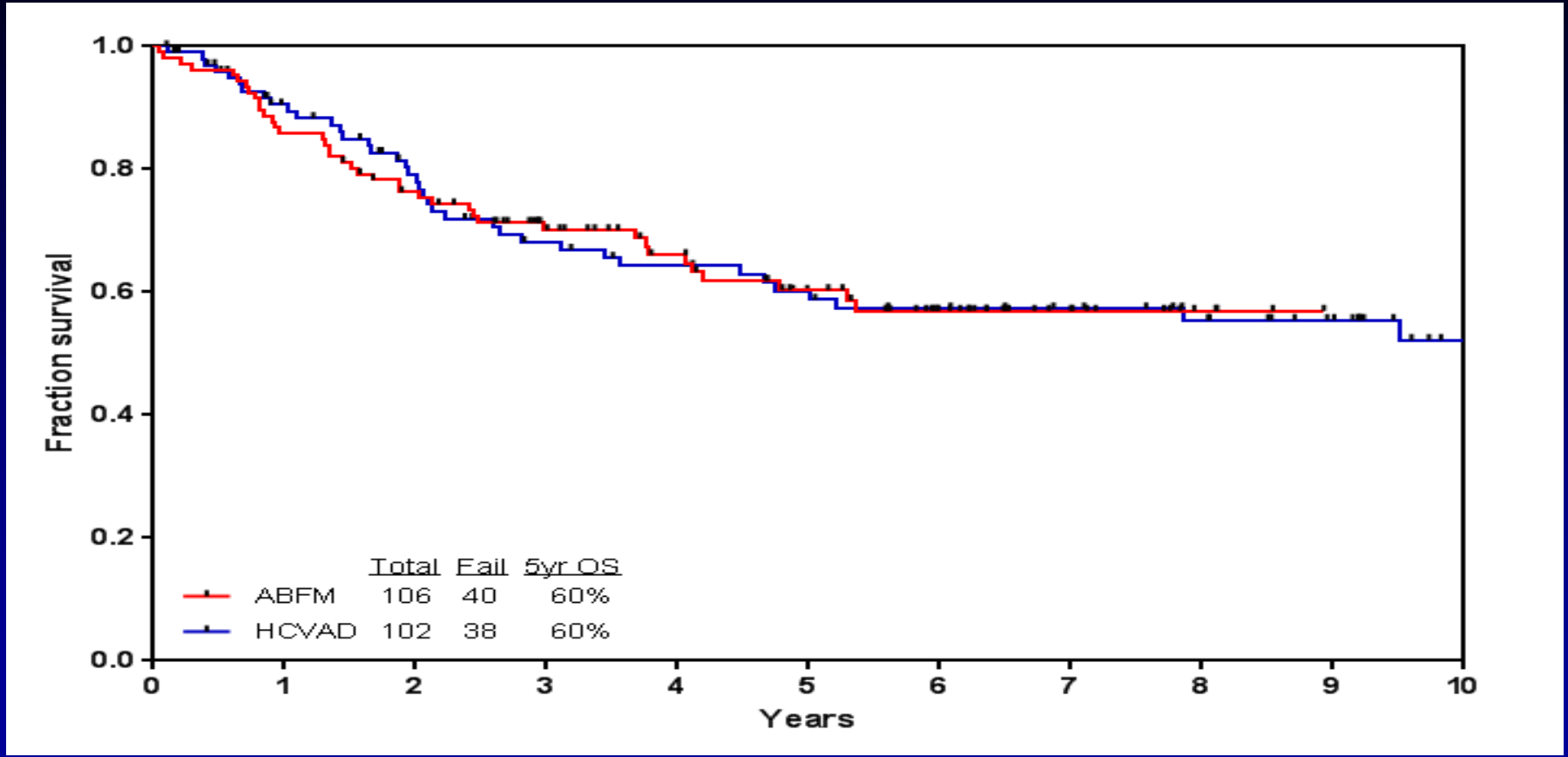
Ph+ ALL: Survival by Decade (MDACC 1984-2023)



	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

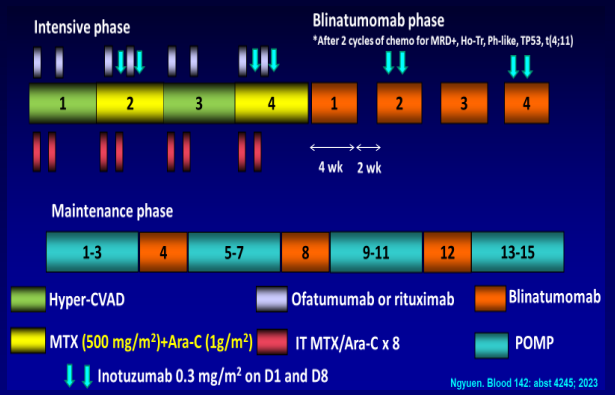
Hyper-CVAD vs ABFM: Overall Survival

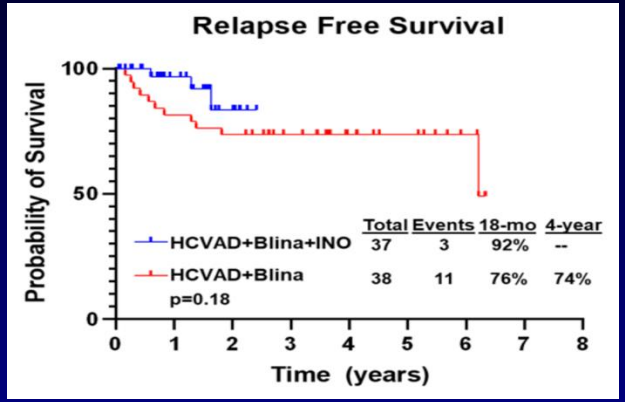


Rytting. *Cancer*. 2014;120:3660-3668; Rytting. *Am J Hematol*. 2016;91:819.

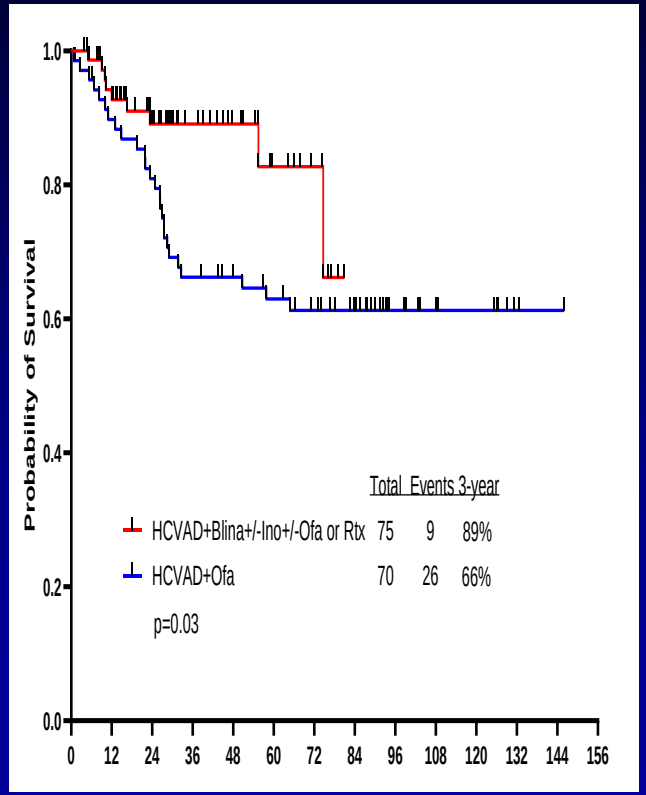
Hyper CVAD-Inotuzumab → Blina in Newly Dx Adult ALL

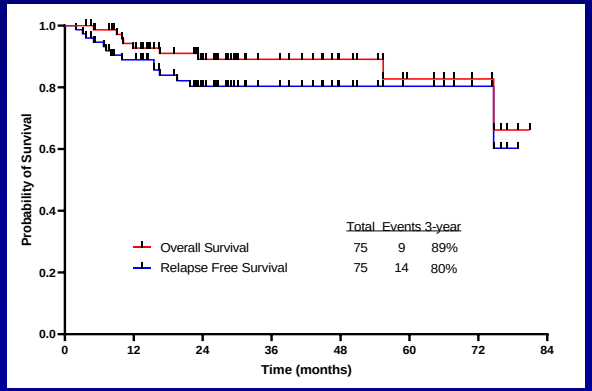
- 75 pts; median age 33 yrs (18-59); Median F/U 26 months (1-77)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 73%; 60-day mortality 0%; 24 (32%) allo-SCT;

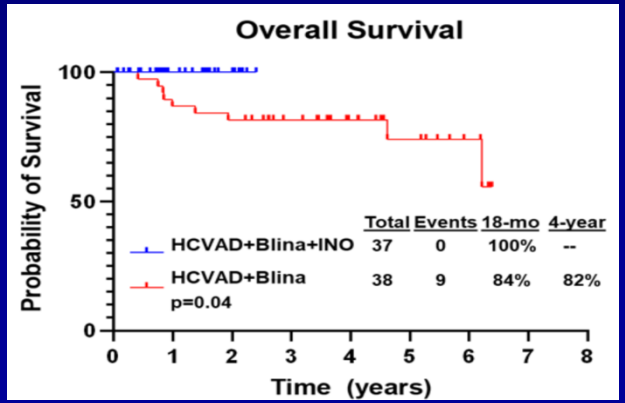




Overall Survival

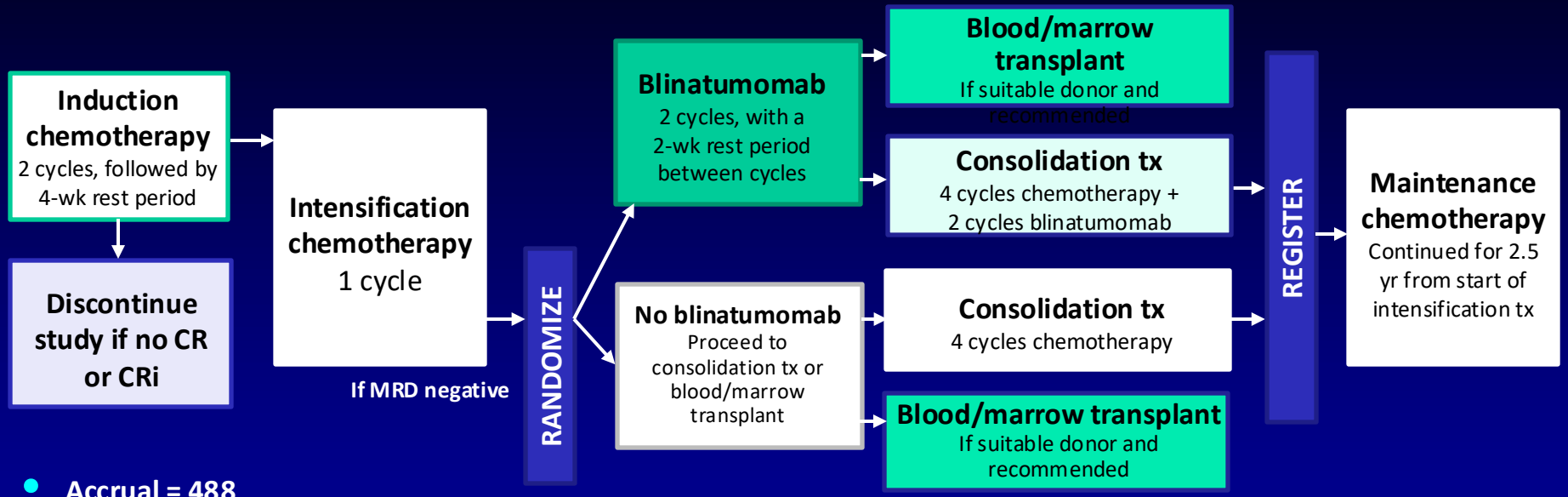






Nguyen. Blood 142: abst 4245; 2023

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



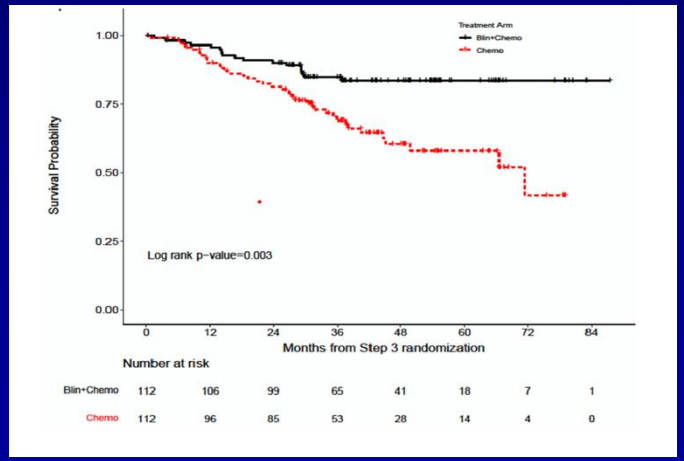
- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

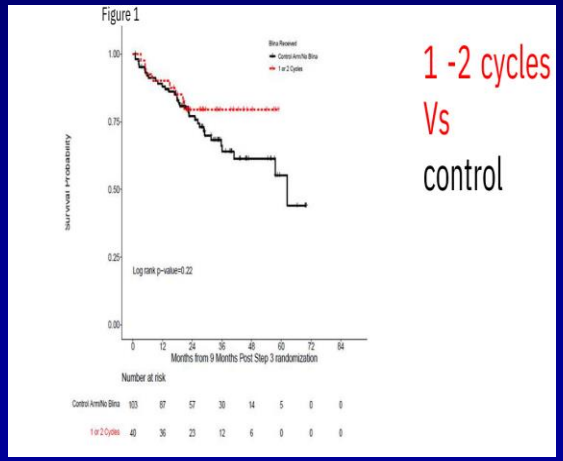
Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

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

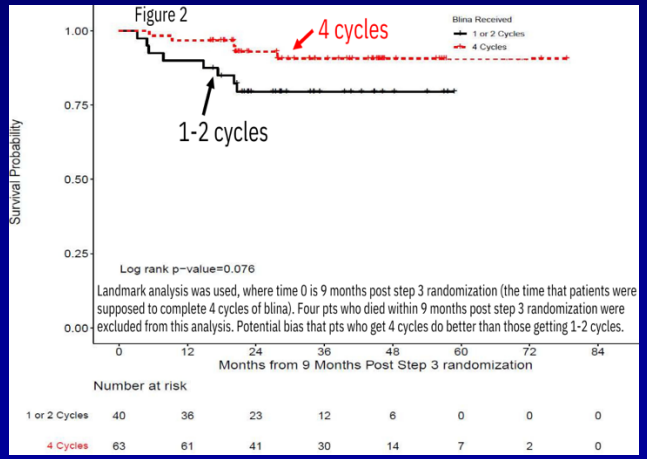
- 488 pts median age 51 yrs (30-70)
- 224 MRD-negative CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median F/U 43 months; median OS NR vs 71.4 mos (HR=0.42; p=0.003)
- No difference in OS if 1-2 cycles of blina vs control (HR: 0.62; p=0.22)
- OS: 1-2 cycles vs 4 cycles (HR: 0.39; p=0.07)

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





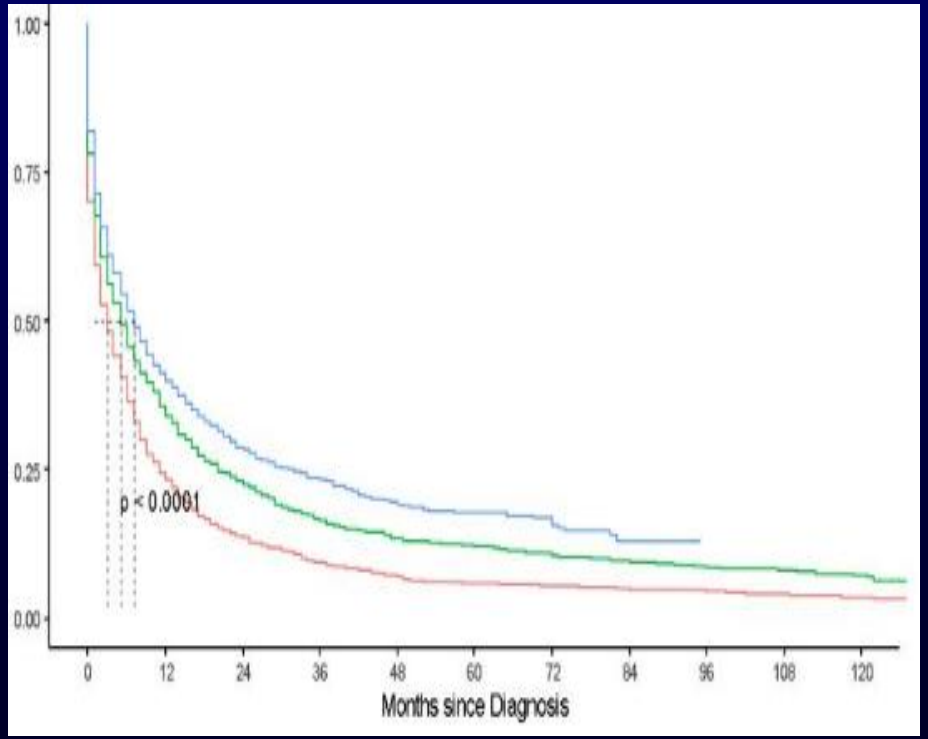
1 -2 cycles
Vs
control

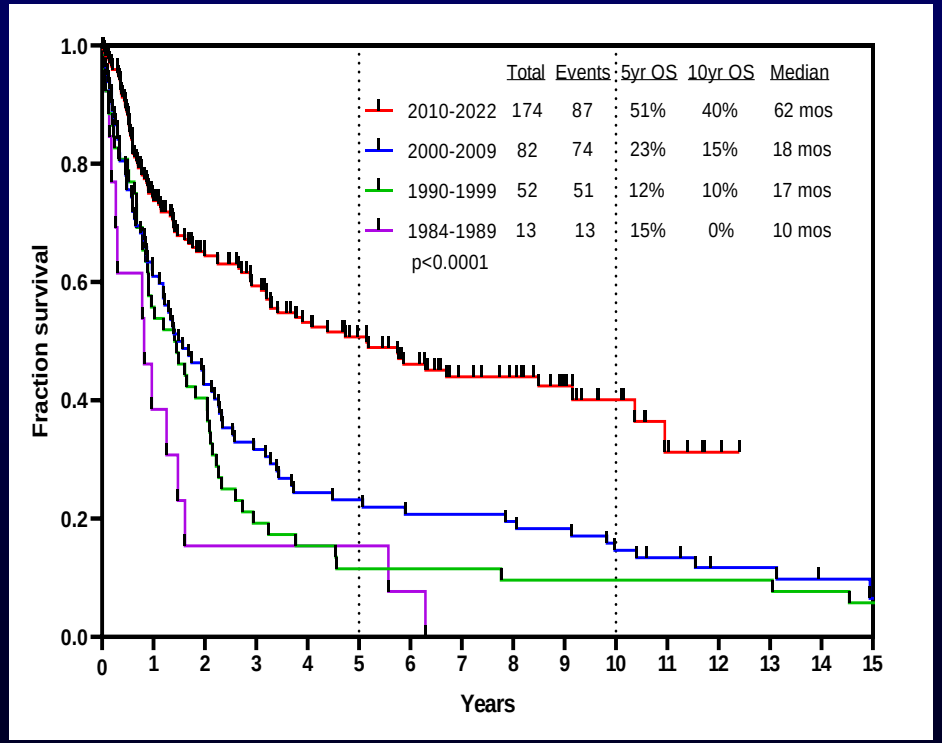


Luger. Blood 142: Abst 2877; 2023

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%

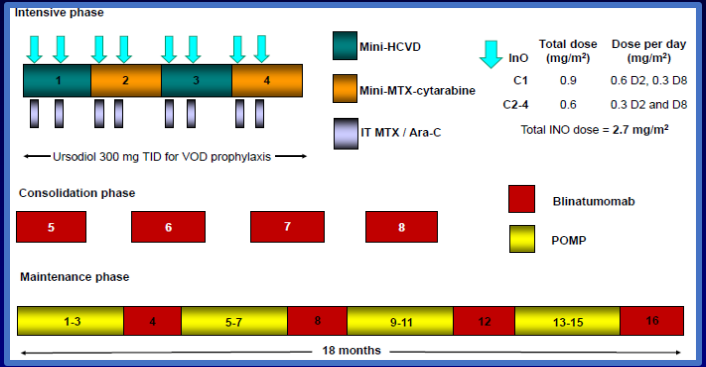




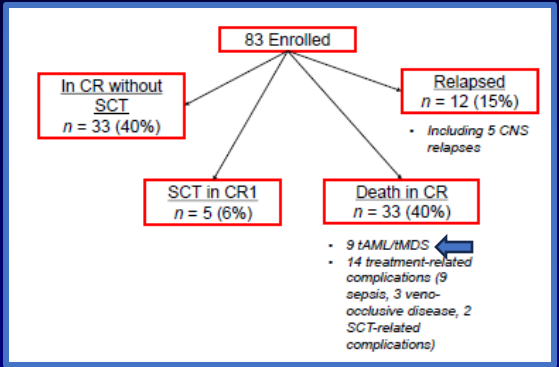
Gupta. Blood 140: abst 1379; 2022

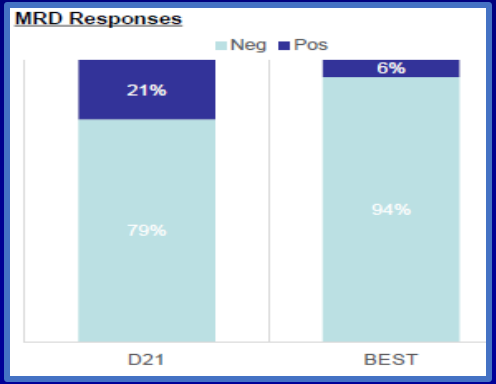
Mini-HCVD + INO ± Blina in Older ALL (N=83)

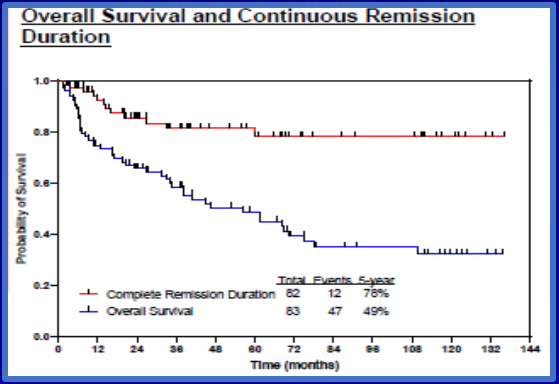
- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: *TP53* 39%; Ph-like 18%; poor cytogenetics 23%
- ORR 99% (CR 90%); MRD negativity 94% (79% at CR)



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)





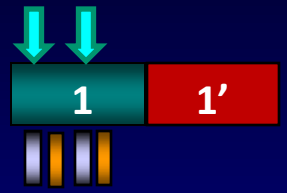


- Median F/U 88 months
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; 6%)
- Death due PD/NR: 12/83 (15%); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (11%); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: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

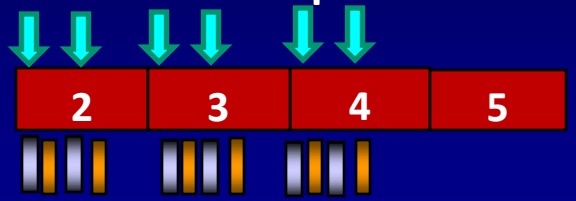
Jen. Blood 142: abst 2878; 2023

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

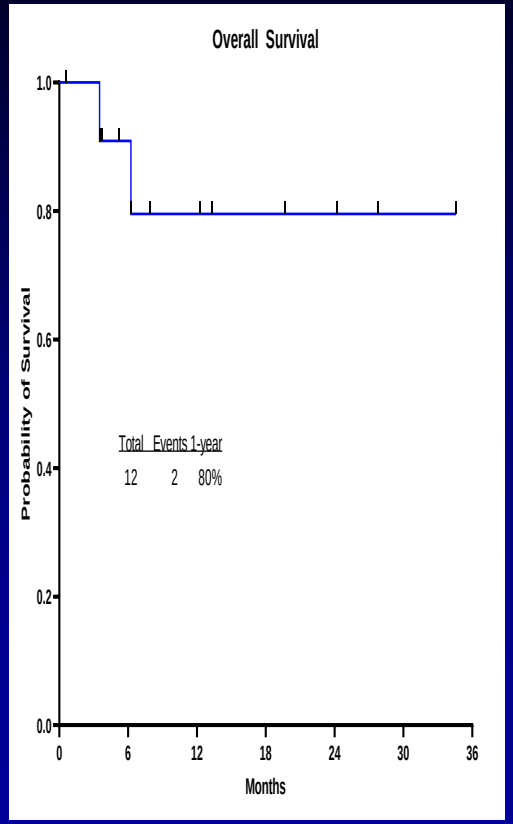
Rituximab if CD20+

1' Blinatumomab for 2 weeks

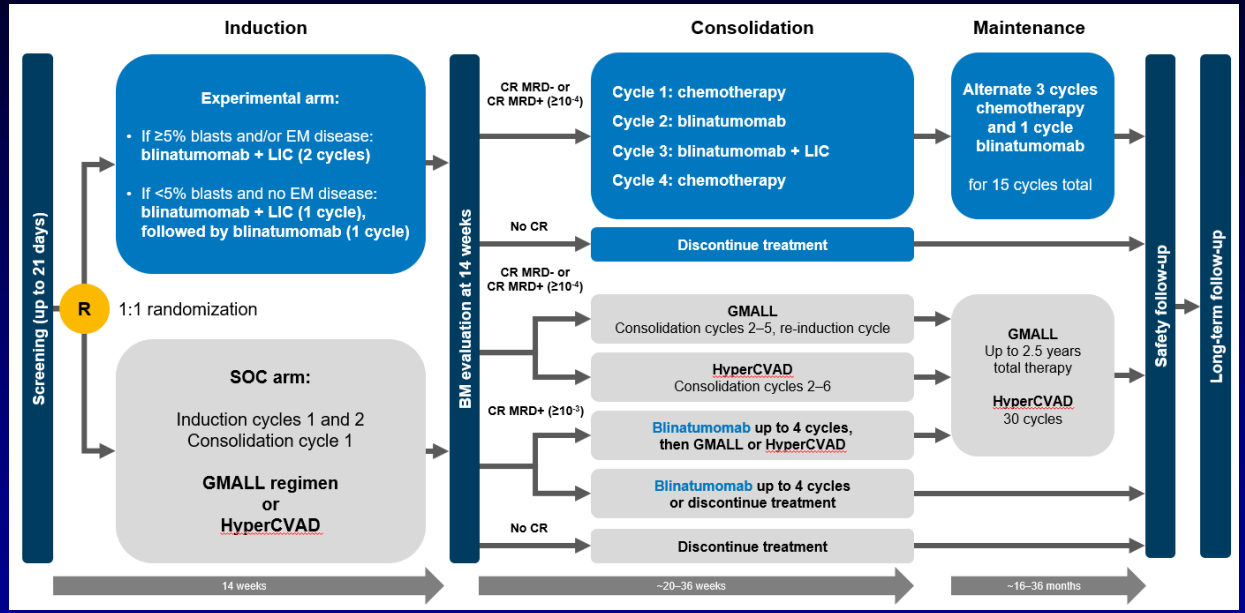
INO*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D1, 0.3 D8
C2-C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m^2

*Ursodiol 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.

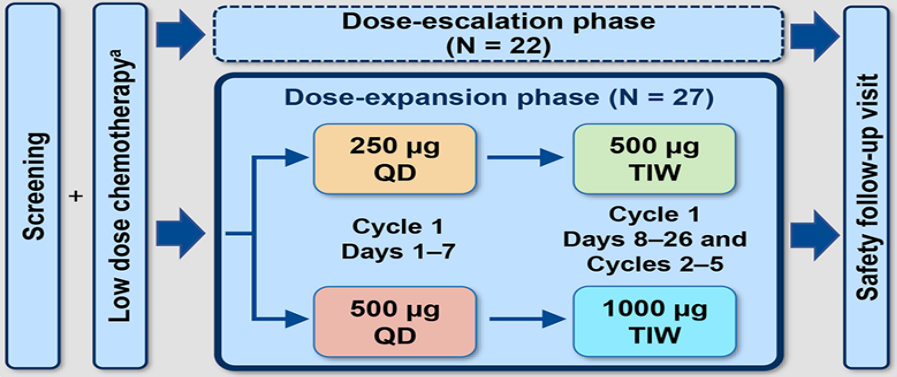
Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia

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

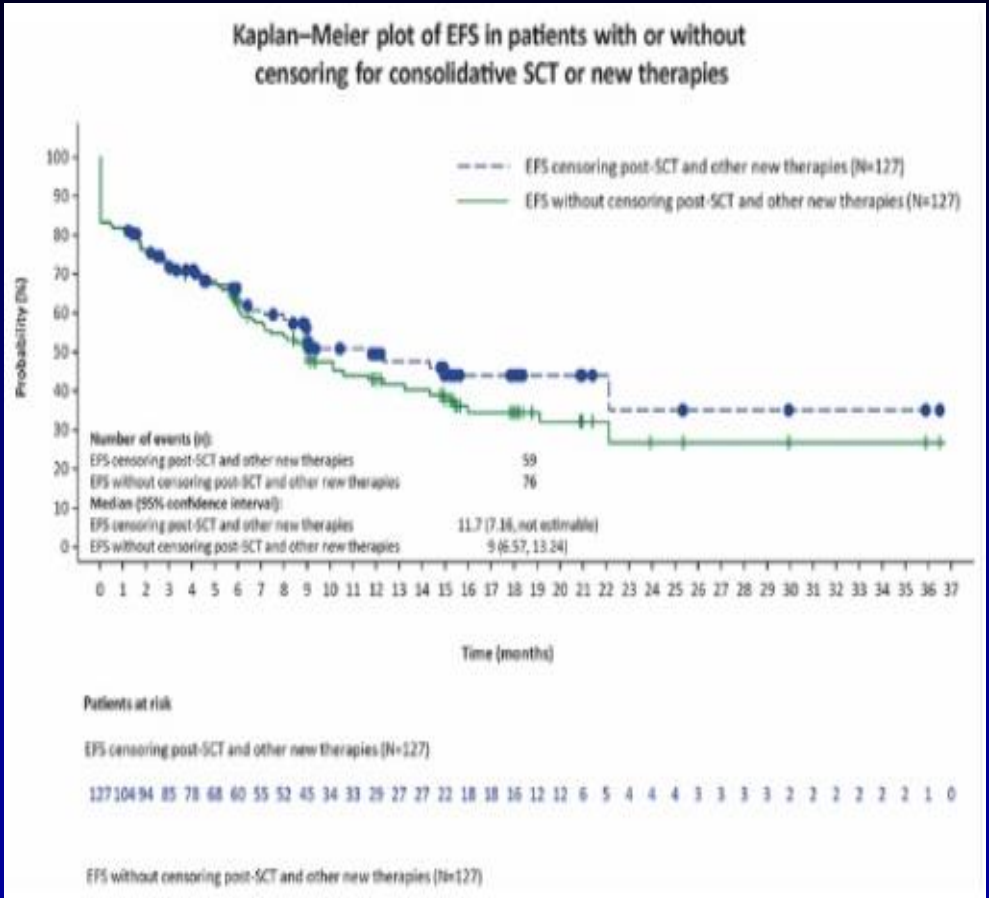
Conclusion

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)

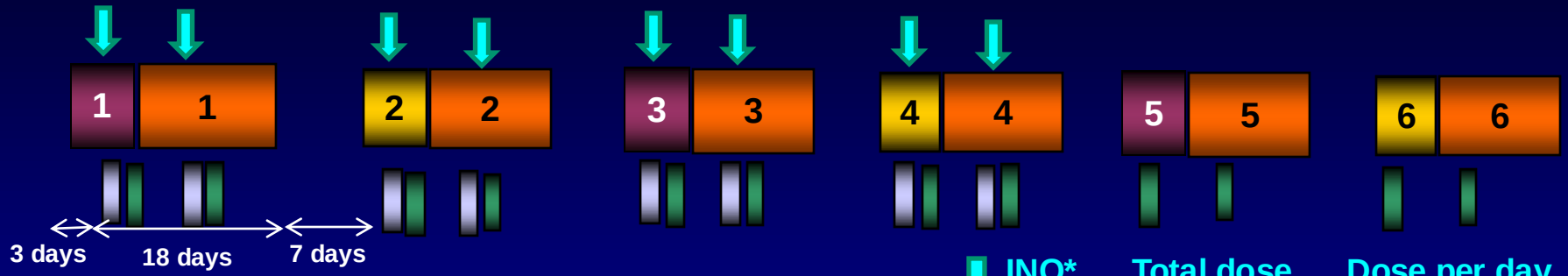
- AUTO 1 fast off-rate CD19 binder CAR T
- 153 enrolled, 127 (83%) infused. Median age 47 yrs
- Prior blina 42%, ino 31%, allo SCT 44%
- cCR-CRi 99/127 = 78% (99/153 = 65%). 19/77 allo SCT
- Loss of CAR T = HR 2.9
- 12-mos EFS 49%, 12-mos OS 61%



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

Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

Consolidation phase

CAR T Consolidation

Mini-HCVD

Mini-MTX, Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

Leukemia Questions?

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- Office: 713-792-4764

Global Leukemia Academy

Q&A

APTITUDE HEALTH®

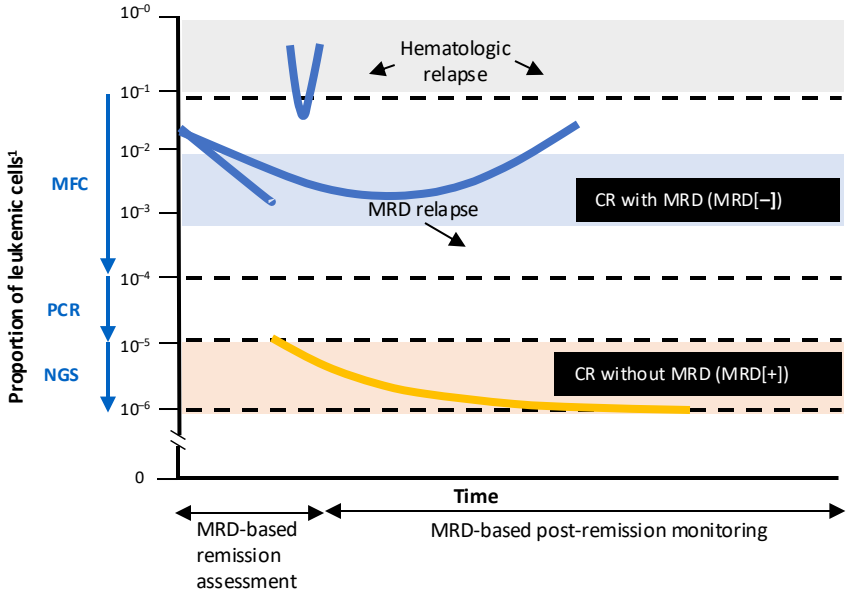
Global Leukemia Academy

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]



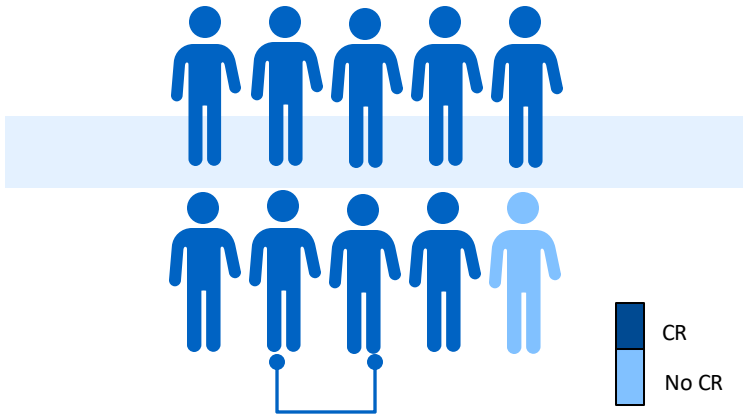
- MRD is defined as the presence of detectable leukemic cells (generally >10^{-4} or 0.01%) within the BM during remission[5,6]
- Studies collectively show the high prognostic value of MRD (both during and after initial induction therapy) in assessing relapse risk for patients with ALL[2]
- Patients 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.

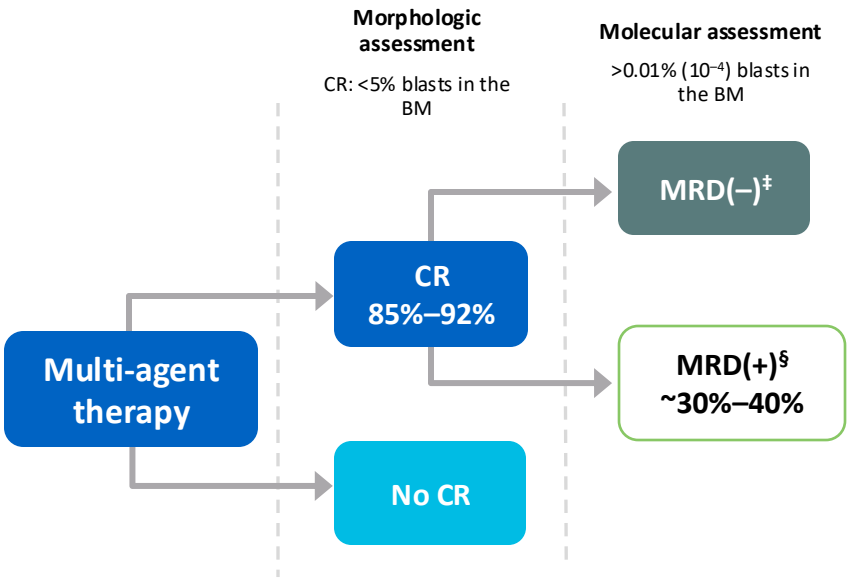
Patients Who Achieve CR May Still Harbor MRD[1-6]

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

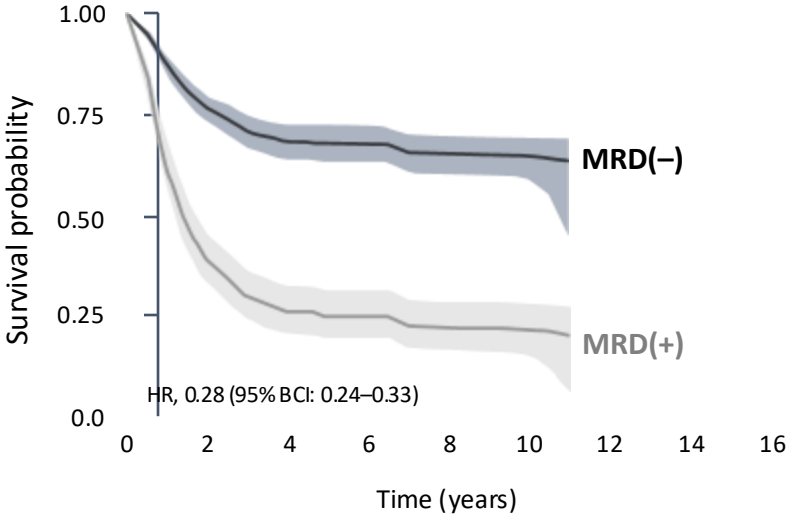
- MRD is prognostic for both adults and children in all ALL subtypes, including[1]
  - B- and T-cell lineage
  - Ph-positive and -negative disease
- Post-treatment detection of MRD in B-ALL[2]
  - MRD status has been shown to predict relapse and has been associated with treatment response

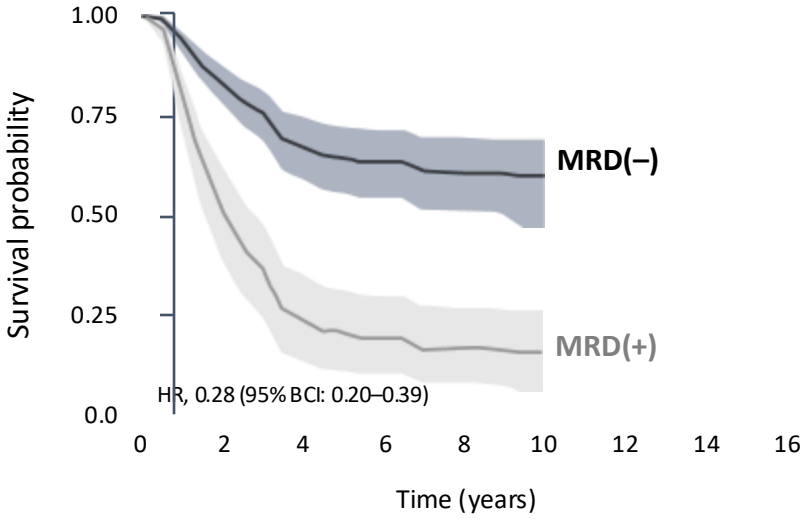
ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome.

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





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

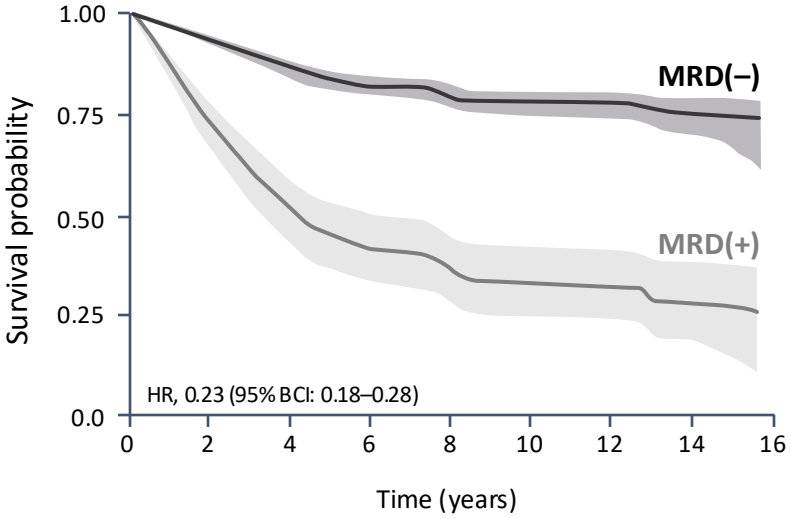
This information is presented for the purpose of demonstrating the utility of MRD testing as a prognostic indicator in B-ALL. Treatment decisions are the sole discretion of the healthcare provider.

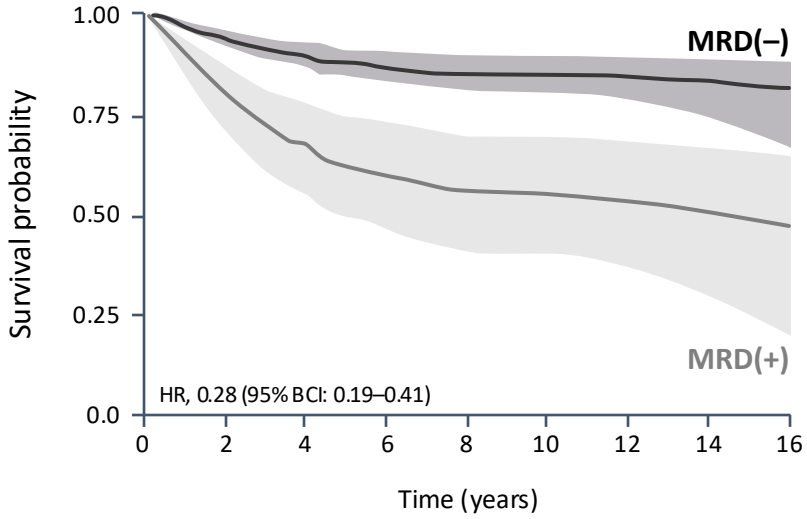
ALL, acute lymphoblastic leukemia; BCI, Bayesian credible intervals; EFS, event-free survival; HR, hazard ratio; MRD, measurable/minimal residual disease; OS, overall survival.

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





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

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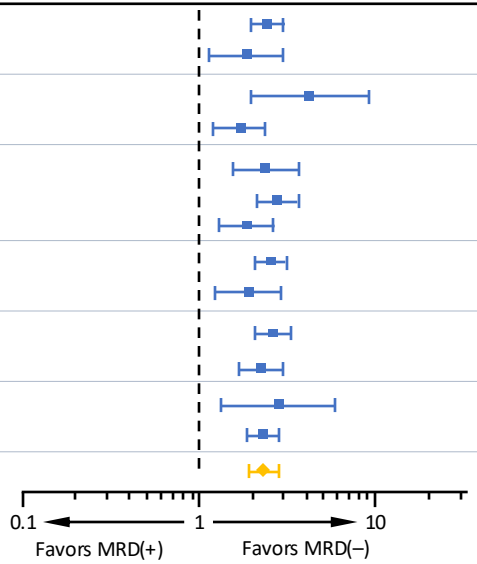
ALL, acute lymphoblastic leukemia; BCI, Bayesian credible intervals; EFS, event-free survival; HR, hazard ratio; MRD, measurable/minimal residual disease; OS, overall survival.

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.

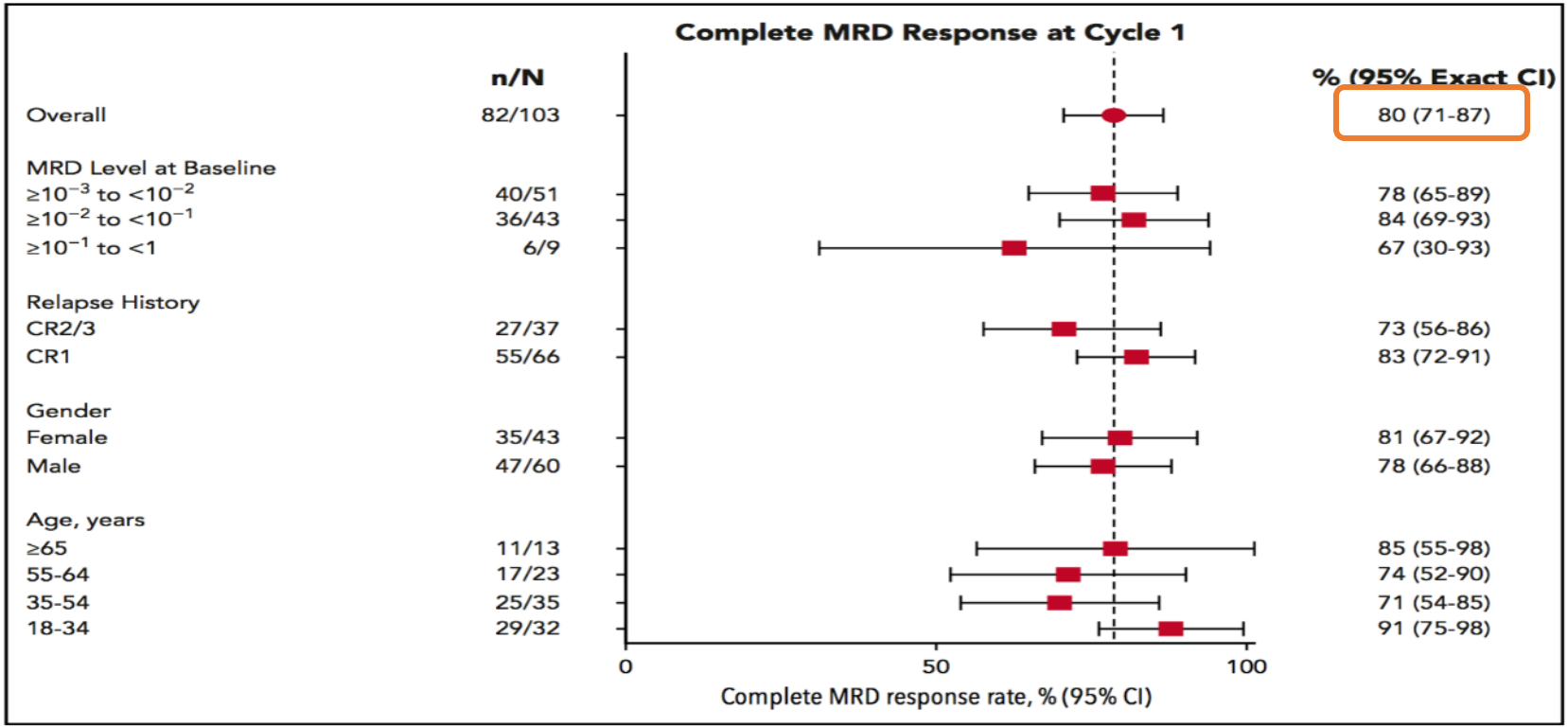
Blinatumomab in MRD+ B-ALL

- **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)

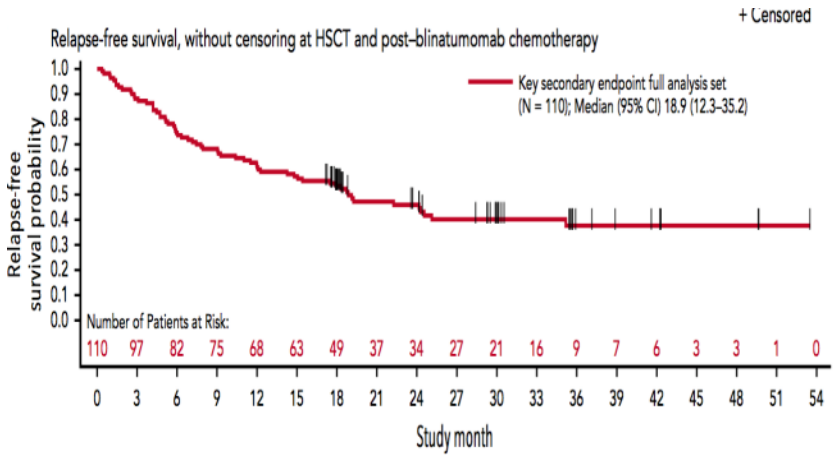
Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

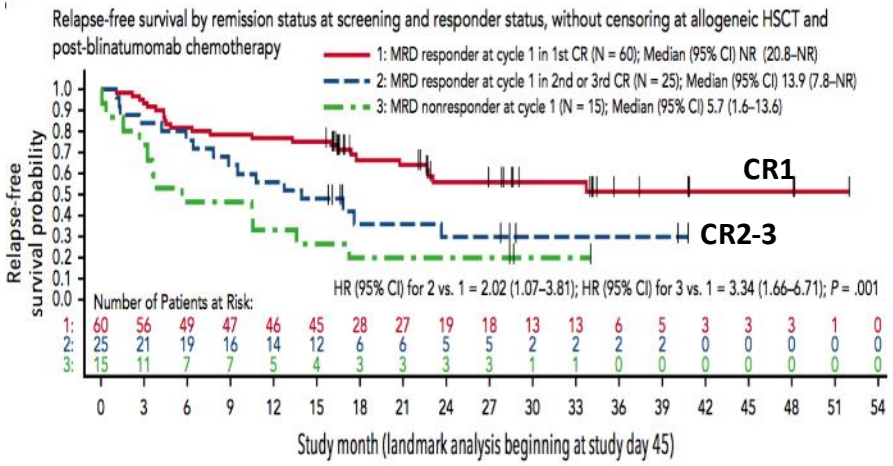
CR Rates by Subgroups in MRD+ B-ALL



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]

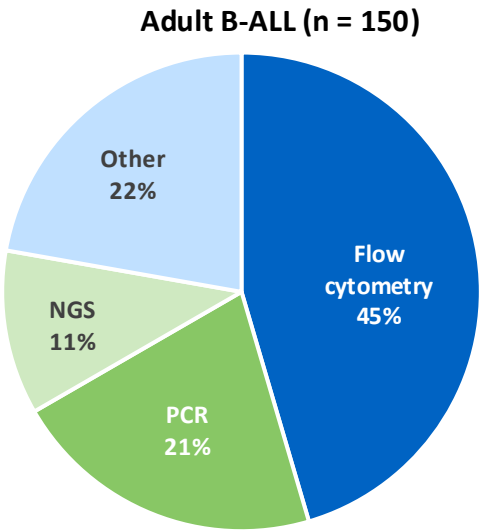
Method	Target	Sensitivity	Some Potential Benefits	Some Potential Limitations
Flow cytometry[1-5]	Leukemia-associated immunophenotypes	3–4 color: 10^{-3} to 10^{-4} 6–9 color: 10^{-4} to 10^{-5}	• Rapid • Target Ag information	• Limited sensitivity/standardization • Difficult to interpret
PCR[1-5]	RT-qPCR: 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

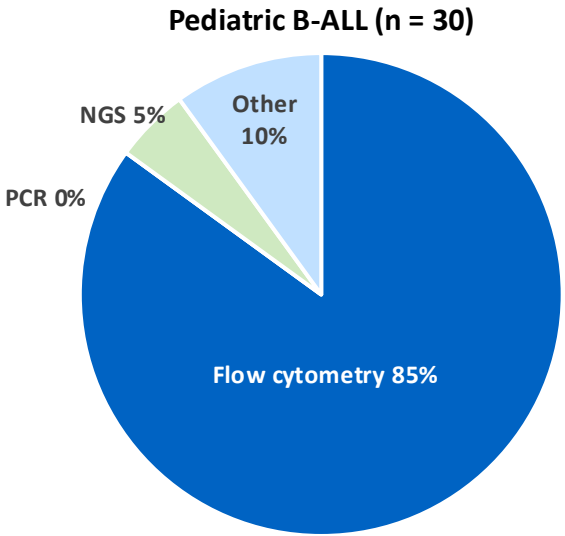
ASO-PCR, allele-specific oligonucleotide PCR; FDA, Food and Drug Administration; Ig, immunoglobulin; MRD, measurable/minimal residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-qPCR, real-time quantitative PCR; TCR, T-cell receptor.

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.

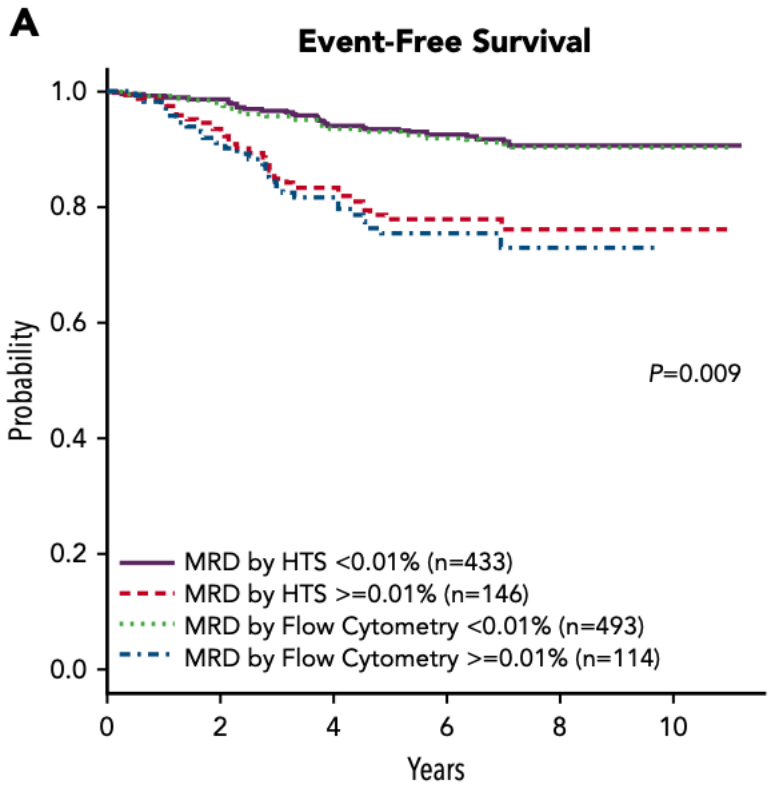
1. Kim C, et al. *Hematology.* 2019;24:70-78 and supplemental data; 2. Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

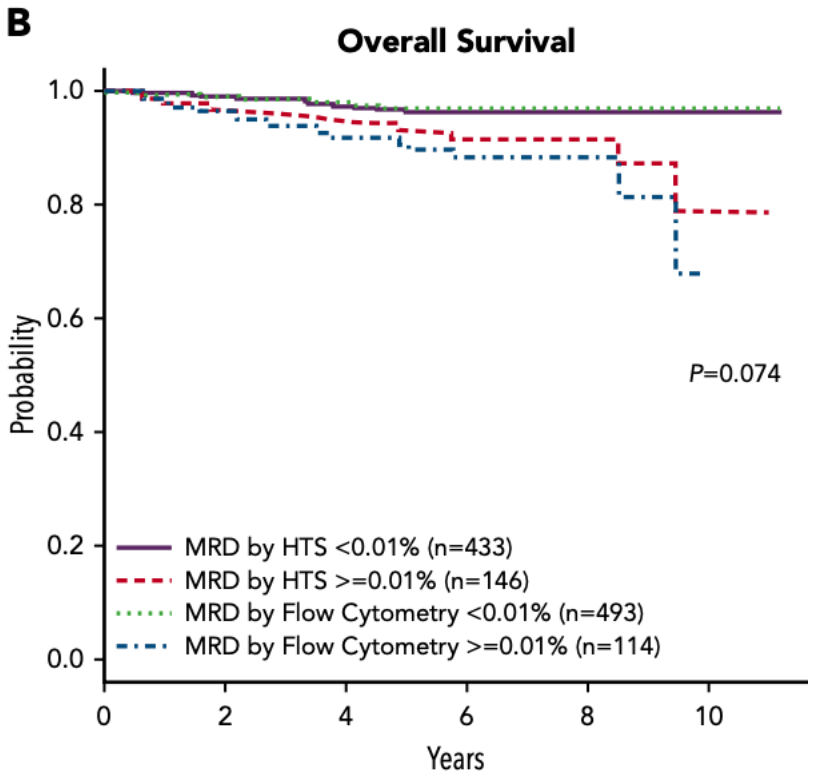
Children's Oncology Group
Comparison of MRD by FCM and NGS

- 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.

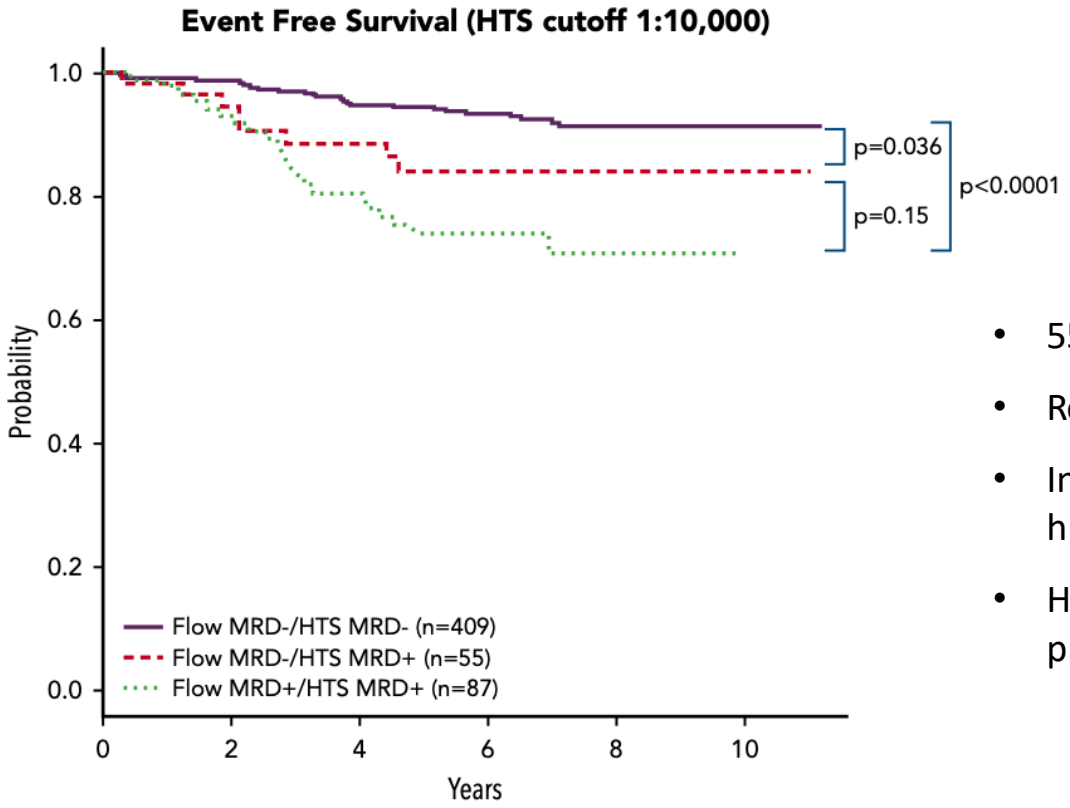
Strong Correlation Between MRD by HTS or FCM (0.01%)





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

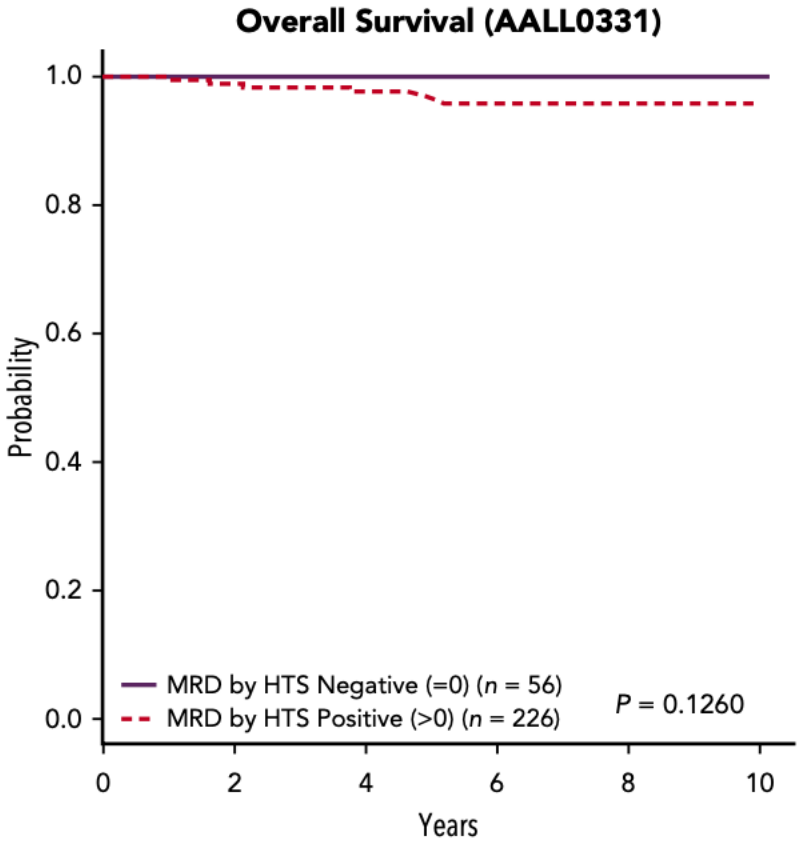
Discordant MRD by HTS or FCM Has Intermediate Prognosis



- 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.

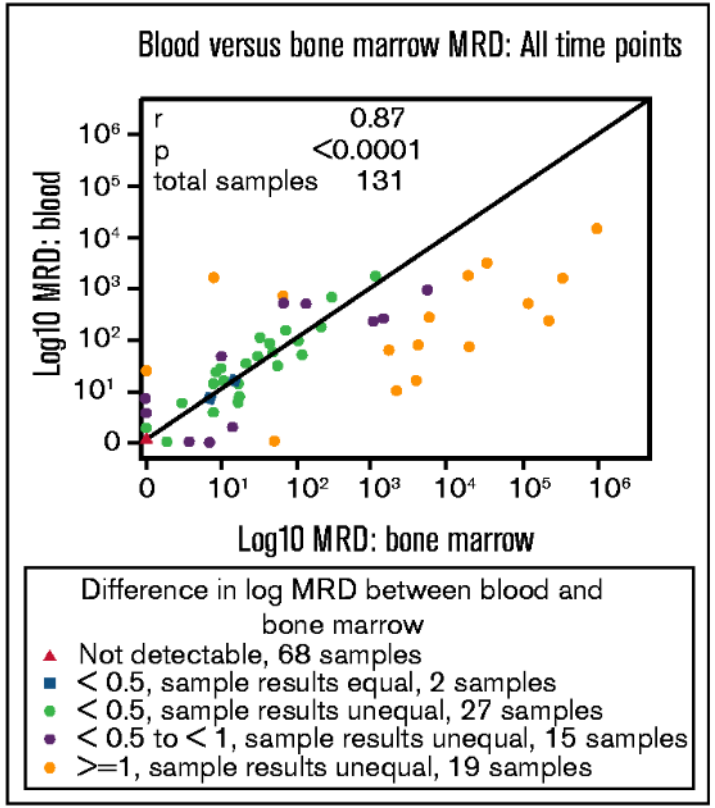
HTS Can Identify Patients With Excellent Outcomes



- 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

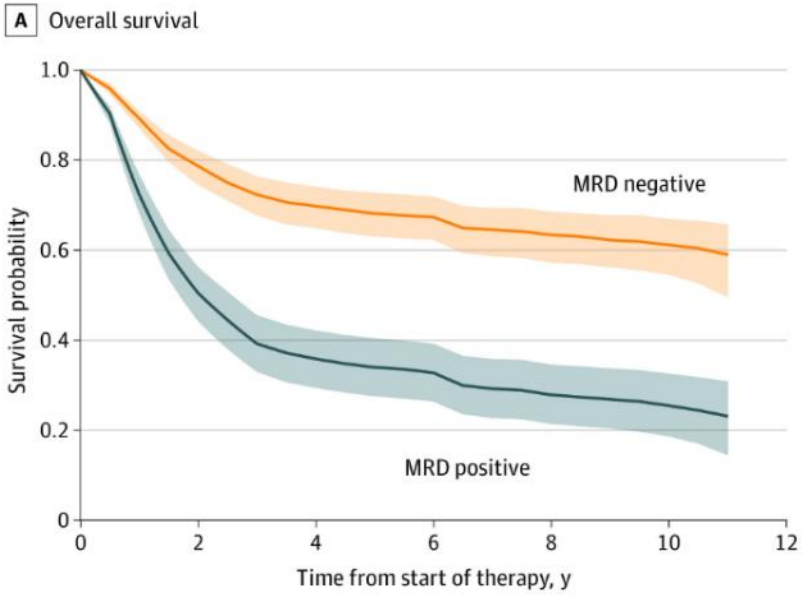
Flow Cytometry	Molecular Biology
Aspirate 5−10 mL BM and use the first pull for MRD assessment	Aspirate 5−10 mL BM and use the first pull for MRD assessment
Use 500,000 to 1,000,000 white blood cells	Patients with mutant *NPM1*, *RUNX1-RUNX1T1*, *CBFB-MYH11*, or *PML-RARA* should have molecular assessment 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

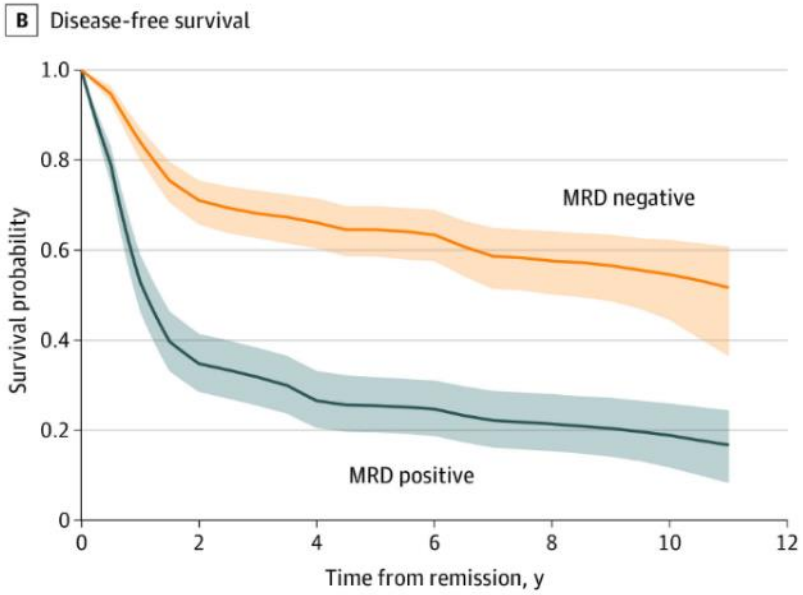
Döhner H, et al. *Blood.* 2017;129(4):424-447; NCCN clinical practice guidelines in oncology: acute myeloid leukemia (Version 2.2021). National Comprehensive Cancer Network® website. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Updated November 12, 2020. Accessed November 19, 2020.

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

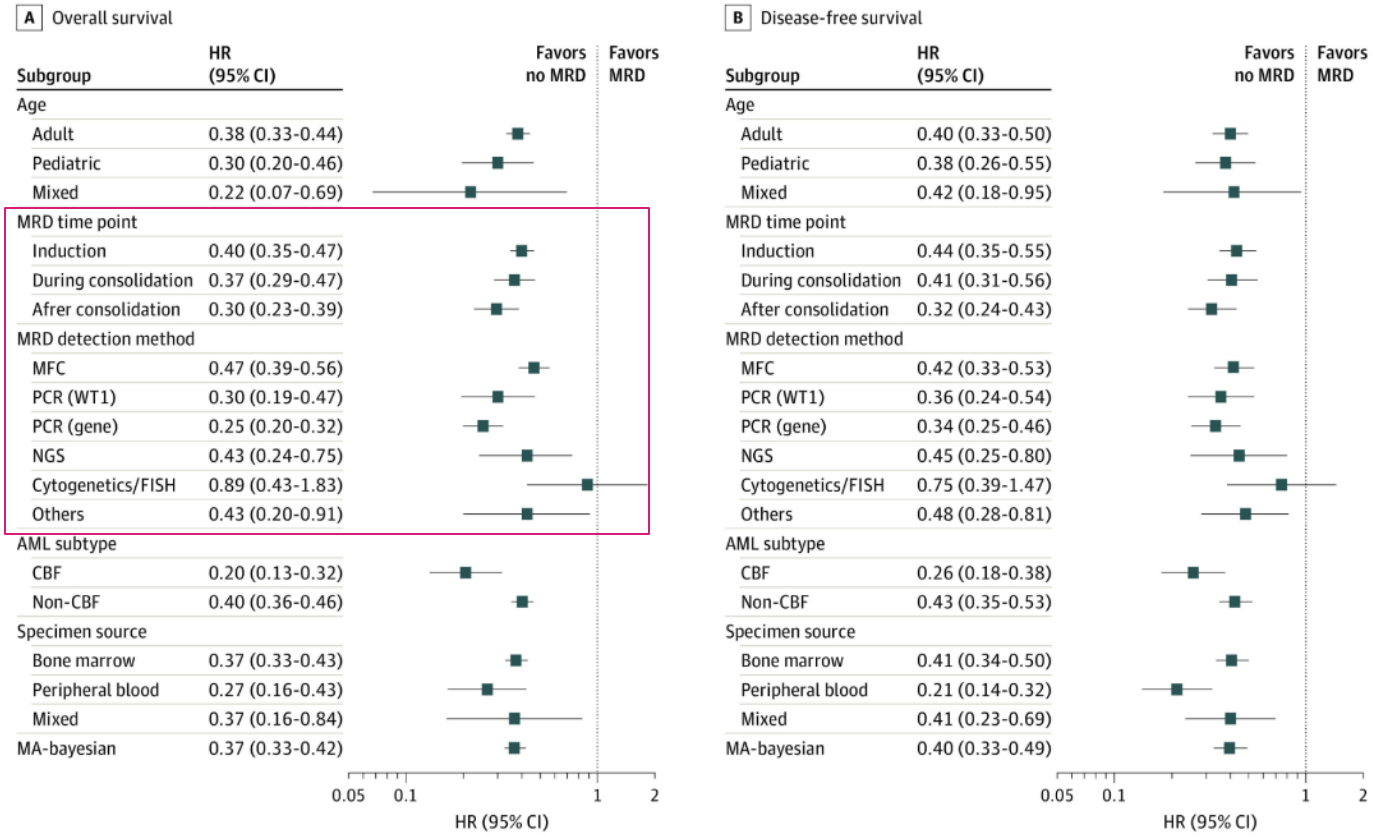
Prognostic Impact of MRD in AML (Meta-analysis)





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

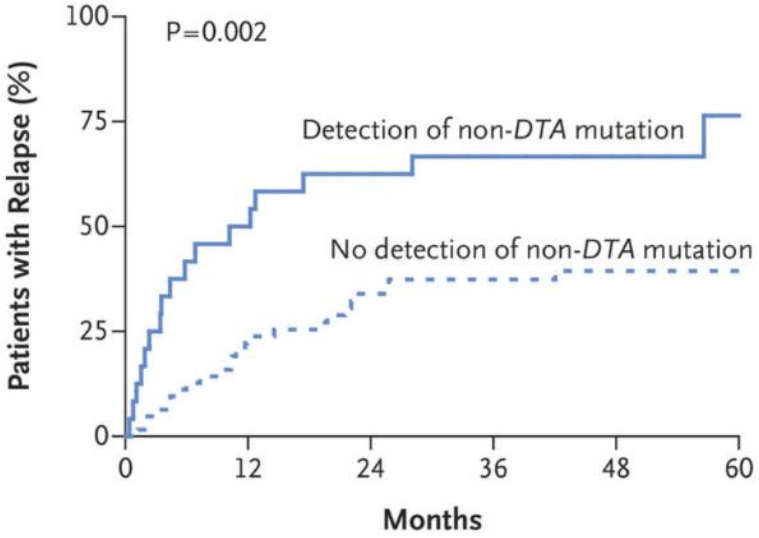
Prognostic Impact of MRD in AML (Meta-analysis)



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

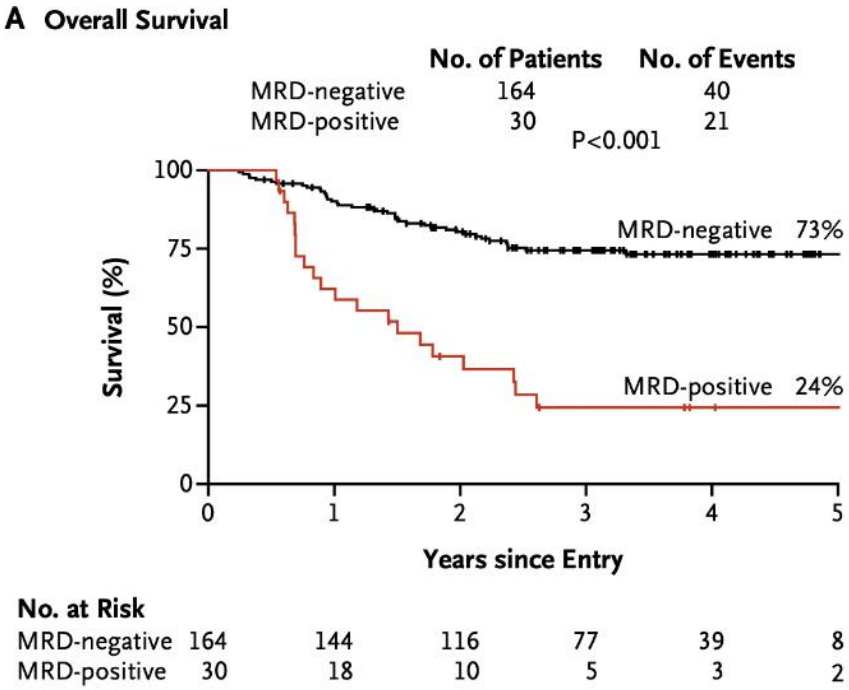


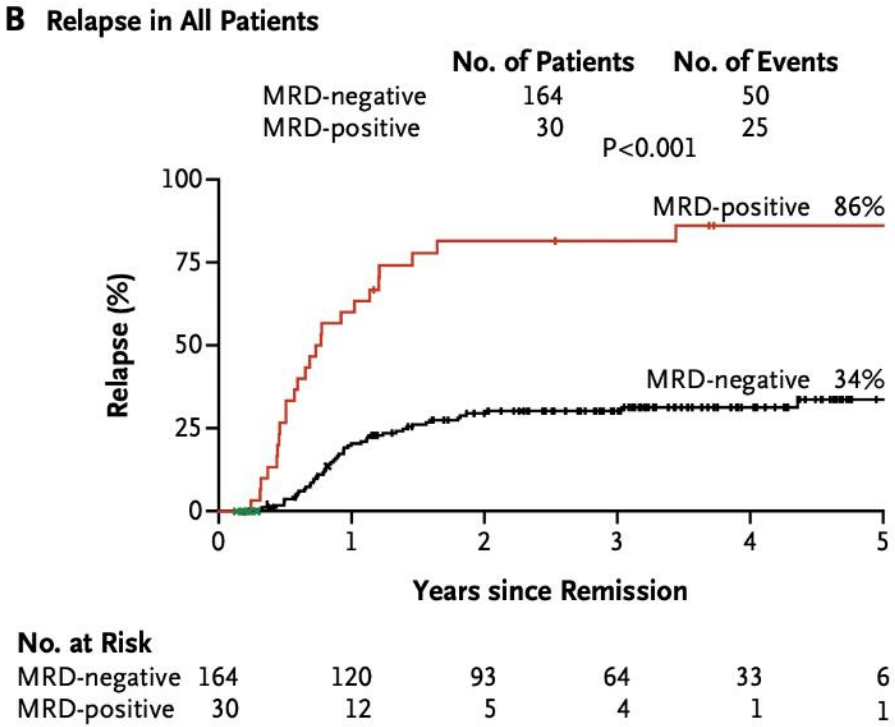
No. at Risk						
Detection	24	11	8	5	4	2
No detection	63	45	33	29	22	17

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

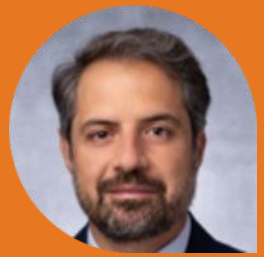
Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Best practices for first-line treatment in ALL

Elias Jabbour



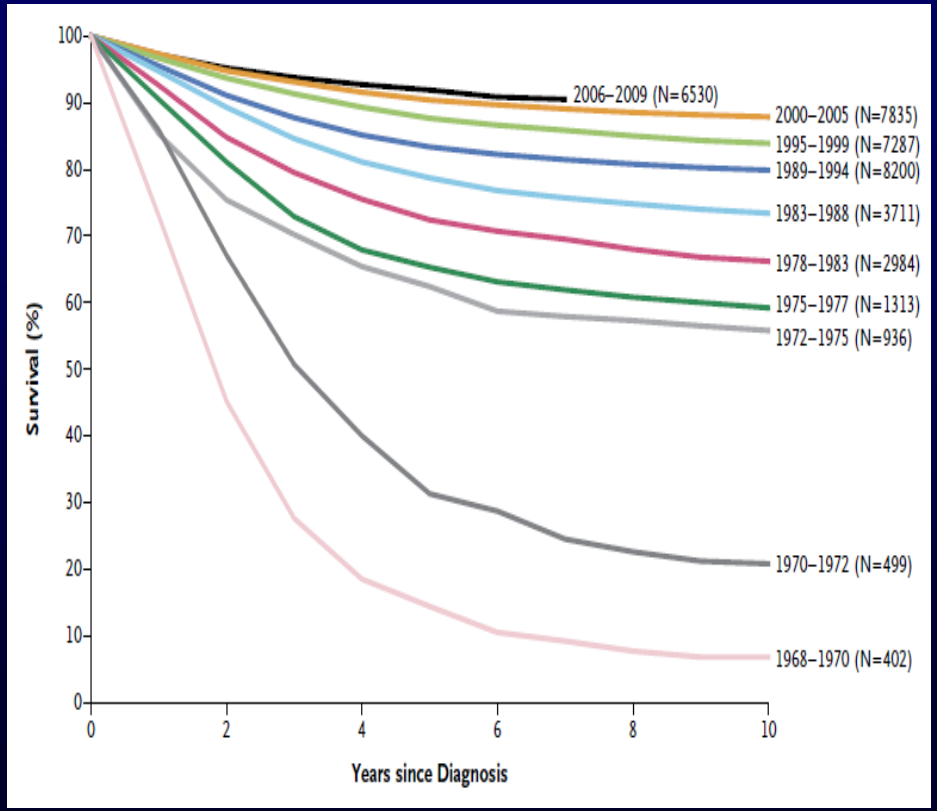
APTITUDE HEALTH®

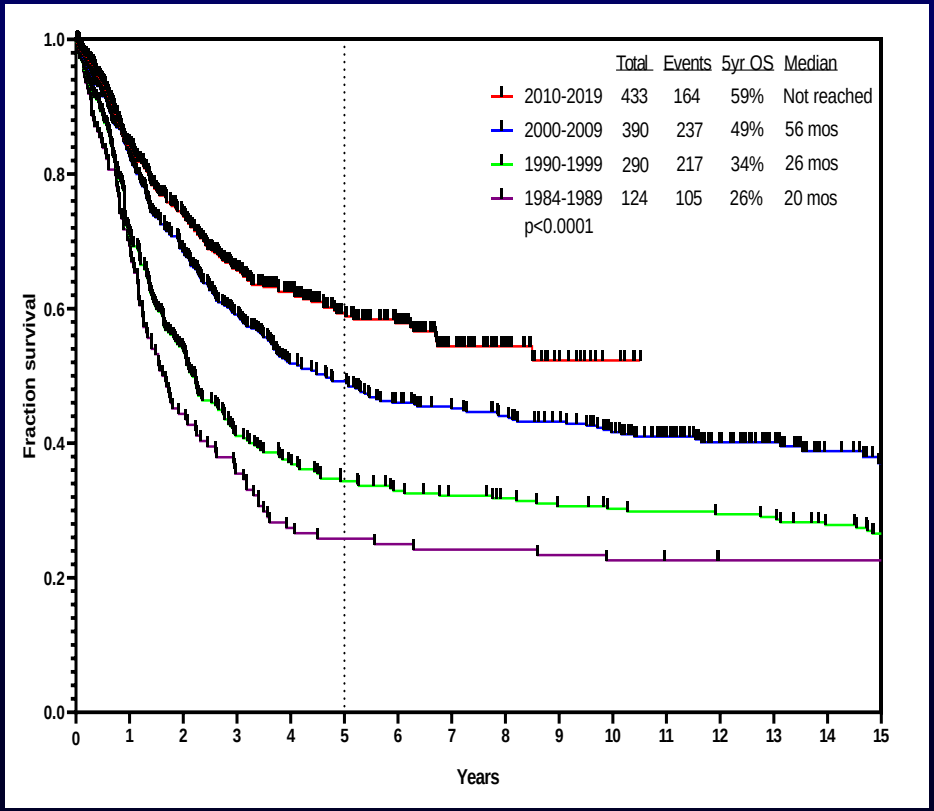
Integration of Immunotherapy in Newly Diagnosed ALL

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

Summer 2024

Survival in Pediatric and Adult ALL with Classical Intensive ChemoRx Regimens

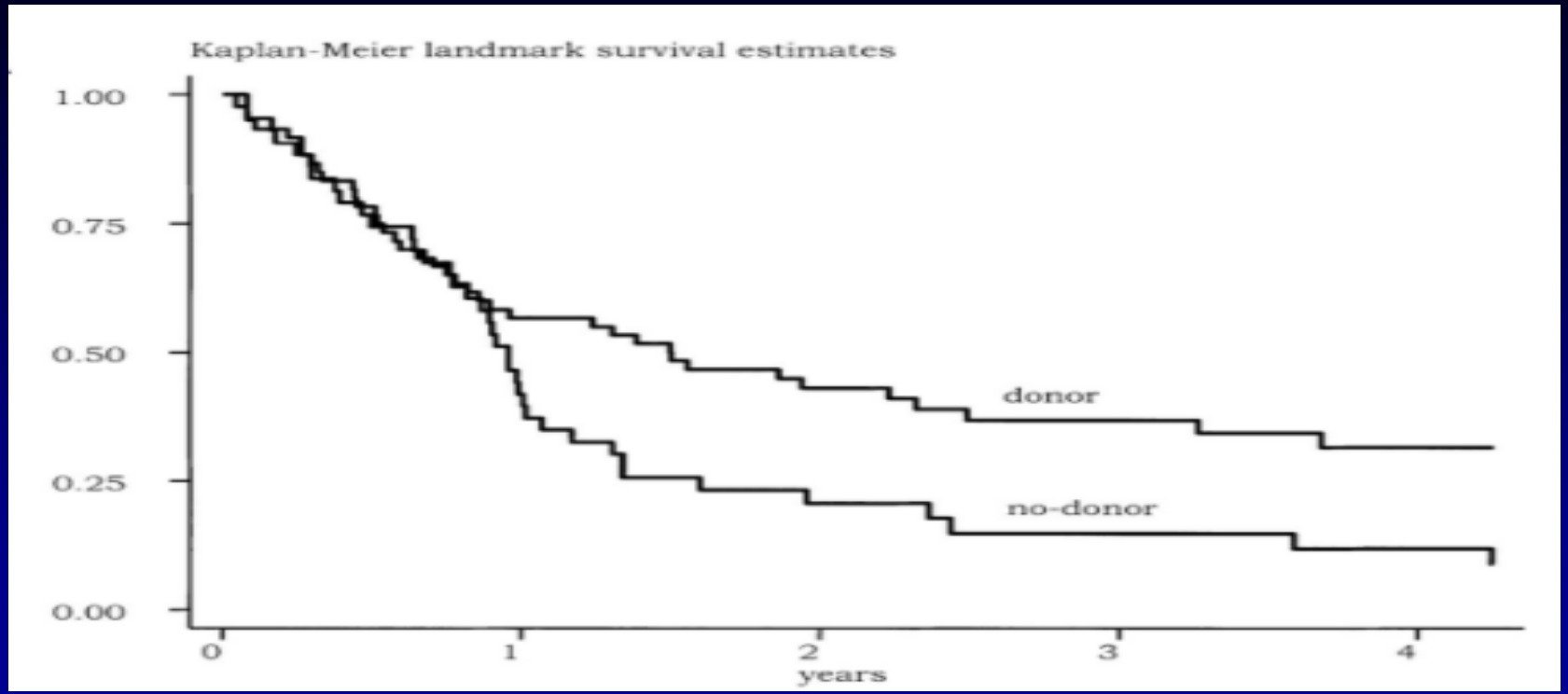




Hunger et al. *N Engl J Med.* 2015;373(16):1541-1552.

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

SCT for Ph+ ALL: Pre-TKI



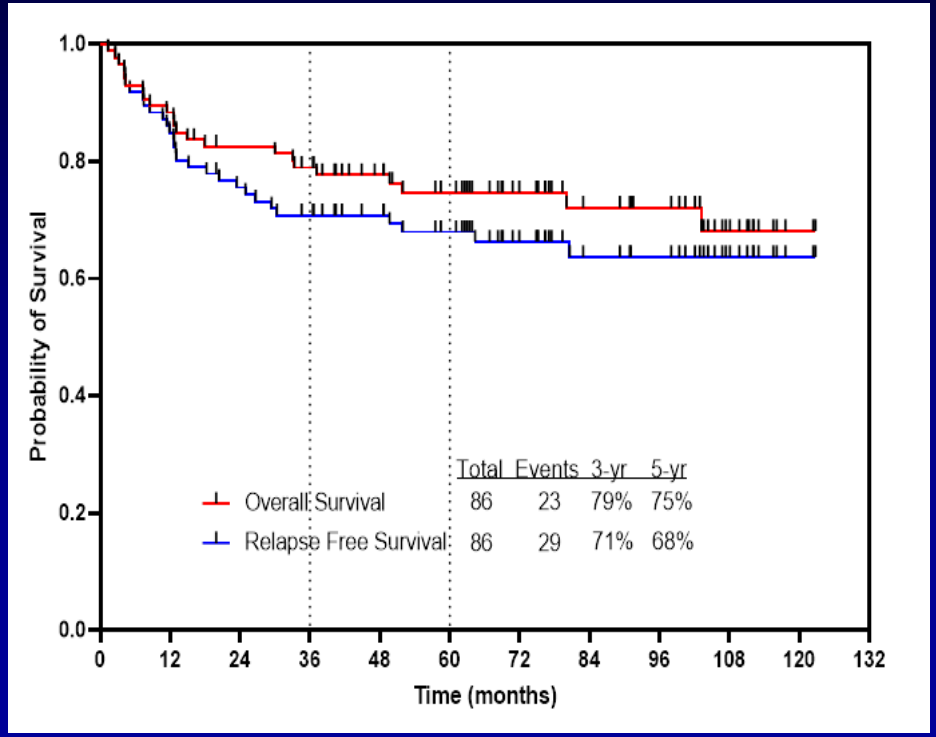
- Donor (n=60) – 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

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

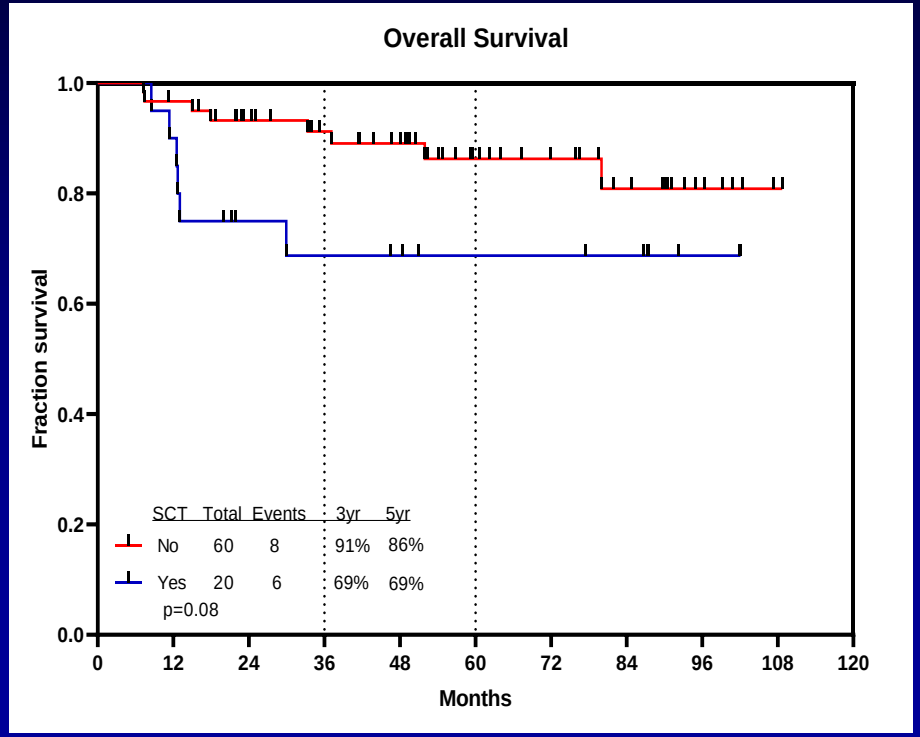
HyperCVAD + Ponatinib in Ph+ ALL

- 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



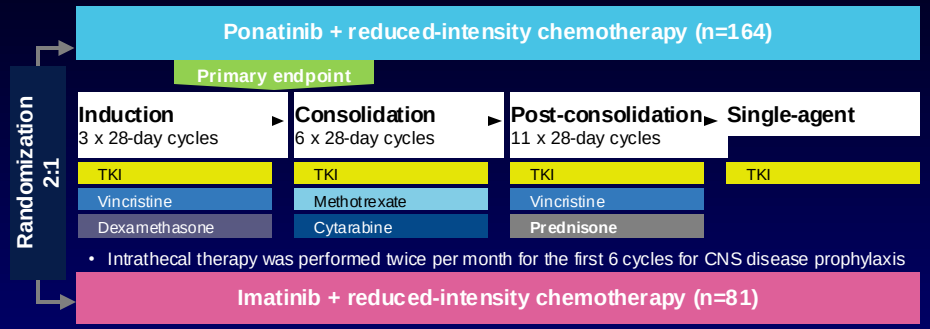
6-month Landmark



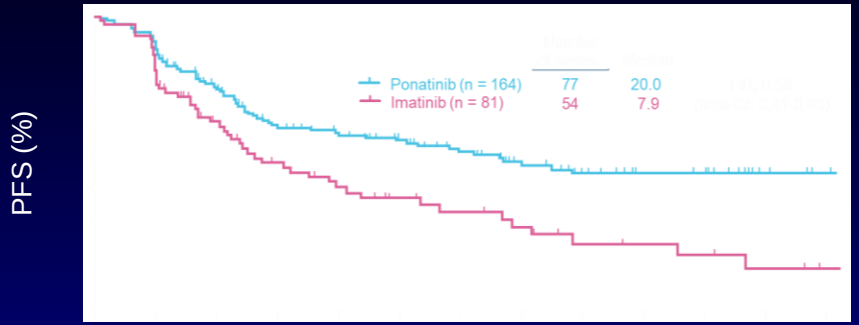
Kantarjian. Am J Haematol 98:493-501;2023

Ponatinib vs Imatinib With Rx in Ph+ ALL: PhALLCON

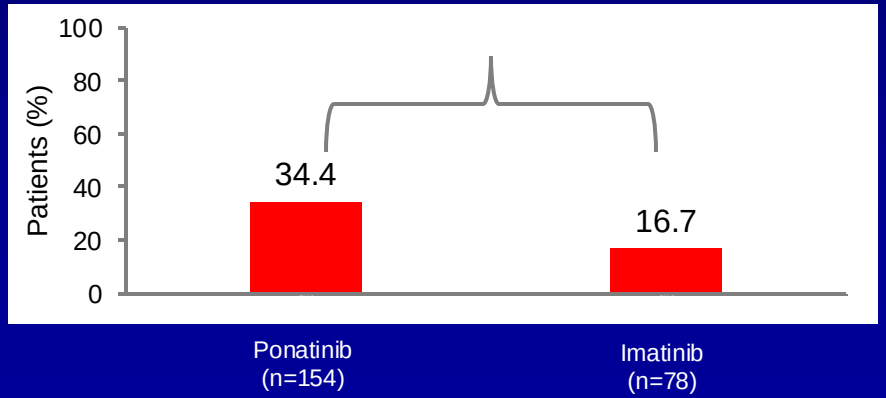
Study design



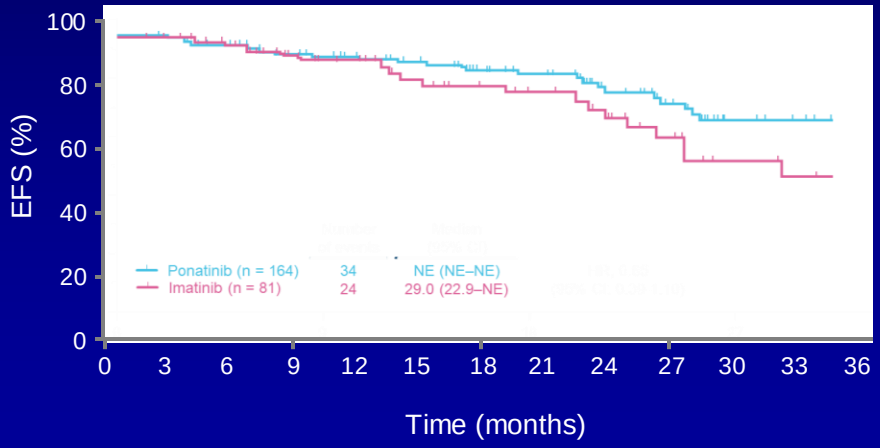
PFS



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

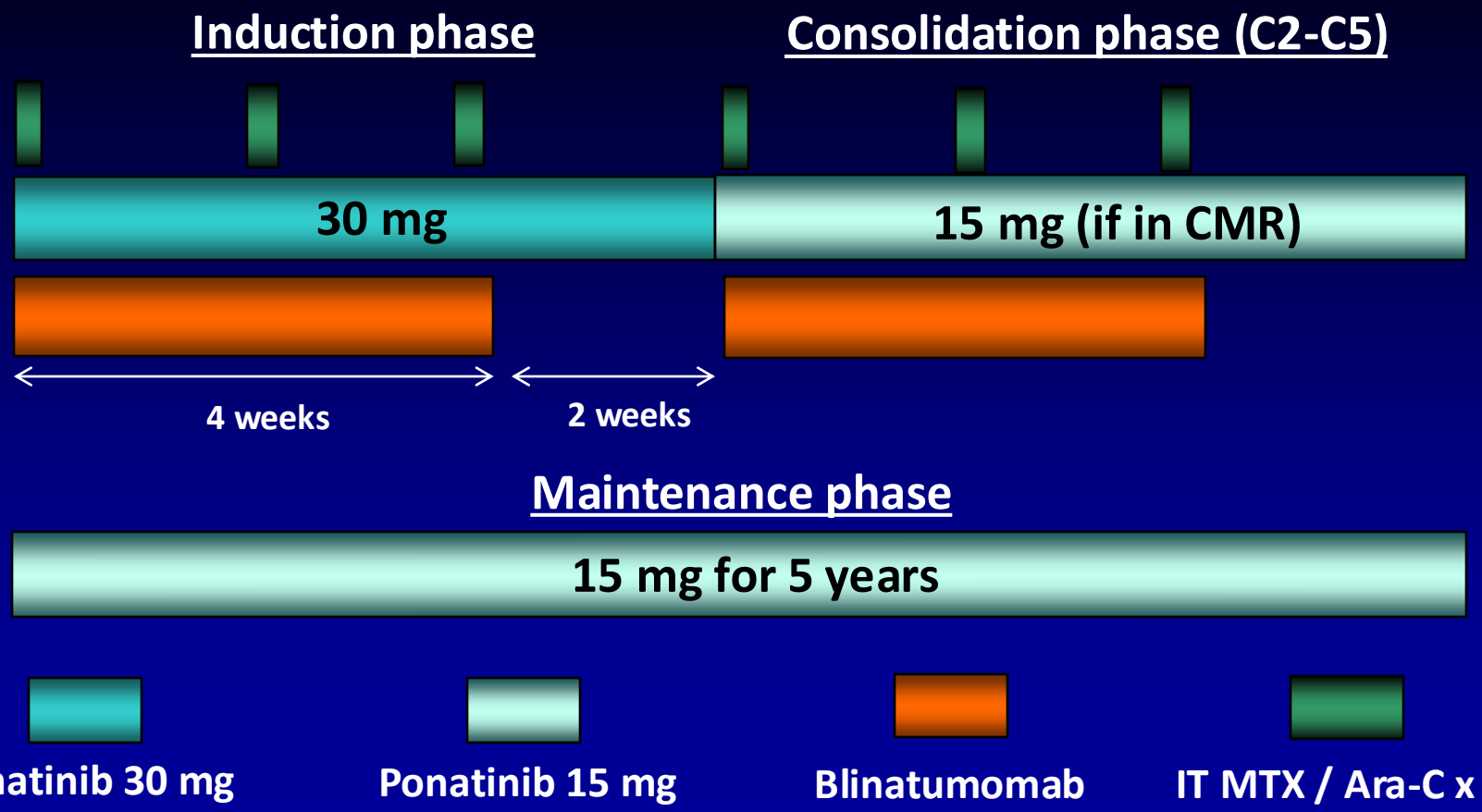


EFS



Jabbour. JAMA. 2024 May 9:e244783.

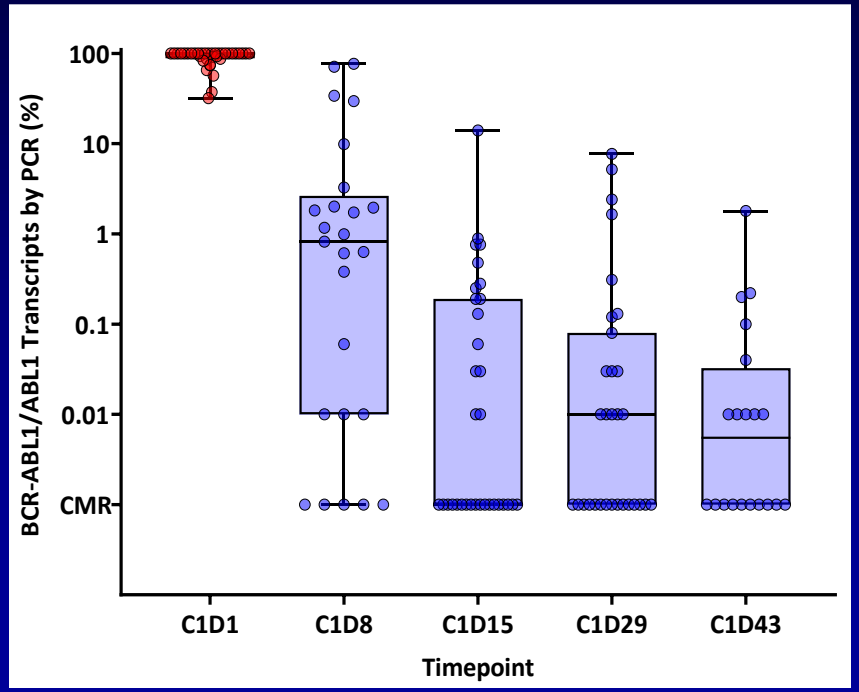
Ponatinib + Blinatumomab in Ph+ ALL: Regimen

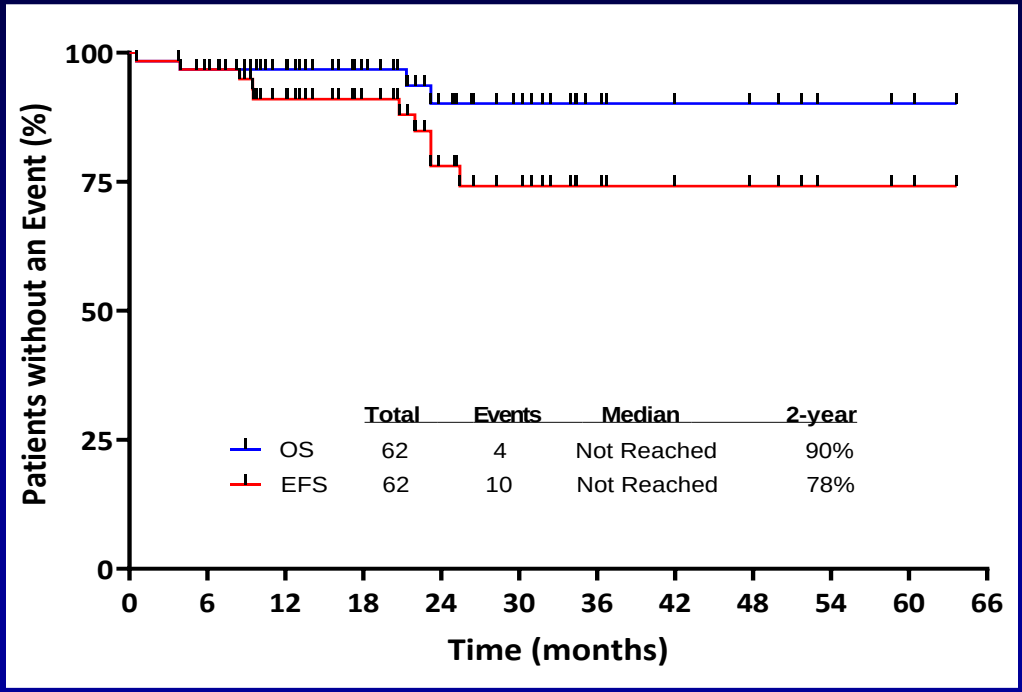


Jabbour. Lancet Haematol. 2023;10(1):e24-e34

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.

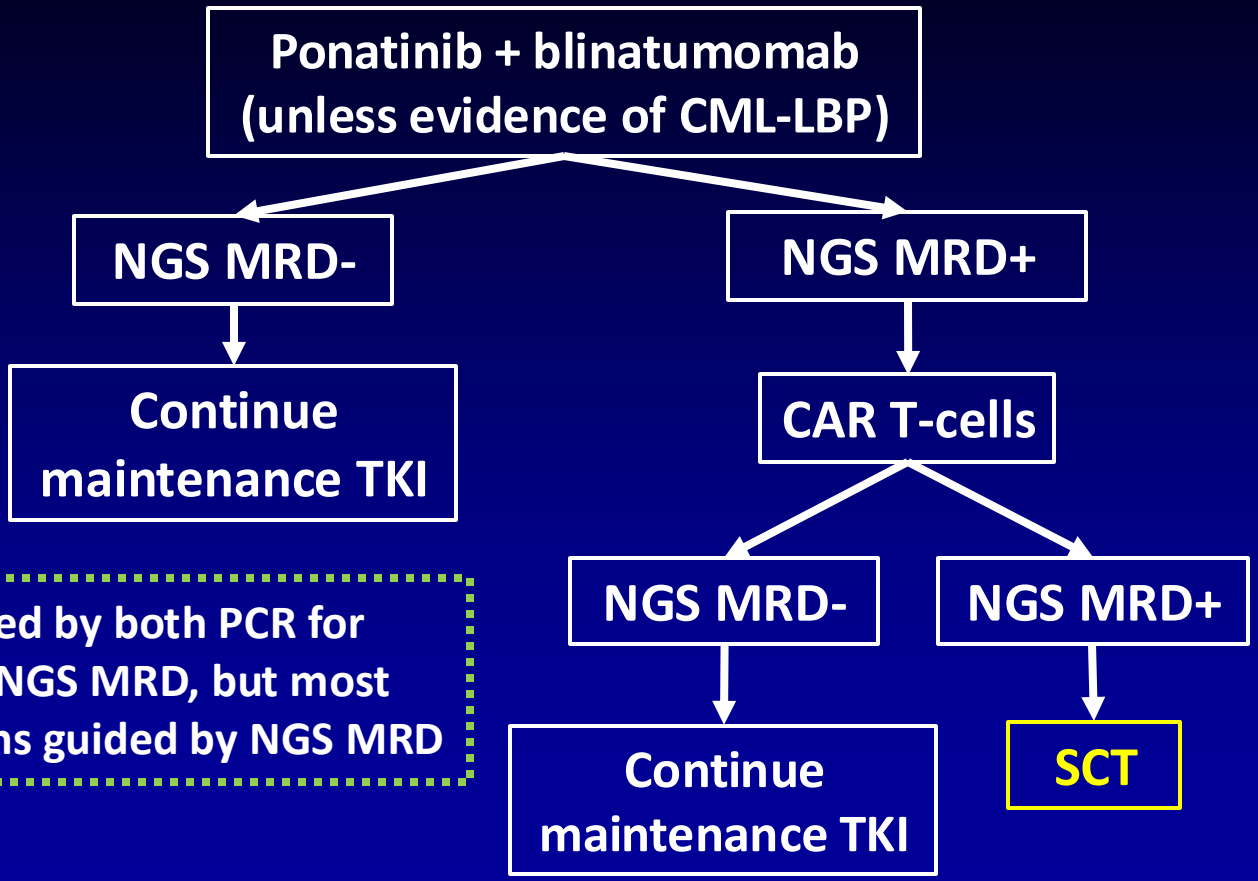
Haddad. Blood 142: abstr 2827;2023

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]

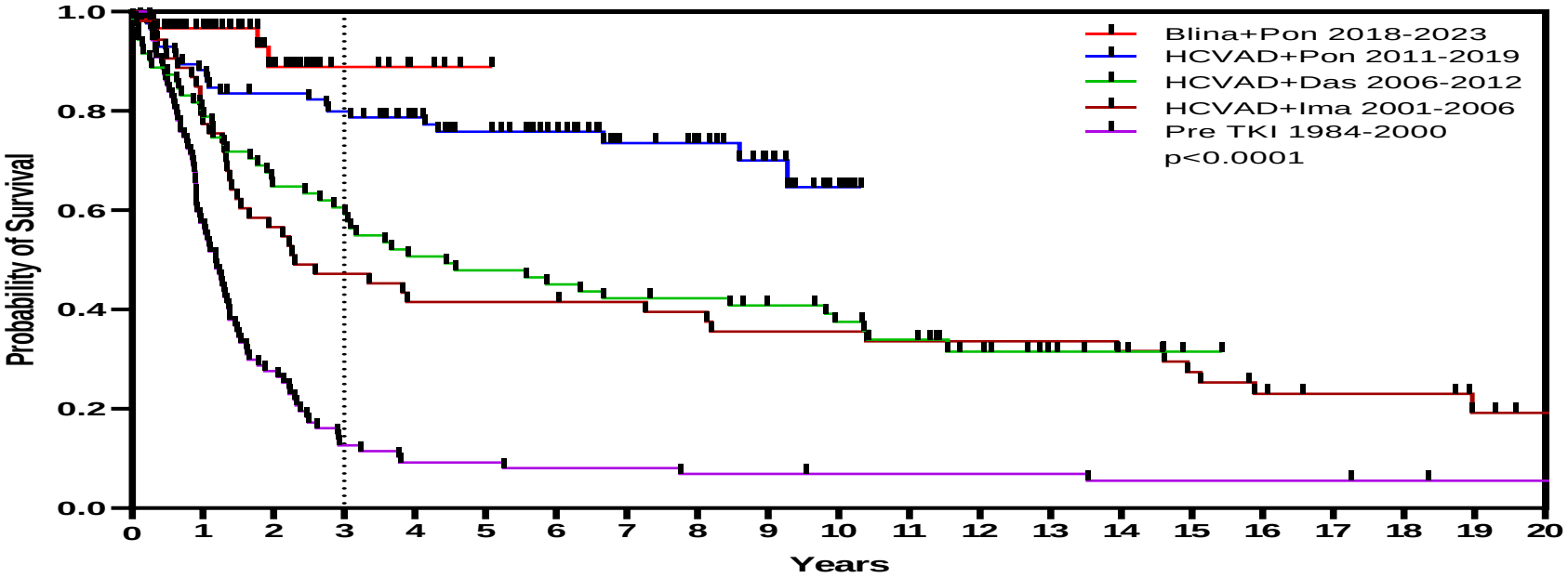
Jabbour. Lancet Haematol. 2023;10(1):e24-e34. Foa. JCO online, December 23; 2023. Advani. Blood 142: Abst 1499; 2023

Research Rx Algorithm for Ph+ ALL



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

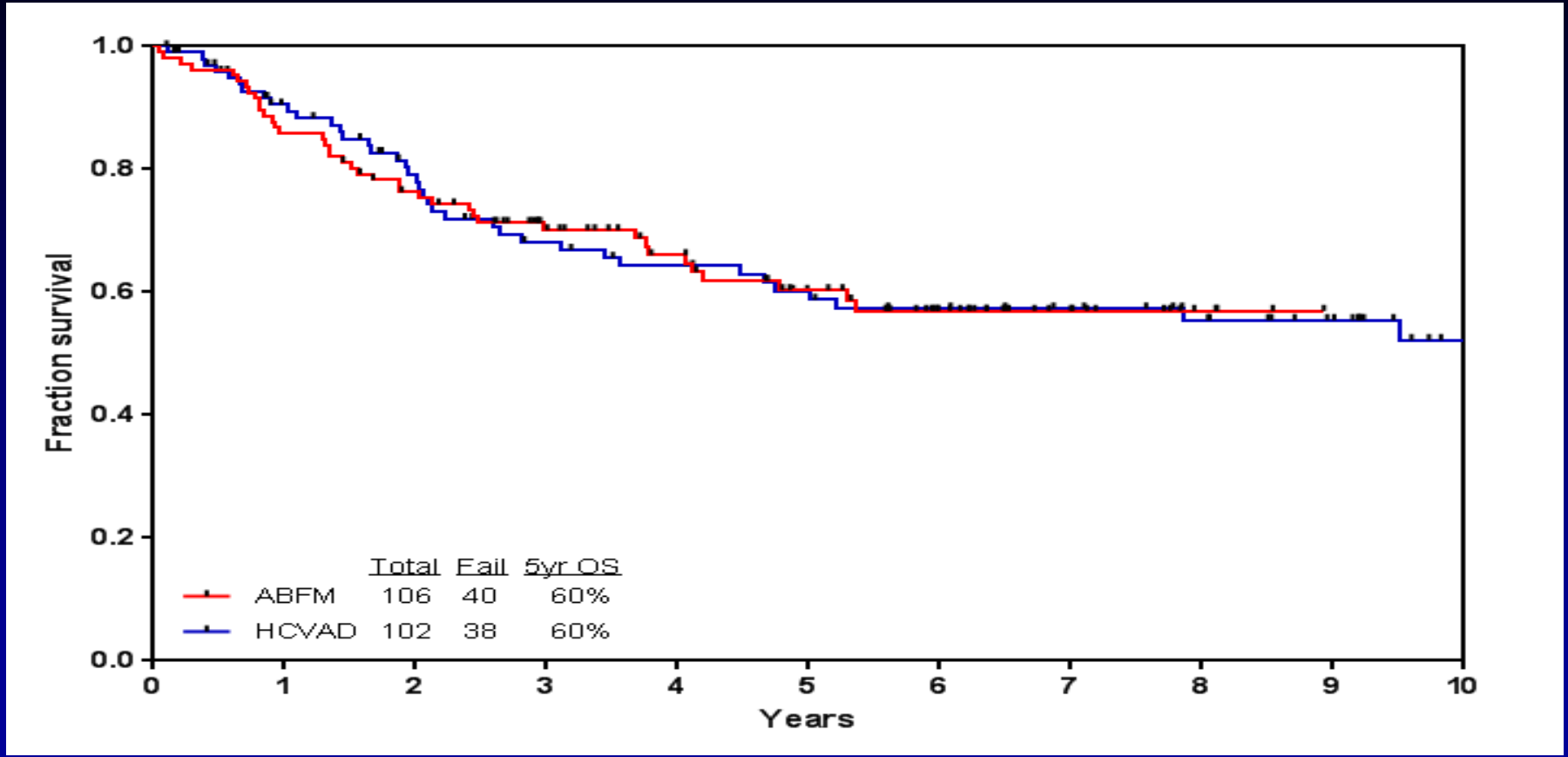
Ph+ ALL: Survival by Decade (MDACC 1984-2023)



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

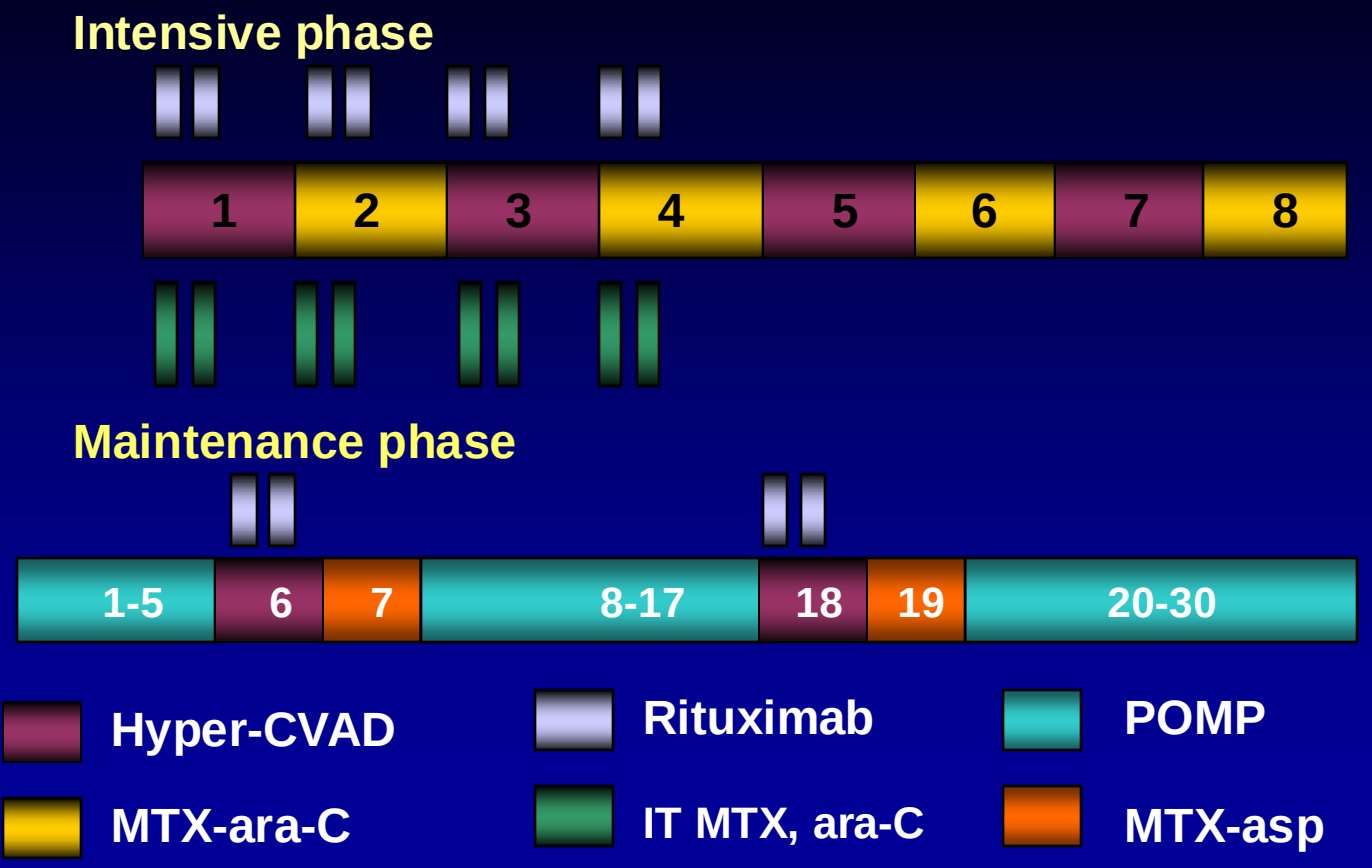
p<0.0001

Hyper-CVAD vs ABFM: Overall Survival



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

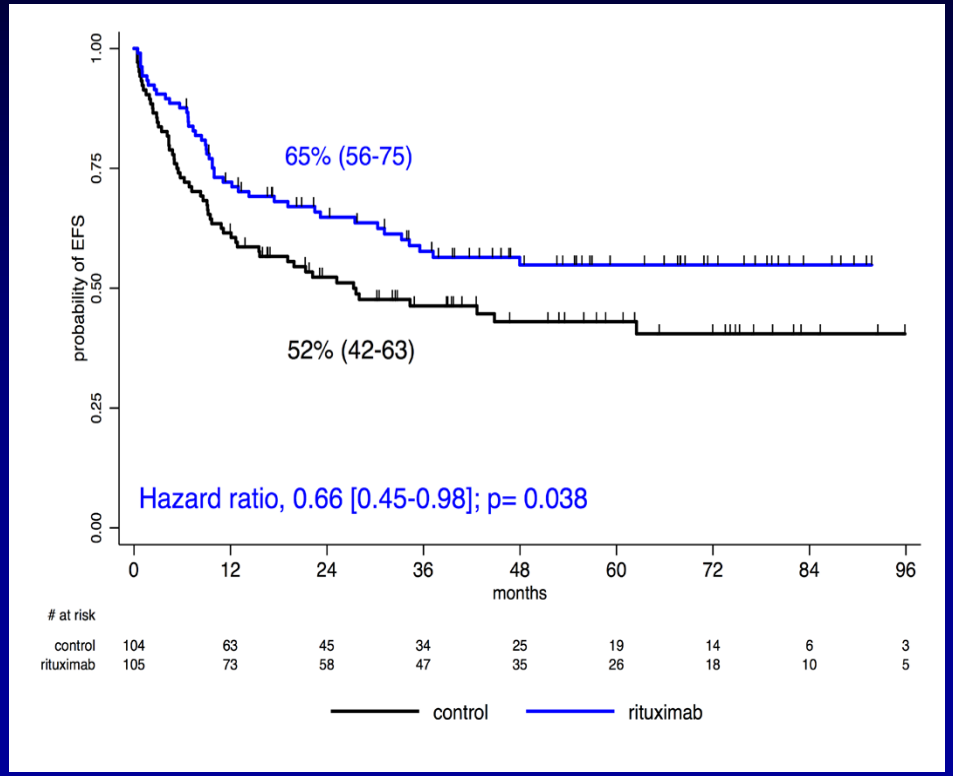
Hyper-CVAD + Rituximab in Precursor B-ALL

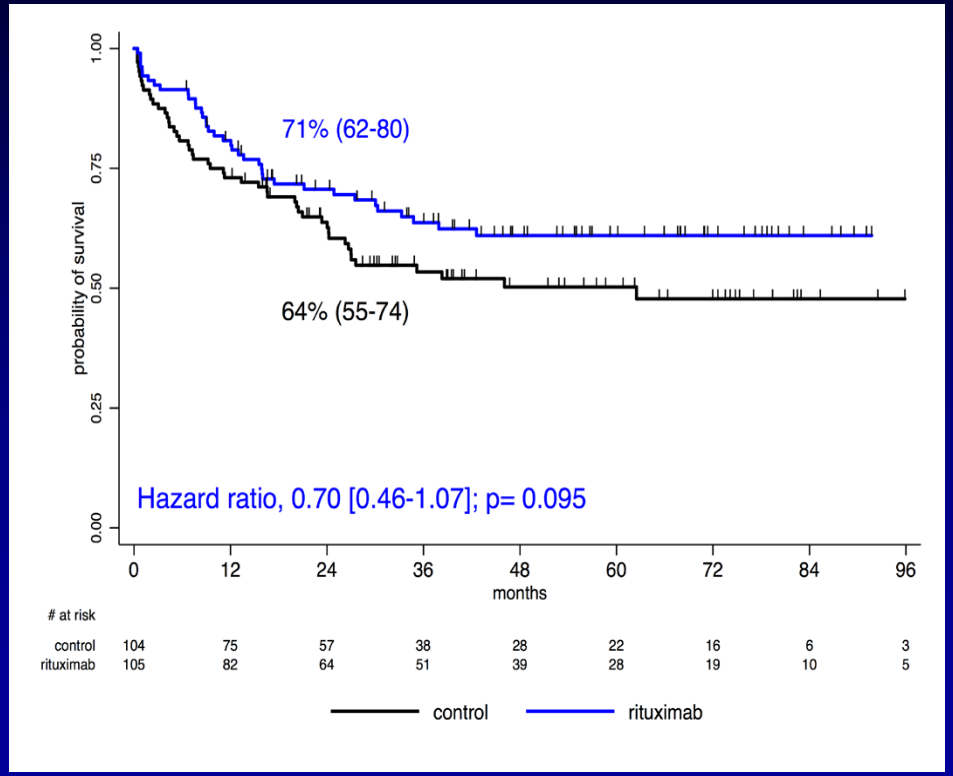


Thomas. JCO 2010; 28:3880-9

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

- Median follow-up 30 months

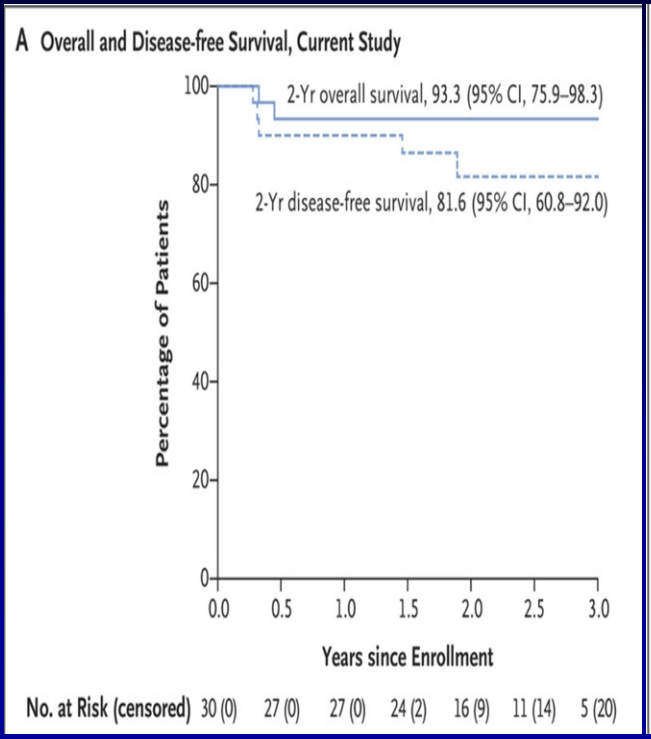


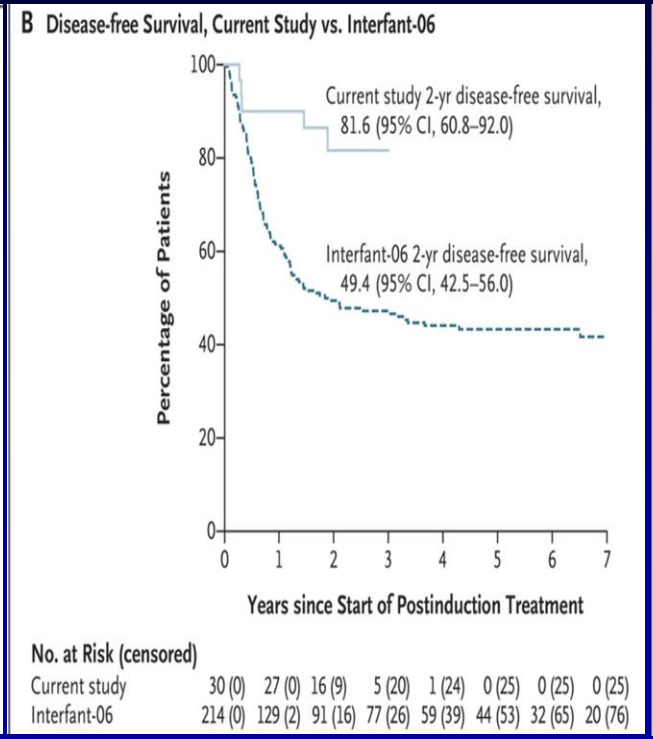


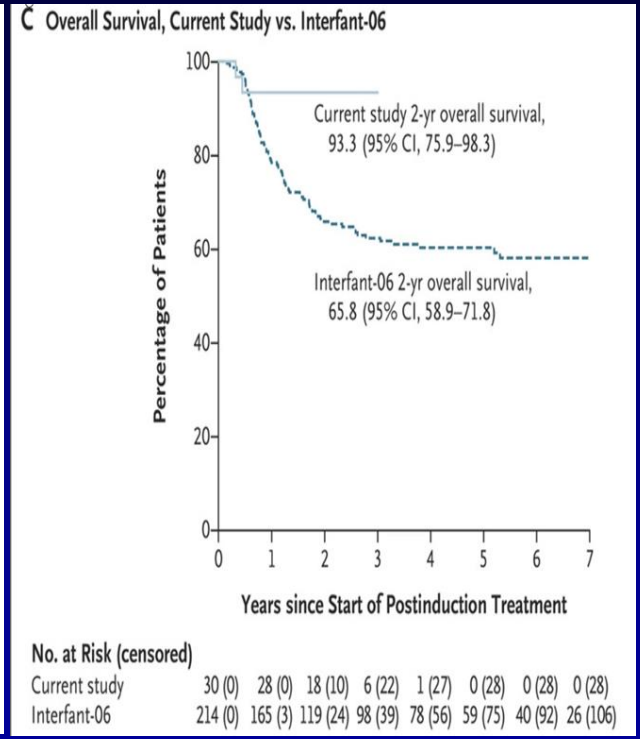
Maury. N Engl J Med. 2016;375:1044-53

ChemoRx + Blina in Newly Dx KMT2A-Rearranged ALL

- 30 infants age <1 yr Rx with chemoRx induction, then 1 course blina consolidation (15 mcg/m² x 28), then chemoRx continuation



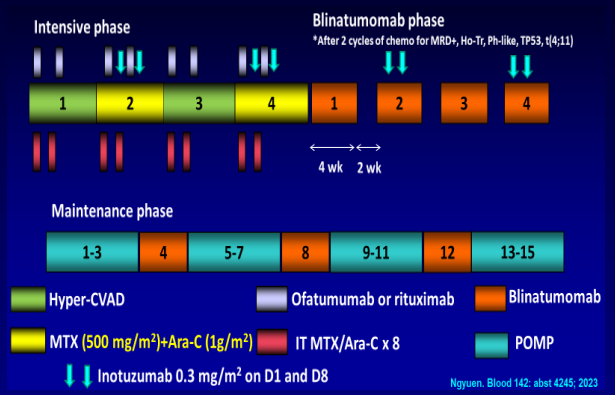


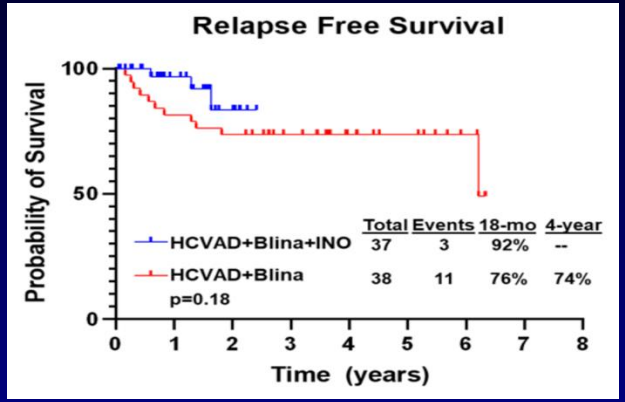


Vam der Sluis. NEJM 388:1572-1581; 2023

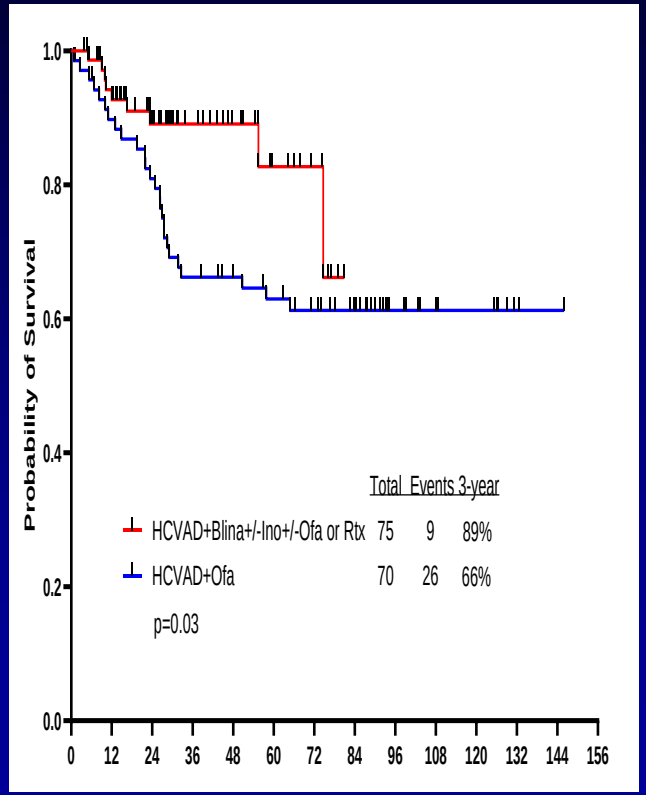
Hyper CVAD-Inotuzumab → Blina in Newly Dx Adult ALL

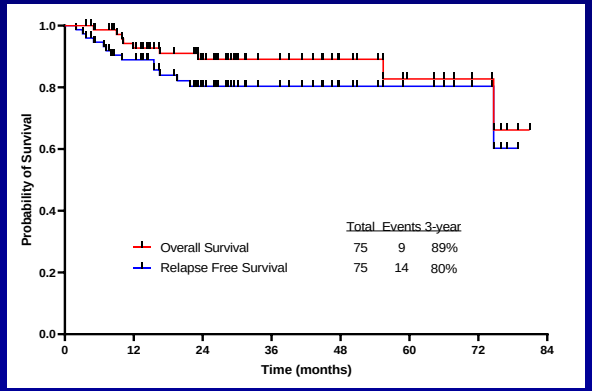
- 75 pts; median age 33 yrs (18-59); Median F/U 26 months (1-77)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 73%; 60-day mortality 0%; 24 (32%) allo-SCT;

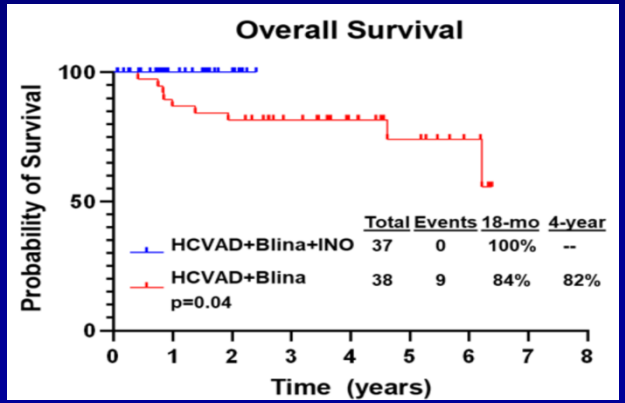




Overall Survival



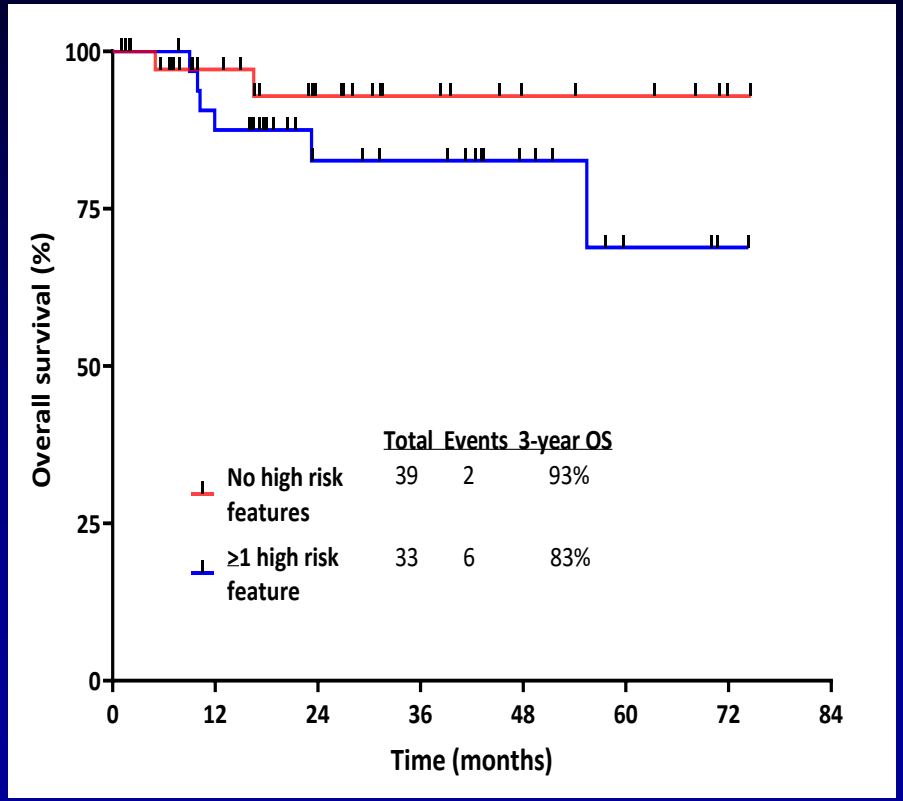




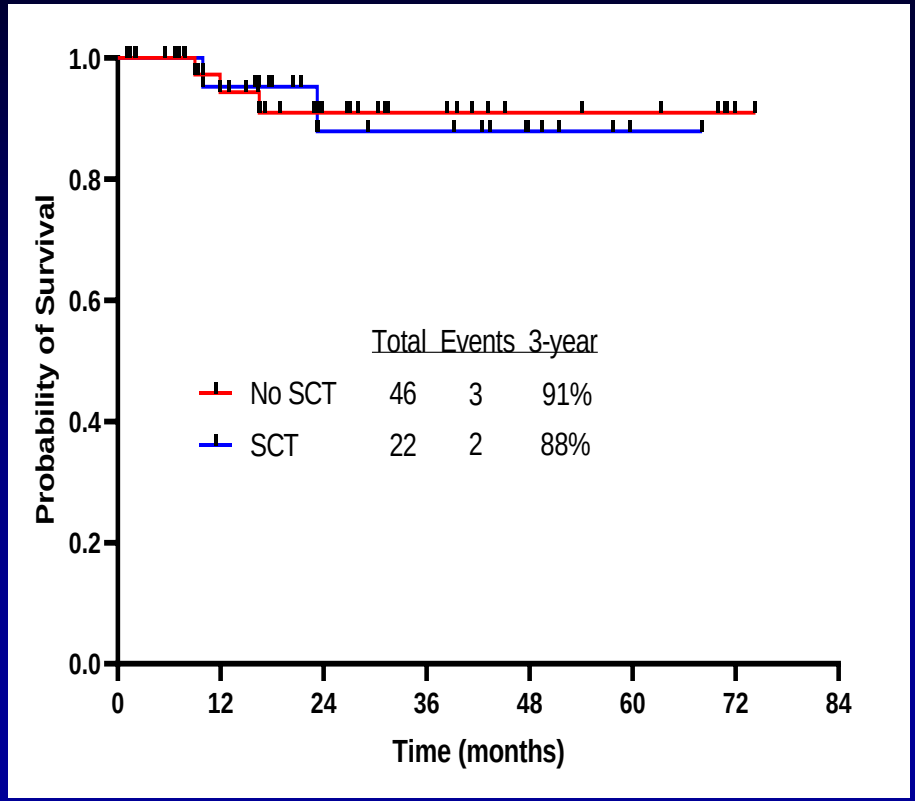
Nguyen. Blood 142: abst 4245; 2023

Hyper-CVAD + Blinatumomab + Inotuzumab in B-ALL

Outcome by ALL Risk

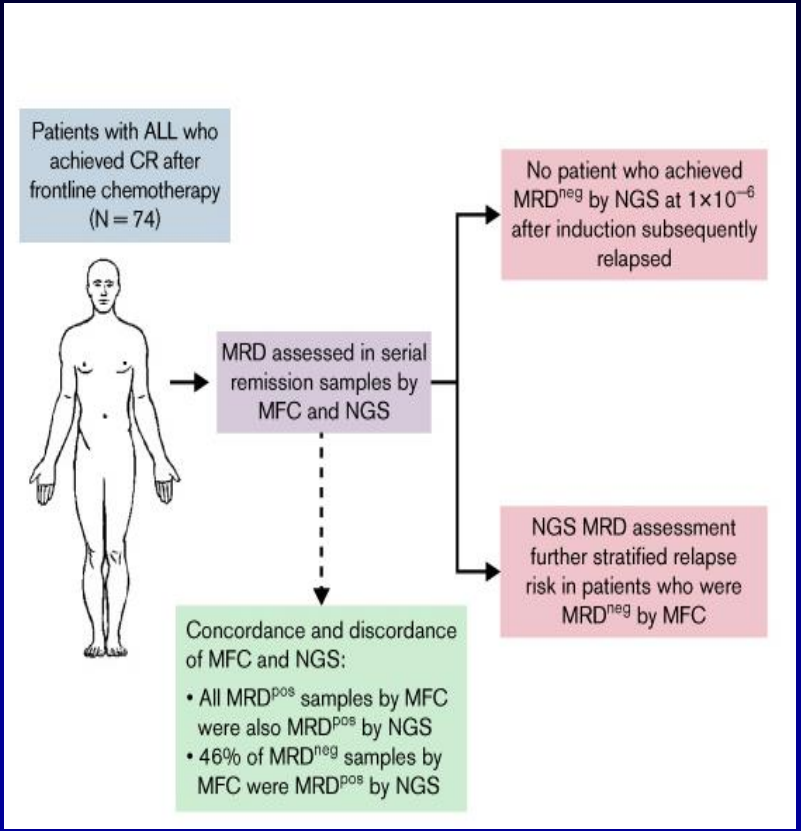


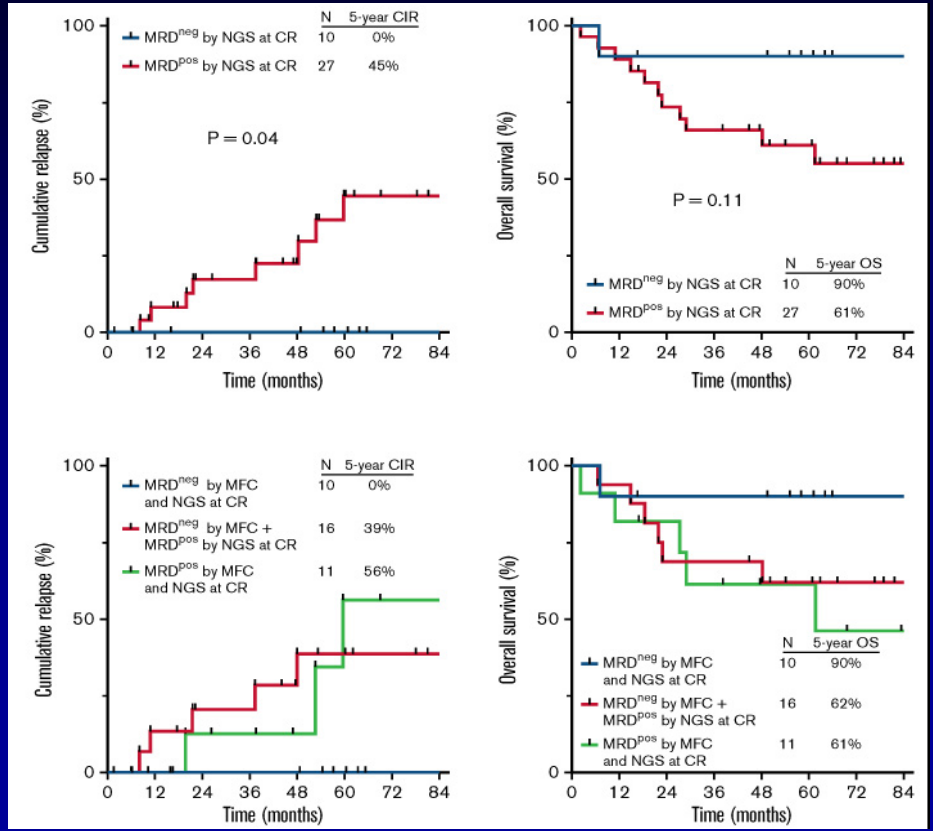
Outcome by ASCT (5-mo landmark)



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

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





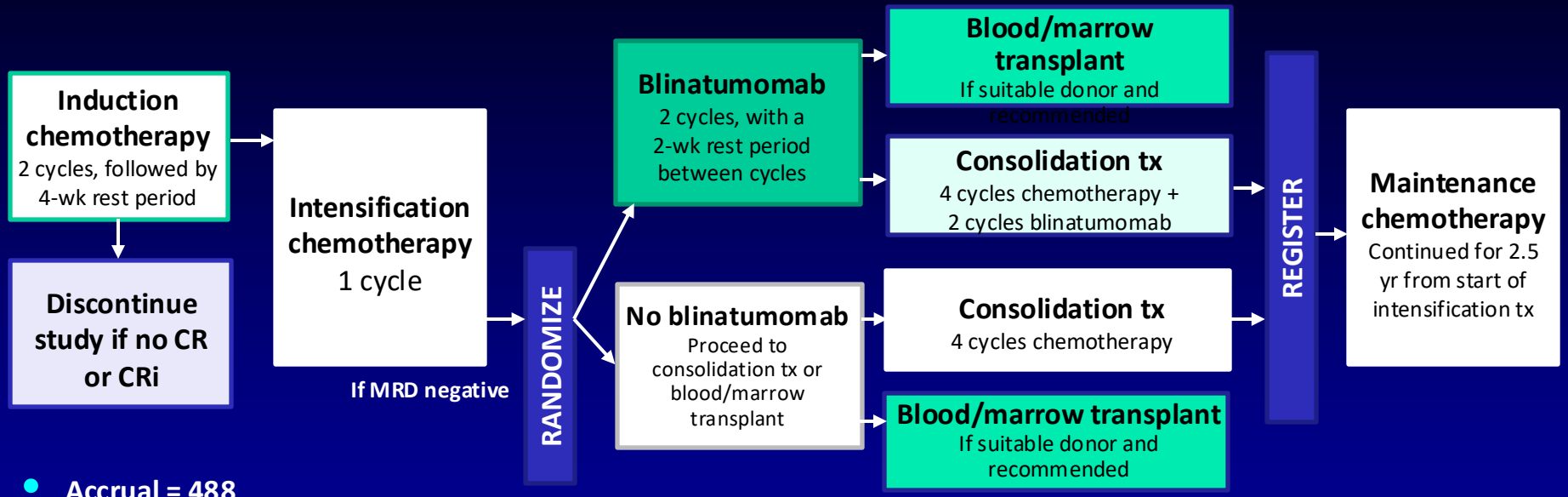
Short. Blood Adv. 2022; 6: 4006-14

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



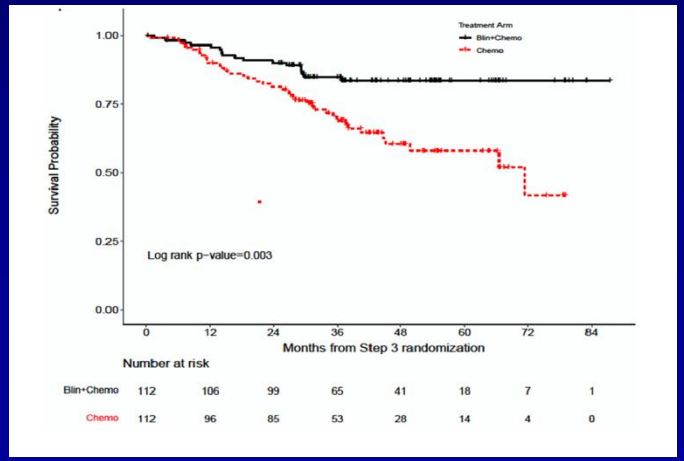
- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

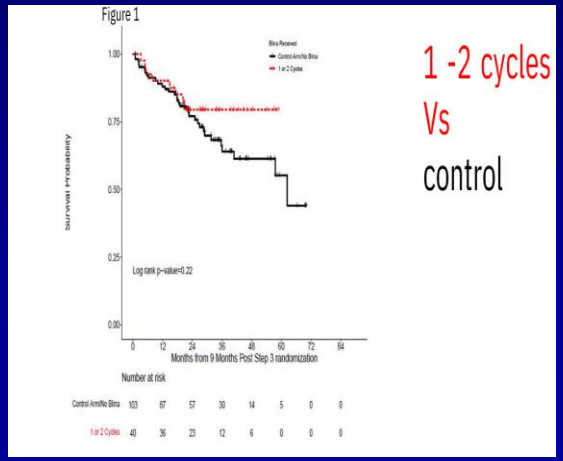
Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

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

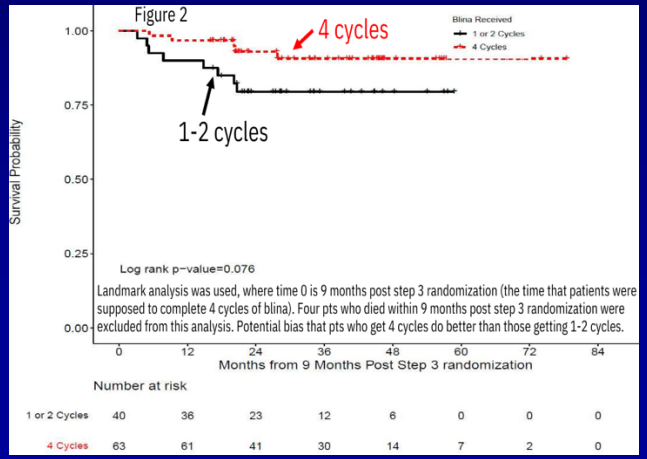
- 488 pts median age 51 yrs (30-70)
- 224 MRD-negative CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median F/U 43 months; median OS NR vs 71.4 mos (HR=0.42; p=0.003)
- No difference in OS if 1-2 cycles of blina vs control (HR: 0.62; p=0.22)
- OS: 1-2 cycles vs 4 cycles (HR: 0.39; p=0.07)

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



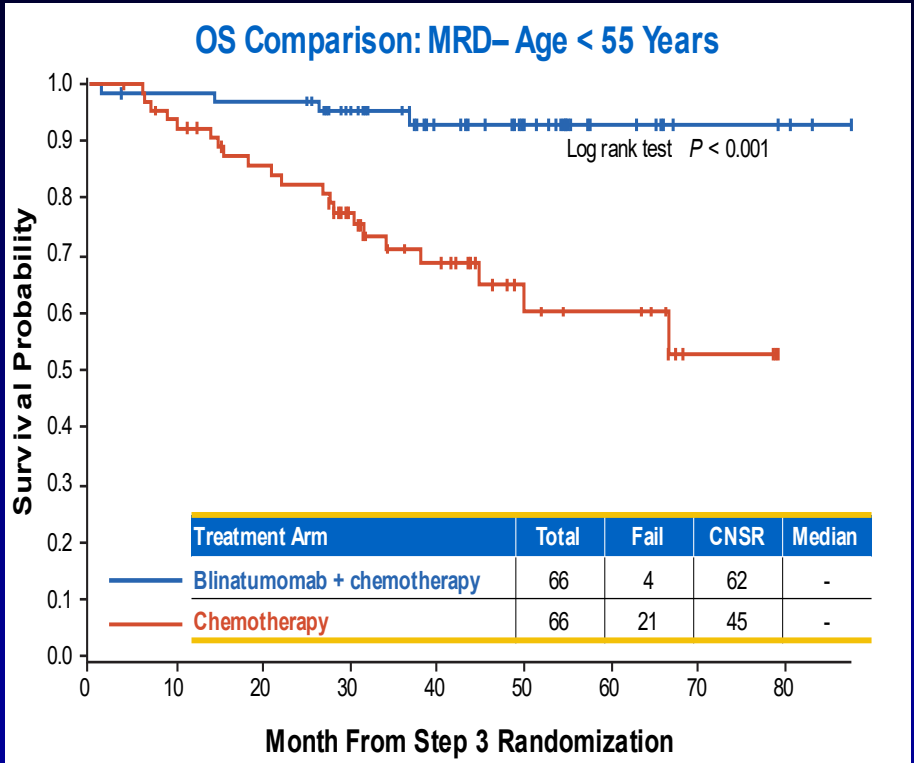


1 -2 cycles
Vs
control



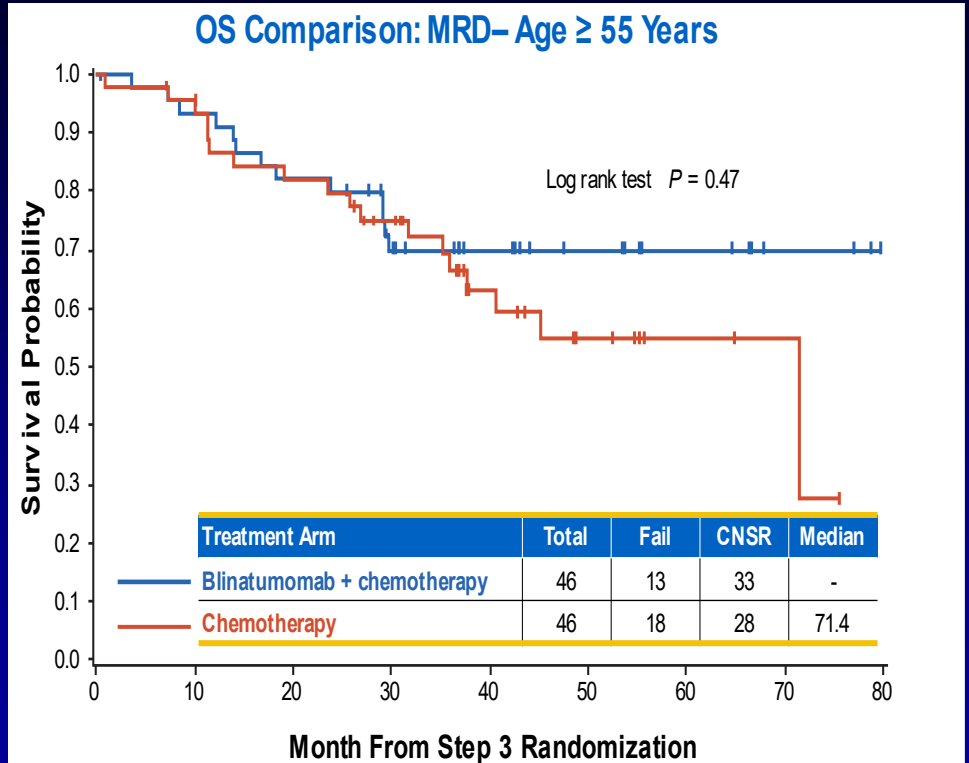
Luger. Blood 142: Abst 2877; 2023

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



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

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



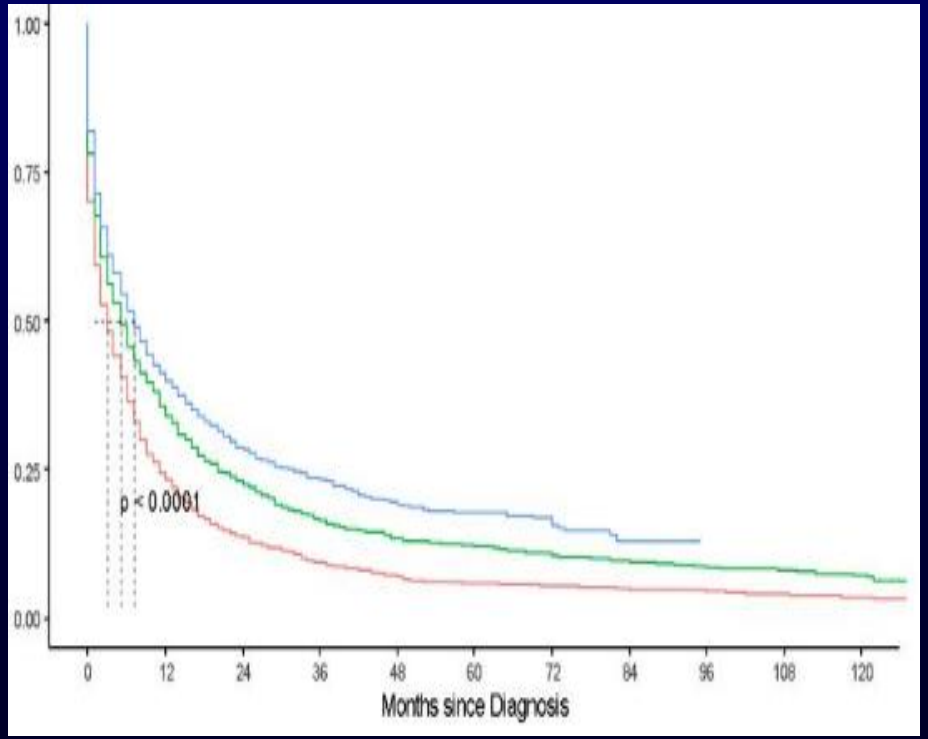
Treatment Arm	Total	Fail	CNSR	Median
Blinatumomab + chemotherapy	46	13	33	-
Chemotherapy	46	18	28	71.4

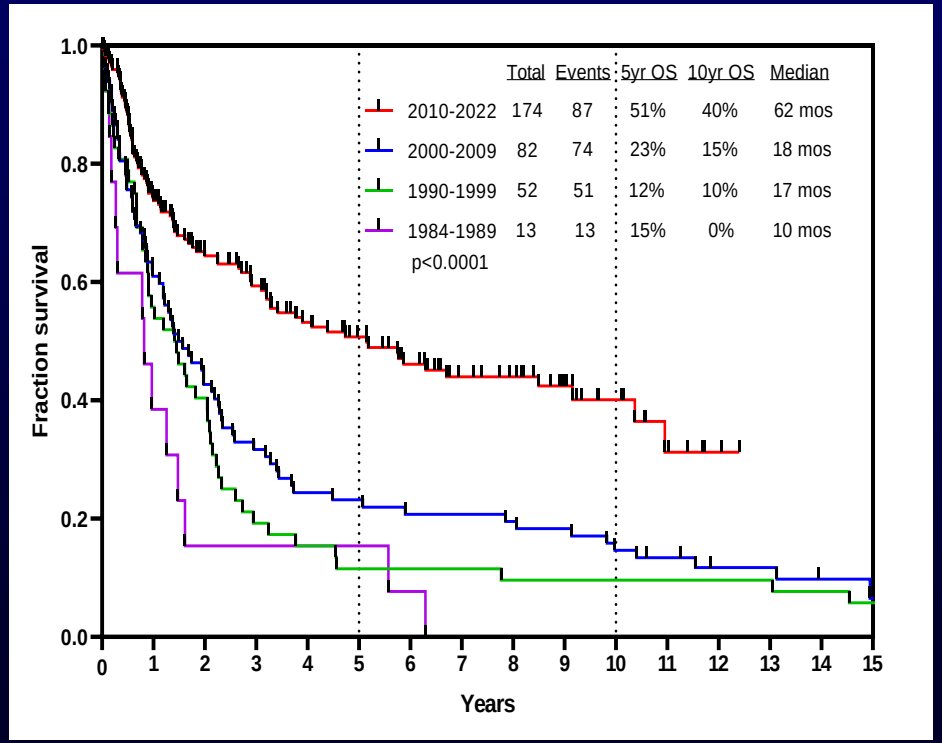
Median OS: NR vs 71.4 months; HR: 0.77; 95% CI: 0.37–1.58; $P = 0.47$

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%

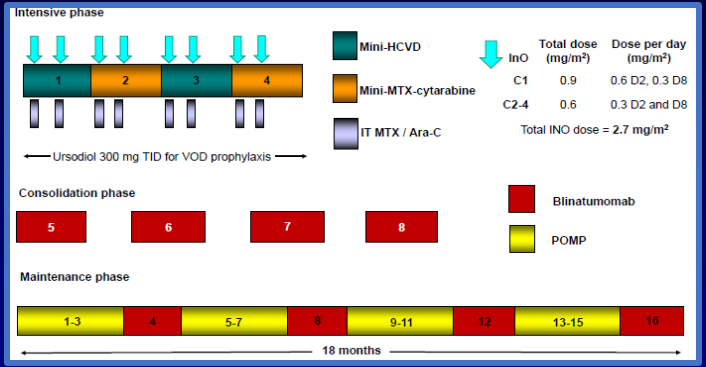




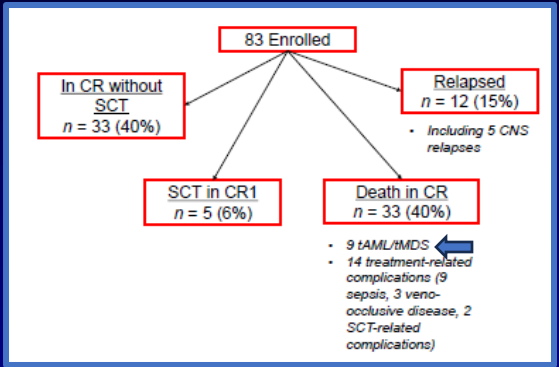
Gupta. Blood 140: abst 1379; 2022

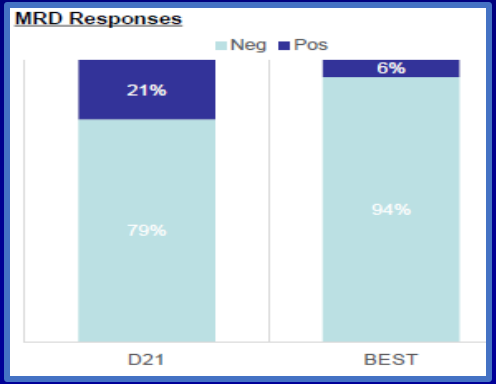
Mini-HCVD + INO ± Blina in Older ALL (N=83)

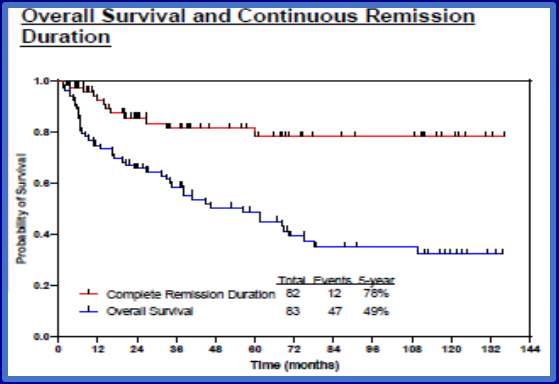
- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: *TP53* 39%; Ph-like 18%; poor cytogenetics 23%
- ORR 99% (CR 90%); MRD negativity 94% (79% at CR)



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)





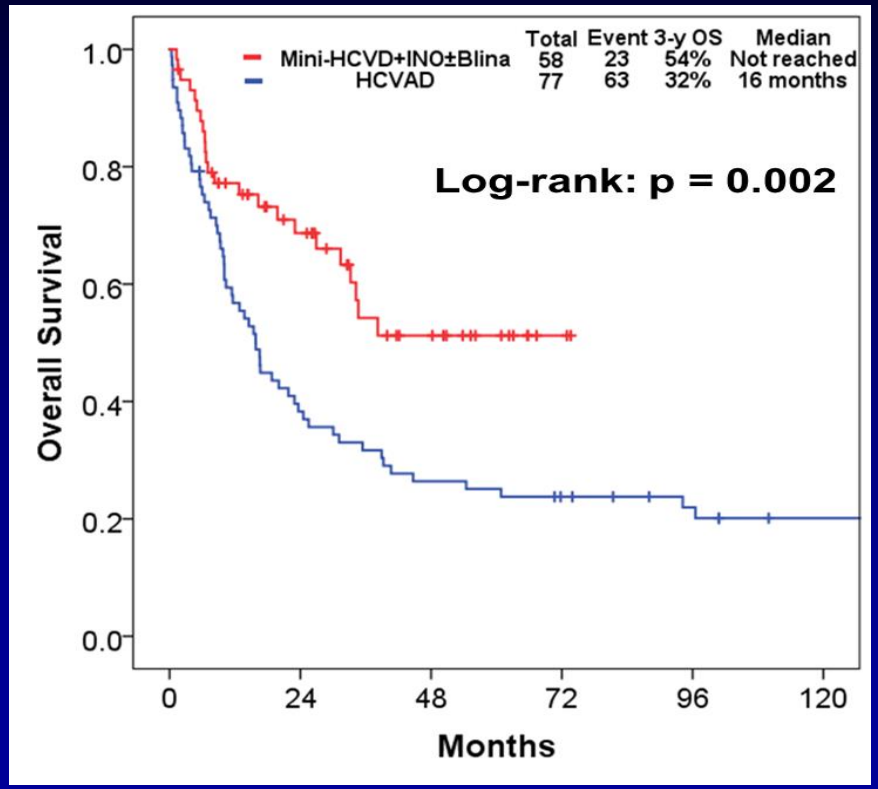


- Median F/U 88 months
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; 6%)
- Death due PD/NR: 12/83 (15%); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (11%); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: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

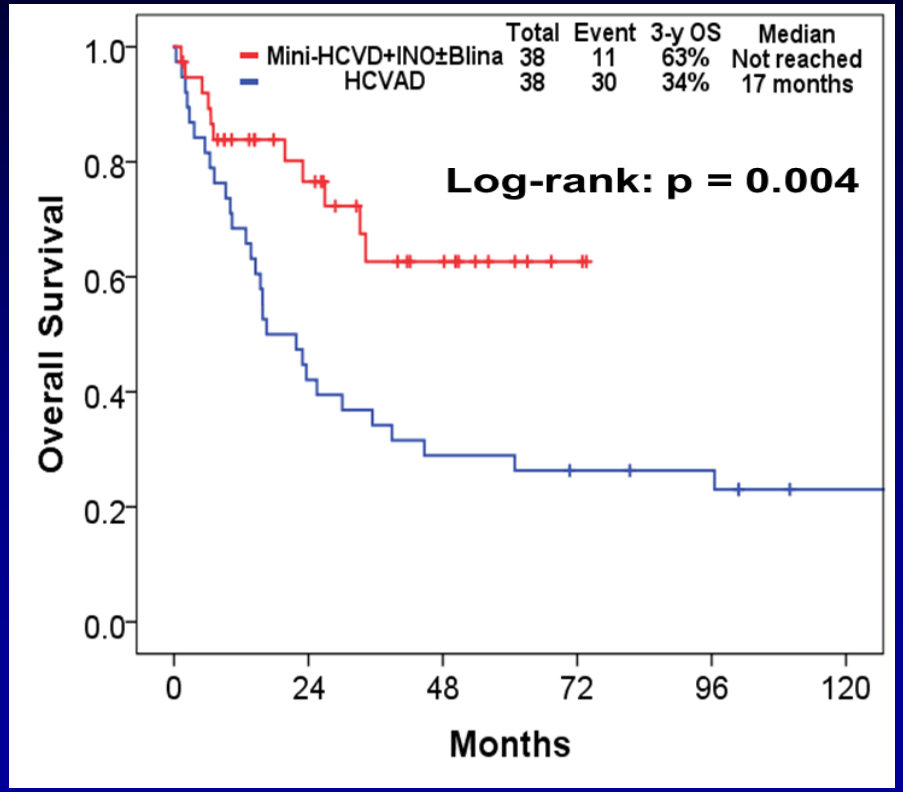
Jen. Blood 142: abst 2878; 2023

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

Pre-matched



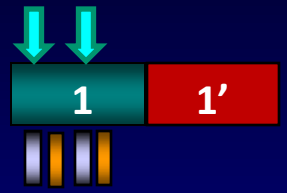
Matched



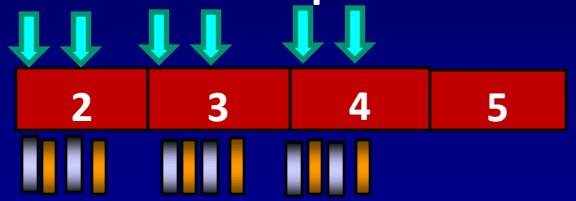
Jabbour E. Cancer. 2019;125(15):2579-2586.

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

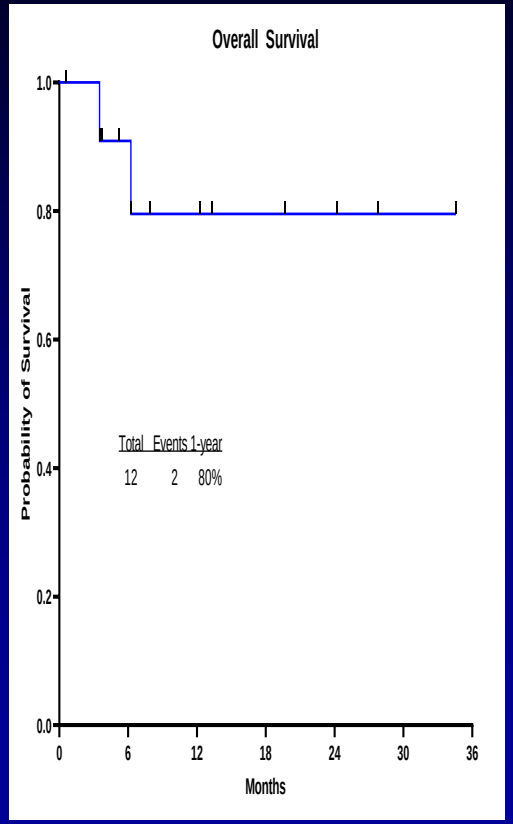
Rituximab if CD20+

1' Blinatumomab for 2 weeks

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

Total INO dose = 2.7 mg/m^2

*Ursodiol 300mg tid for VOD prophylaxis

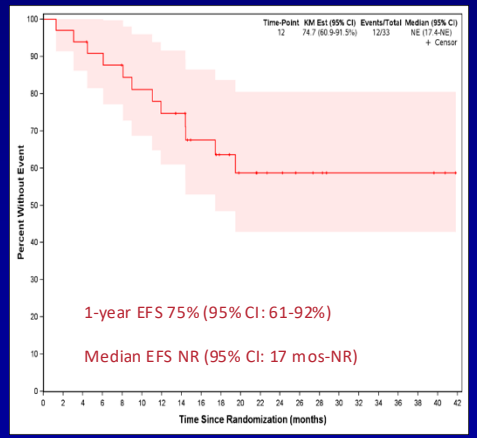


Chemo Rx-Free Inotuzumab + Blinatumomab in Pre–B-ALL (Alliance A 041703)

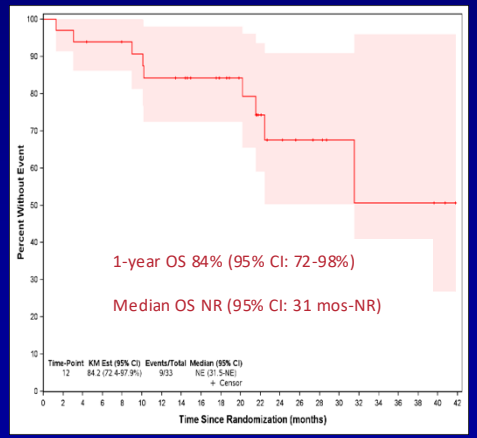
- 33 pts; median age 71 yrs (60-84). Median CD22 92%. F/U 22 months
- Induction: INO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 & 15 (1.8 mg/m^2)
- Maintenance: If CR-CRi INO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) x 2 then BLINA x 2
- If no CR-CRi—BLINA 28m cg/D x21 then x 28 x 3
- IT x 8
- CR 85% post INO x 3; cumulative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

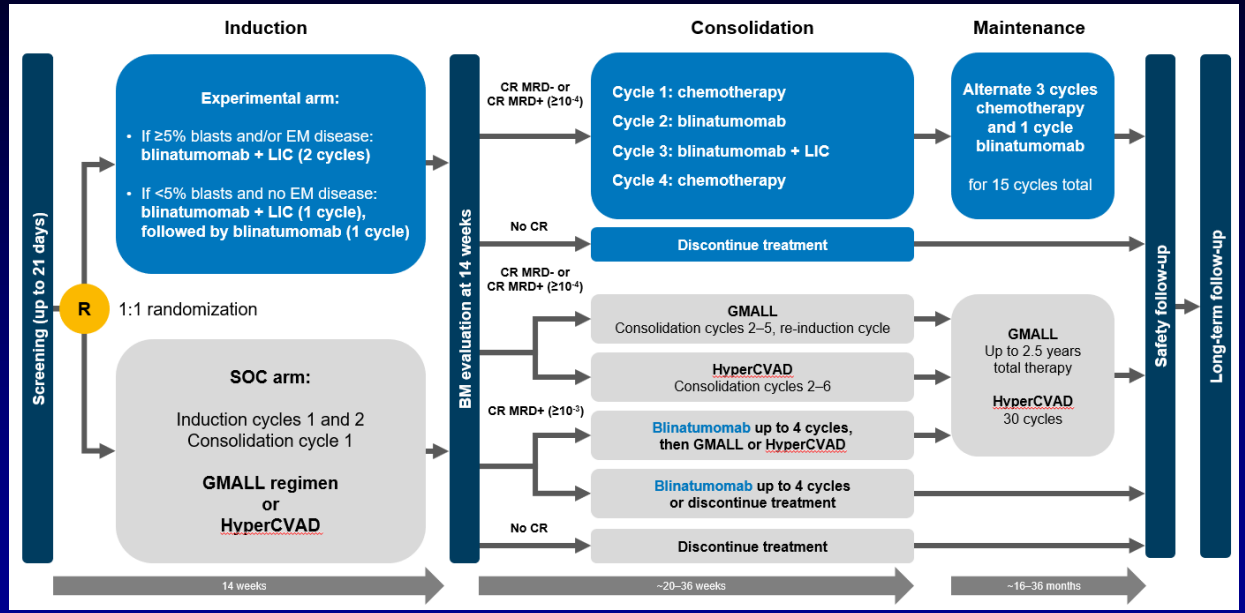


OS



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

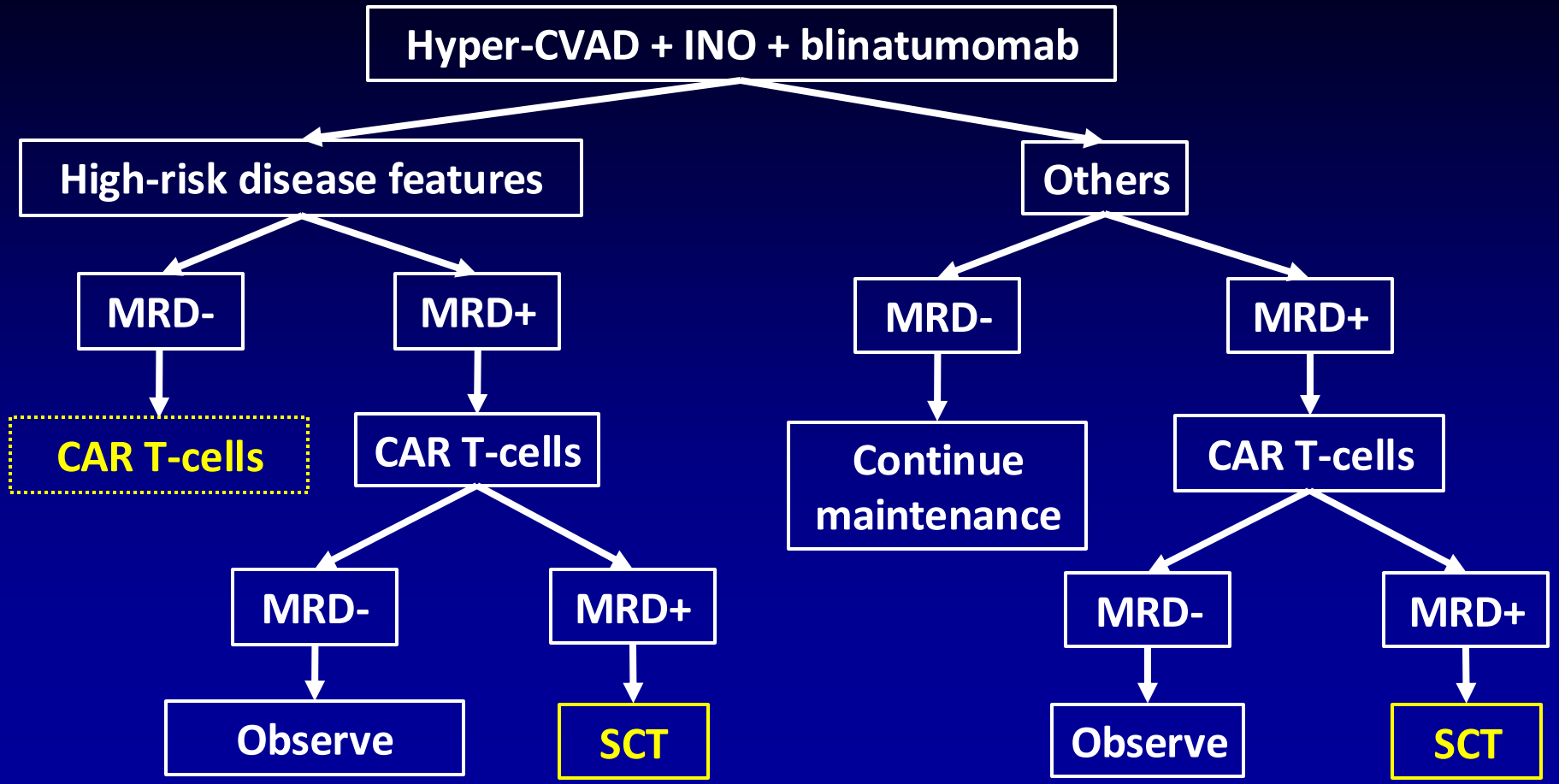
Jabbour E, et al. ASH 2022; Abstract 2732;
NCT04994717. Available at https://clinicaltrials.gov/ct2/show/NCT04994717. Accessed January 2024.

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

Q&A

APTITUDE HEALTH®

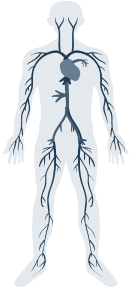
Global Leukemia Academy

AYA patients with ALL: Current treatment approach for this diverse patient population

Jae Park

APTITUDE HEALTH®

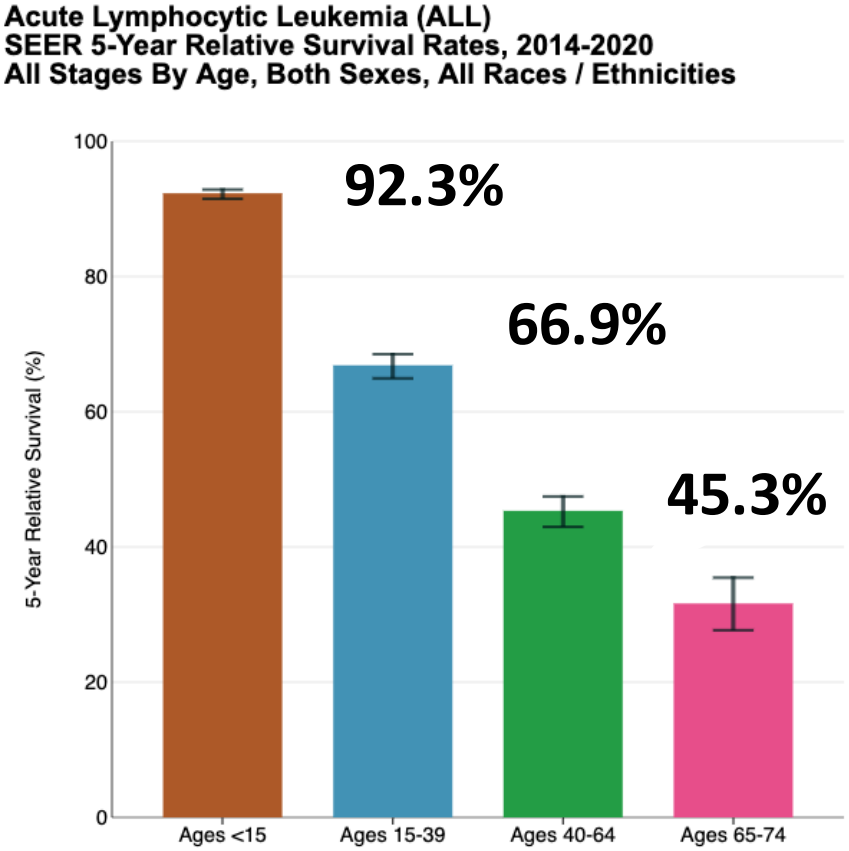
Why is it important to talk about this?



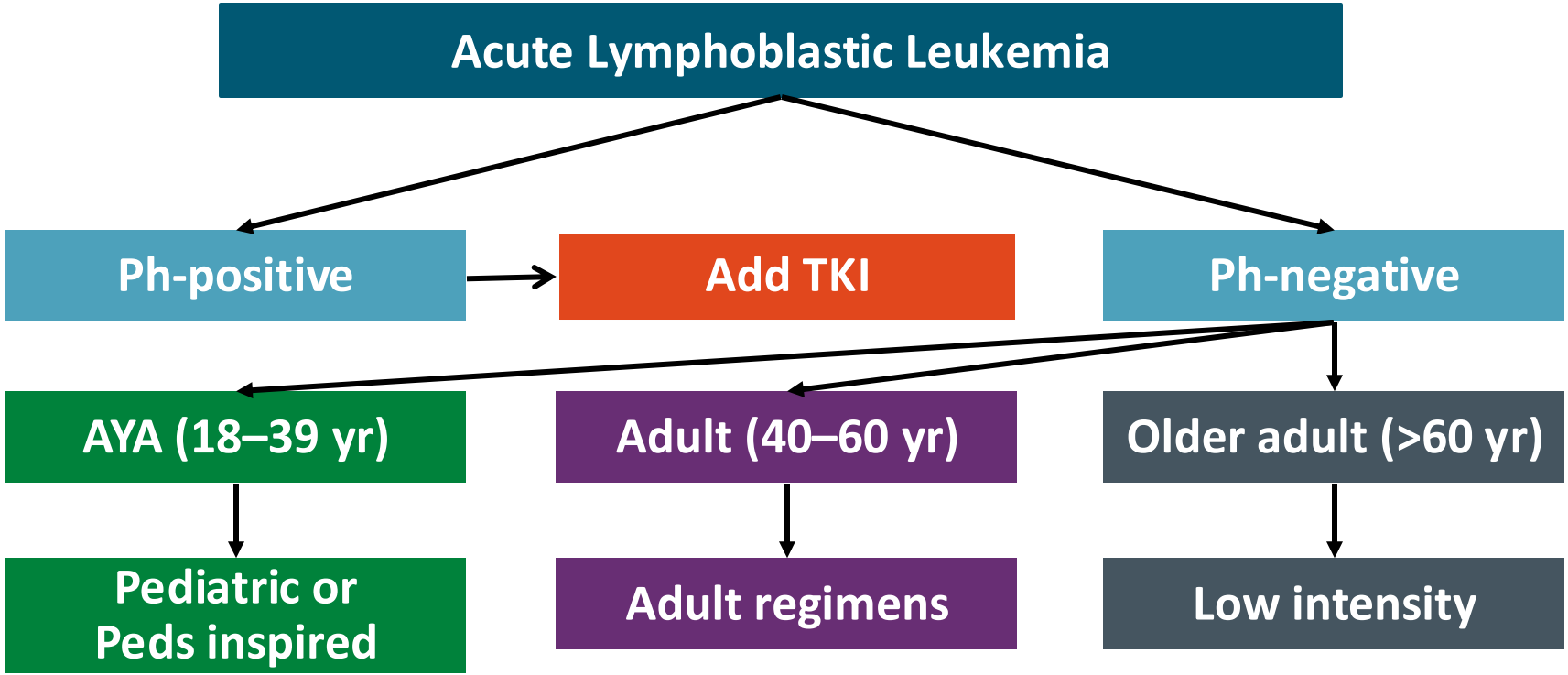
Adolescent and young adults (AYA): 15–39 years

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


Acute Lymphoblastic Leukemia
Ph-positive
Add TKI
Ph-negative
AYA (18–39 yr)
Adult (40–60 yr)
Older adult (>60 yr)
Pediatric or Peds inspired
Adult regimens
Low intensity

Definition of AYA Can Vary Depending on Trial

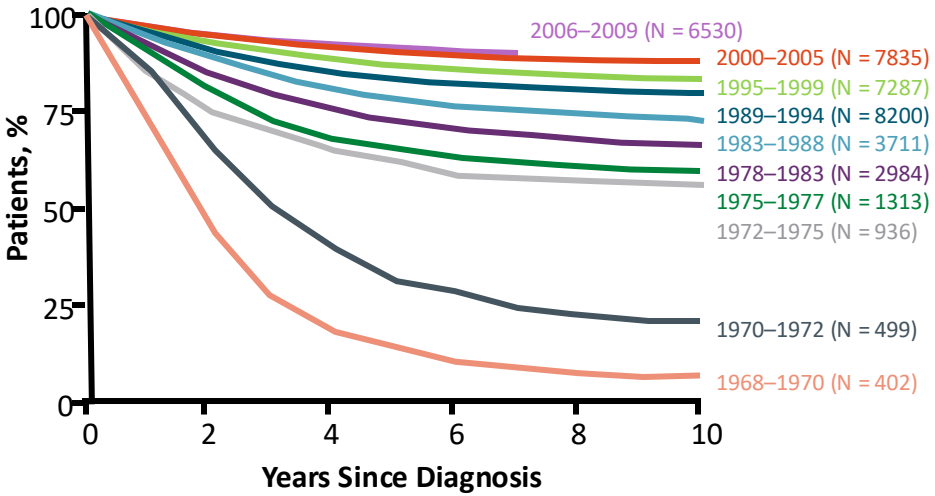
Group	Age Group (yr)
DFCI	18–50
Spanish	15–30
French	15–60
CALGB 10403	17–39
SWOG 805	18–50

AYA definition is relatively loose and driven by tolerability of therapy

DeAngelo DJ, et al. *Leukemia*. 2015;29:526-534; Huguet F, et al. *J Clin Oncol*. 2009;27:911-918; Ribera JM, et al. *J Clin Oncol*. 2008;26:1843-1849.

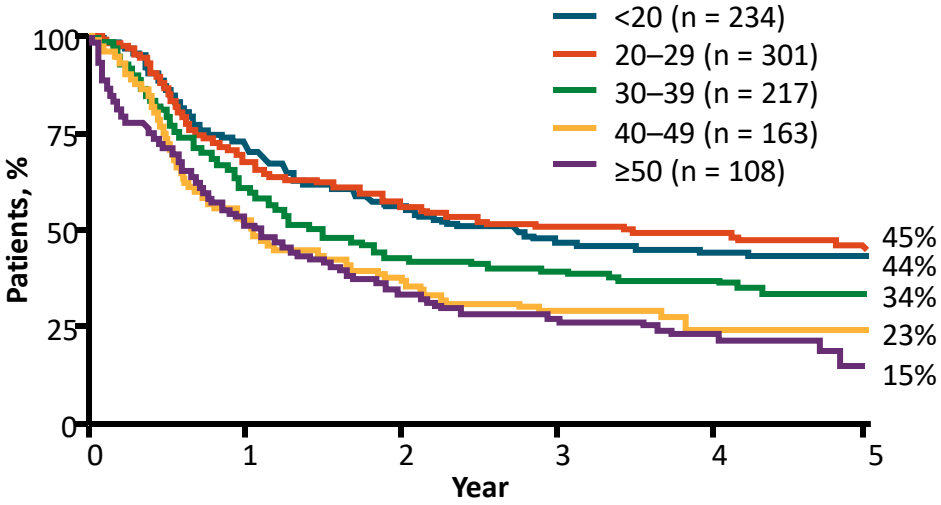
Problem: Poor Outcomes in ALL in Adults

OS among children with ALL in clinical trials: 1968–2009[1]



ALL in Children: A Success Story

OS by age among adults with Ph-negative ALL in ECOG E2993[2]



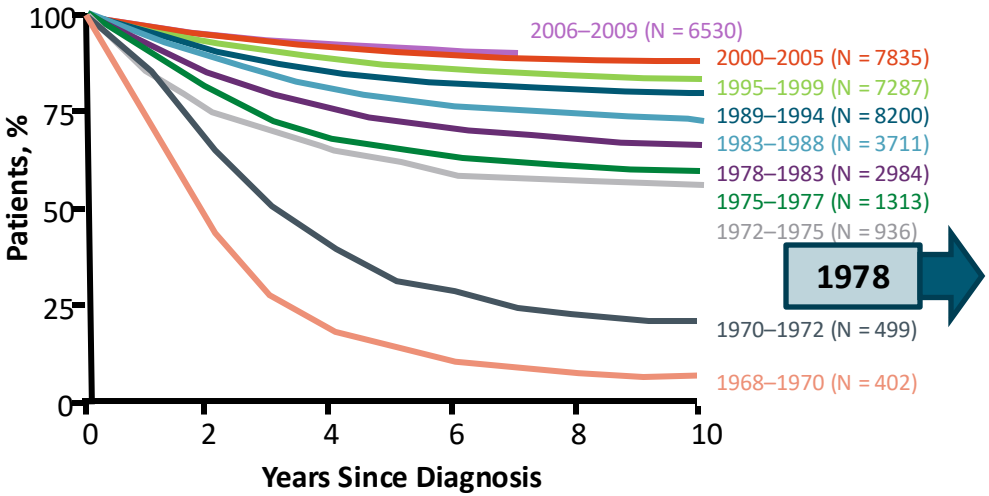
ALL in Adults: We Have a Problem!

One Size Does NOT Fit All!

1. Hunger SP, et al. *N Engl J Med.* 2015;373:1541-1552; 2. Rowe JM, et al. *Blood.* 2005;106:3760-3767.

ALL in Children: A Success Story

OS among children with ALL in clinical trials: 1968–2009



First anti-asparaginase (ASNase) approved by FDA

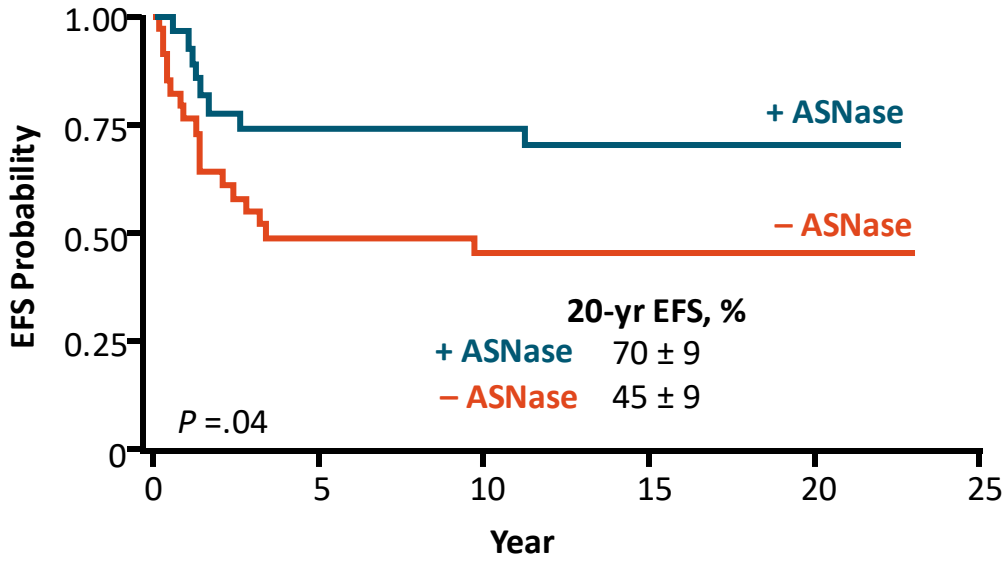
Native *E coli*-derived L-asparaginase in multiagent chemotherapy regimens for treatment of patients with ALL

ALL in Children: A Success Story

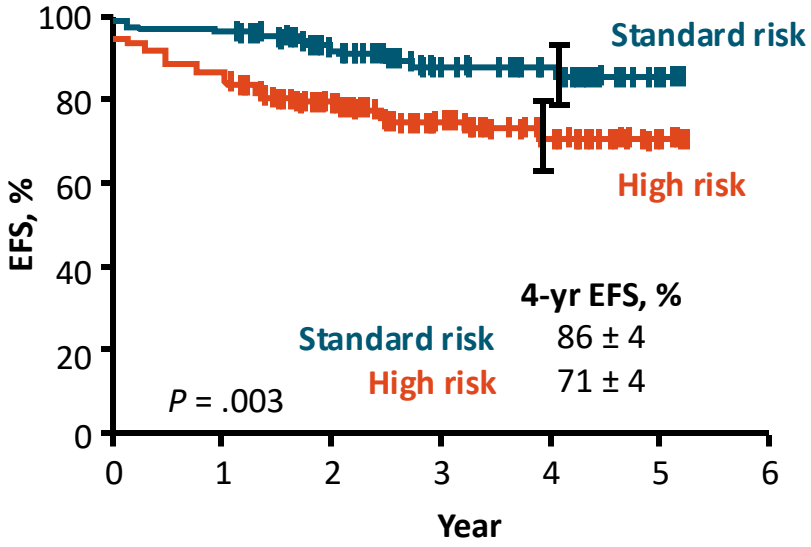
Hunger SP, et al. *N Engl J Med*. 2015;373:1541-1552.

Why Do We Use Asparaginase?

Protocol 77-01:
3-drug induction ± weekly high-dose ASNase[1]



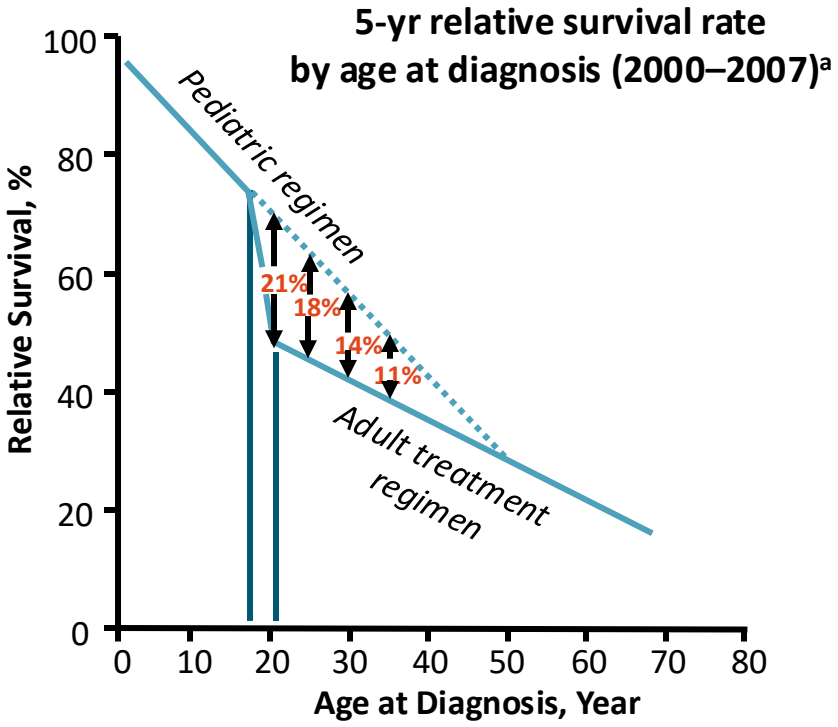
4-drug induction ± intensive ASNase[2]



1. Courtesy of Steve Sallan, MD; 2. Clavell LA, et al. *N Engl J Med.* 1986;315:657-663.

Adolescents and Young Adults With ALL Have Inferior Outcomes Compared With Children

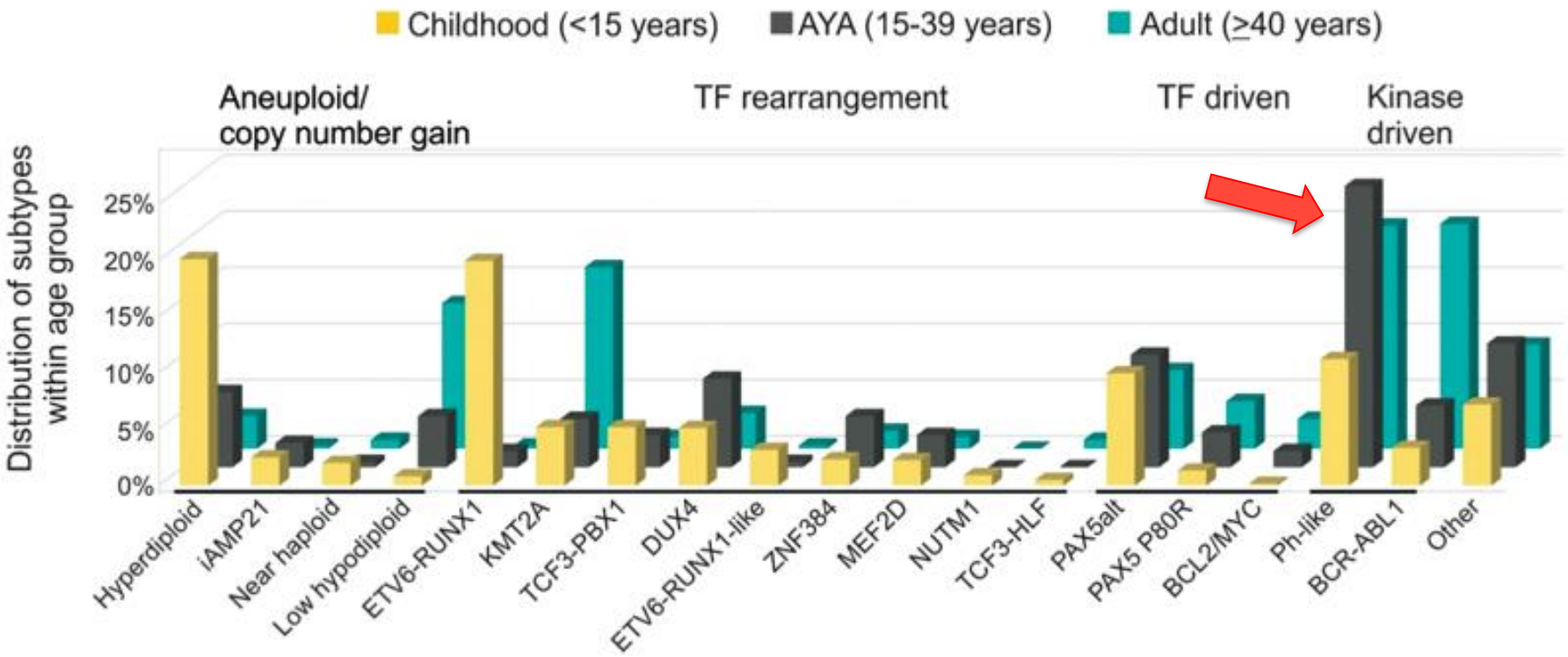
- Acute leukemia is a leading cause of cancer mortality in US in AYA patients aged 15–39 yr
- AYA patients with ALL have worse survival than children
- A major clinical advance was recognition that pediatric regimens improve outcomes among AYA



Siegel SE, et al. *JAMA Oncol.* 2018;4:725-734; National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Cancer Among Adolescents and Young Adults (AYAs) (Ages 15–39). 2022.

[a]Extrapolation by joinpoint analysis into adult age range.

Genetic Aberrations in ALL

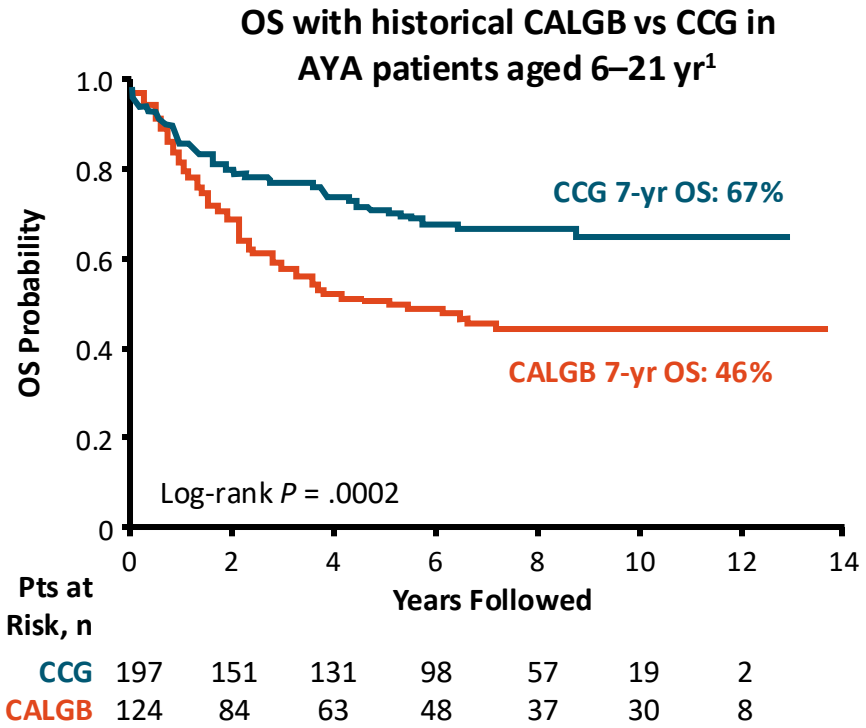


Roberts KG, et al. *Hematology Am Soc Hematol Educ Program*. 2018;2018:137-145.

Outcomes in AYA Patients Improved With Pediatric Regimens

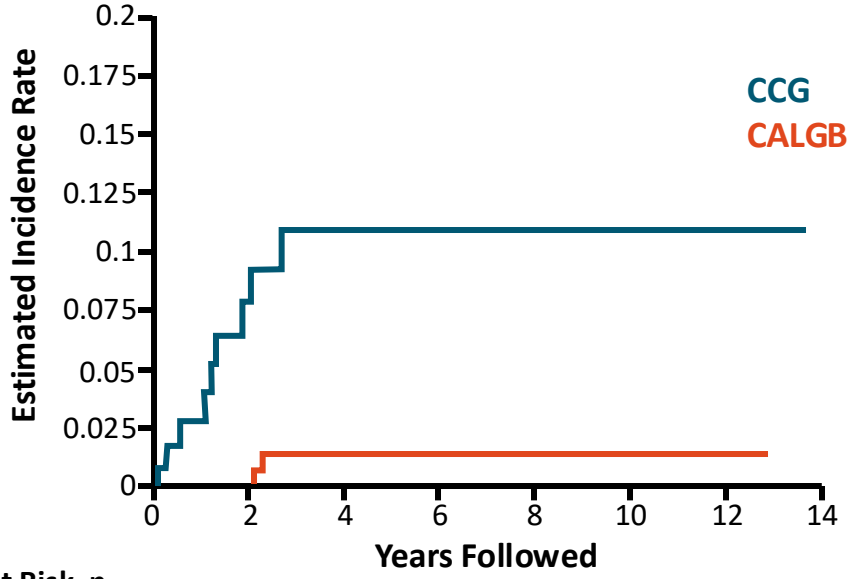
- AYA patients with ALL have better outcomes when receiving pediatric-inspired regimens
  - Reported by Stock et al in 2008 retrospective study of AYA patients aged **16–20 yr** who received treatment on **pediatric (CCG)** or **adult (CALGB) trials** from 1988–2001
  - Replicated by several groups

Regimen	No. AYA	7-Yr OS, %	Relative HR	Log-Rank *P* Value
CCG	197	67	--	.0002
CALGB	124	46	1.9	--



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

Pediatric Regimens Decrease CNS Relapse Rates in AYA Patients



	7-yr rate, %	Relative incidence rate
CCG	1	9.2 (CI: 2.0–42.7;
CALGB	11	log-rank *P* = .0006)

Patients at Risk, n

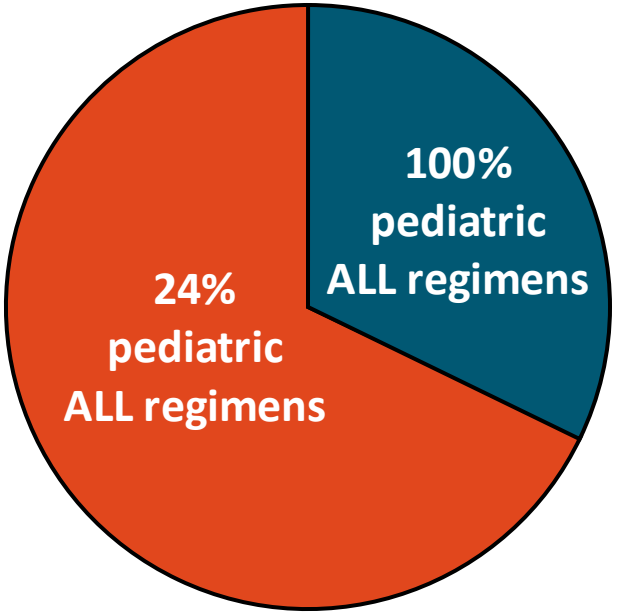
CCG ICNS	197	145	120	93	56	19	2
CALGB ICNS	124	66	47	34	27	21	6

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

Regimens Used in AYA Patients With ALL

- California residents aged 15–39 yr at time of ALL diagnosis between January 1, 2004, and December 31, 2014, from the California Cancer Registry

AYA patients with ALL receiving pediatric regimens by treatment setting (N = 1473)



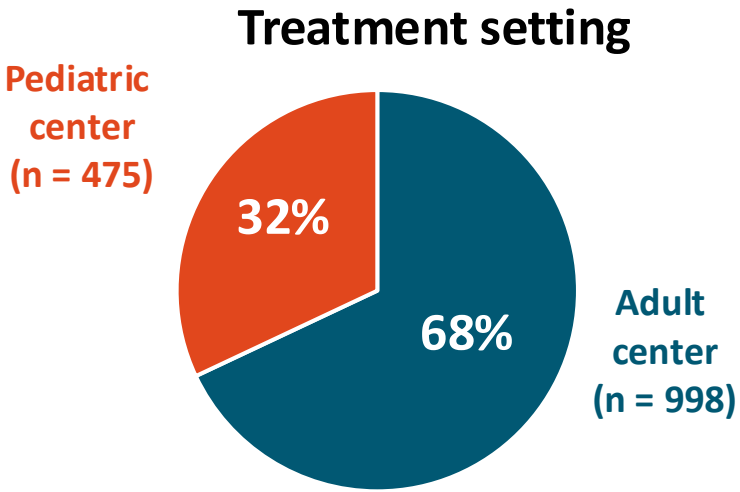
Pediatric cancer treatment setting (n = 475)

Adult cancer treatment setting (n = 998)

Muffly L, et al. *Blood Adv.* 2018;2:895-903.

AYA ALL: Patterns of Care and Outcomes

- Observational study of frontline ALL regimens in AYA patients in California from 2004–2014 (N = 1473)



- Adult regimens (75.6%)
  - Hyper-CVAD: 42.6%
  - Cooperative Group: 17.4%
  - Linker: 11.6%
  - Other: 3.8%
- Pediatric regimens (24.3%)
  - C10403: 9.3%
  - BFM: 6.2%
  - Cooperative Group: 5.2%
  - Other: 3.4%

Muffly L, et al. *Blood Adv.* 2018;2:895-903.

Principles of Pediatric vs Adult ALL Regimens

- Multiple chemotherapy drugs
- **More** asparaginase and corticosteroids
- **Less** myelotoxic drug
  - Anthracyclines
  - Alkylating agents
- Better time- and dose-adherence
- Allo-BMT only for very high risk

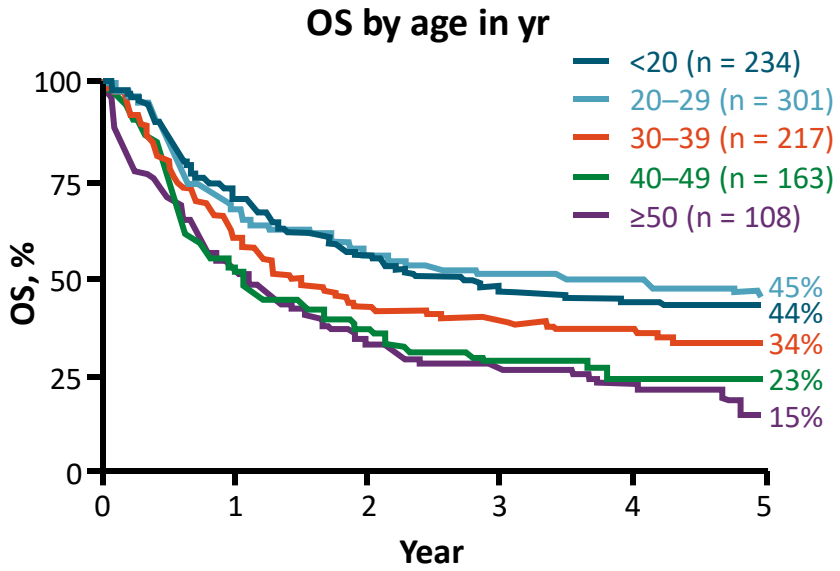
CALGB 10403

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

Prognosis of AYA Patients Improved With Pediatric Regimens

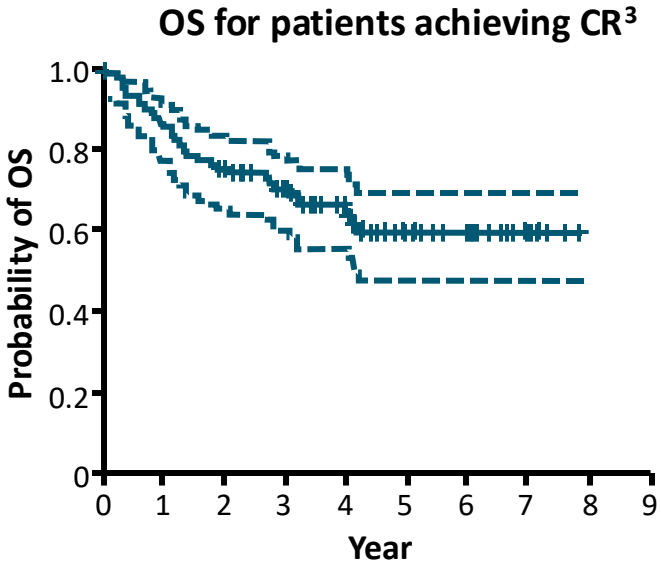
E2993 "Adult" protocol[1]

5-yr OS for patients aged 20–50 yr: 20% to 45%



DFCI "Pediatric" protocol[2,3]

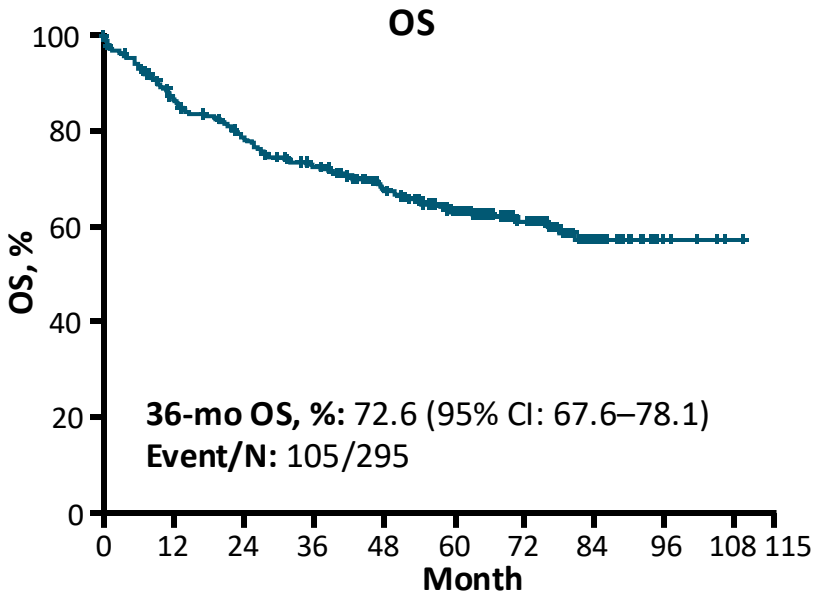
5-yr OS for patients aged 20–50 yr: 60% to 70%



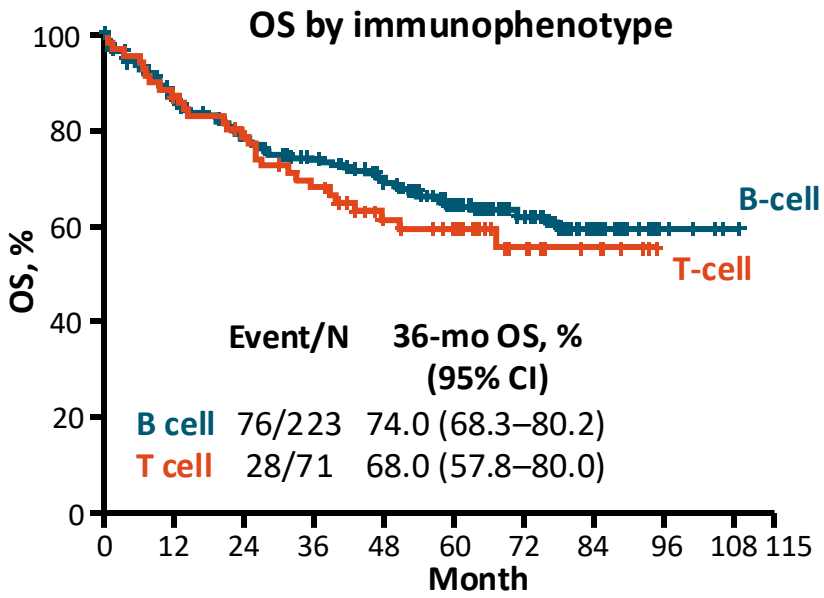
1. Rowe JM, et al. *Blood*. 2005;106:3760-3767; 2. Vrooman LM, et al. *J Clin Oncol*. 2013;31:1202-1210; 3. DeAngelo DJ, et al. *Leukemia*. 2015;29:526-534.

Improved Survival for AYA Patients: CALGB 10403

- 72% survival at 3 years

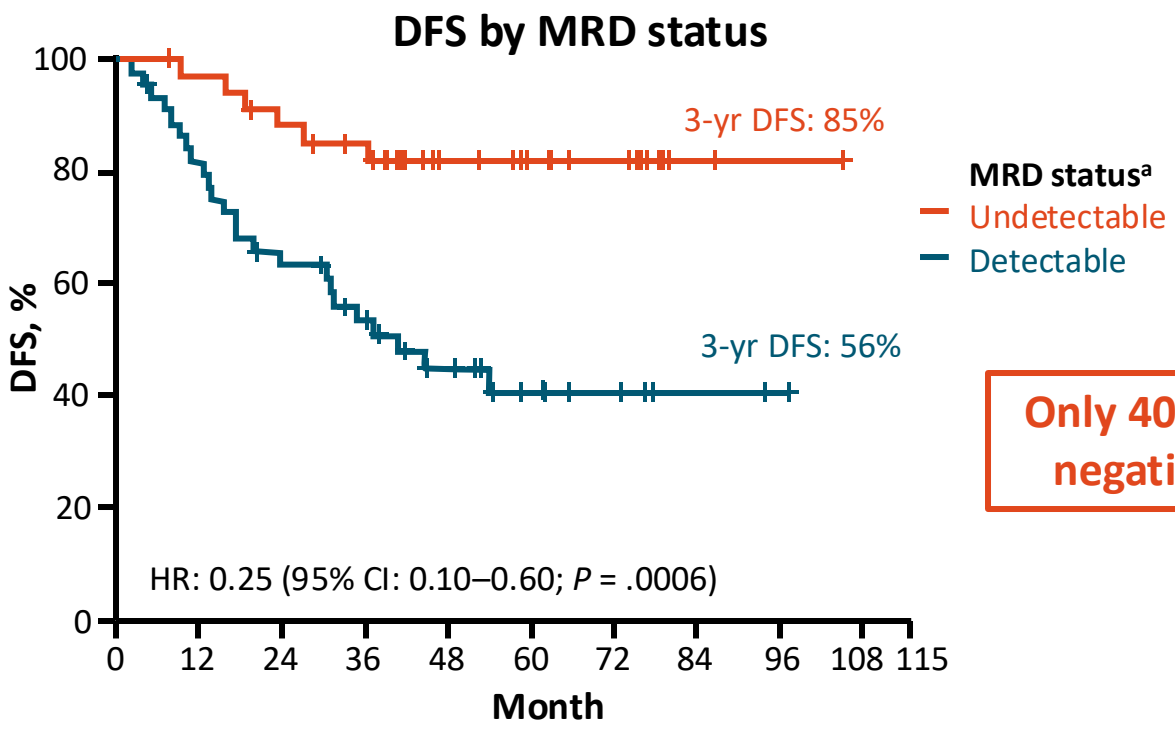


- Immunophenotype: B cell vs T cell



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

Early MRD Eradication: CALGB 10403

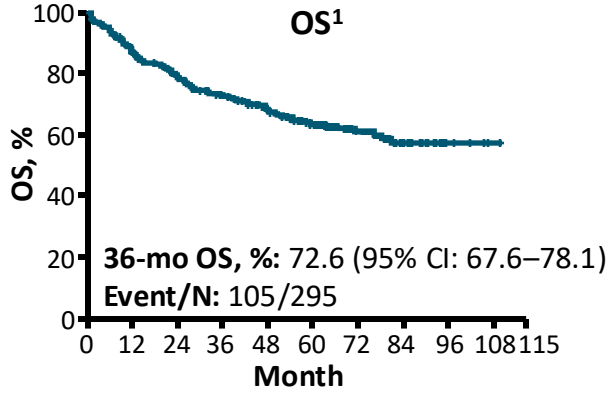


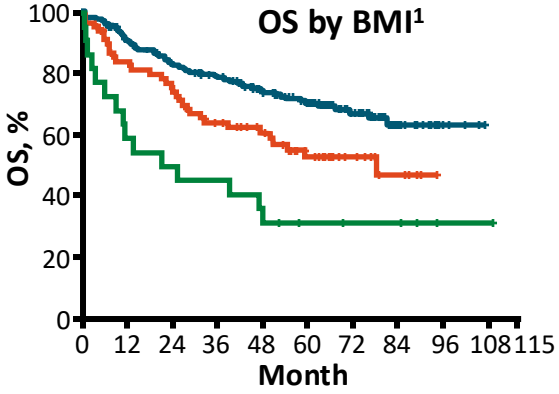
Only 40% of patients are MRD negative early in treatment

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

[a]QT-PCR following induction.

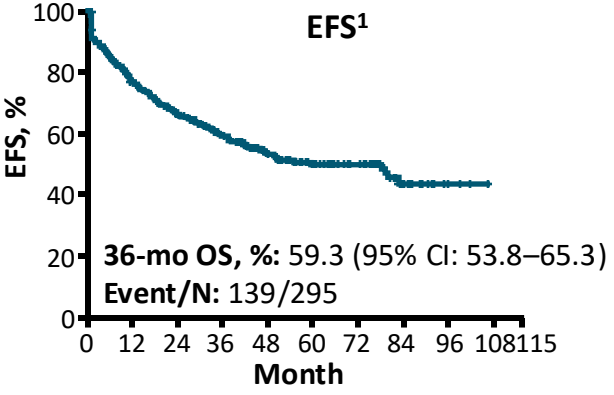
CALGB 10403: Outcomes With Pediatric Regimen in AYA Patients

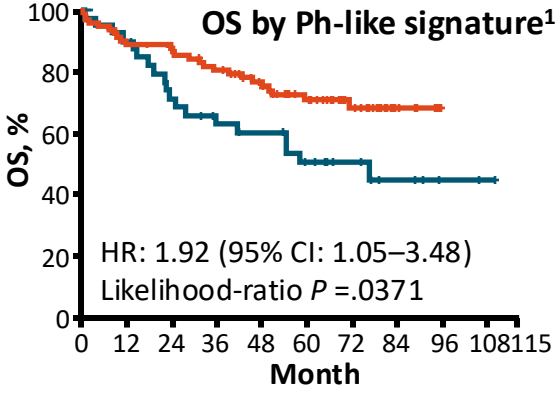




BMI, kg/m²	36-mo OS, % (95% CI)
<30	78.8 (73.2–84.9)
30–40	64.3 (54.0–76.6)
40+	45.5 (28.8–71.8)

3-yr OS[1]: 72%
3-yr EFS[1]: 59%
CALGB OS[2]: 46%

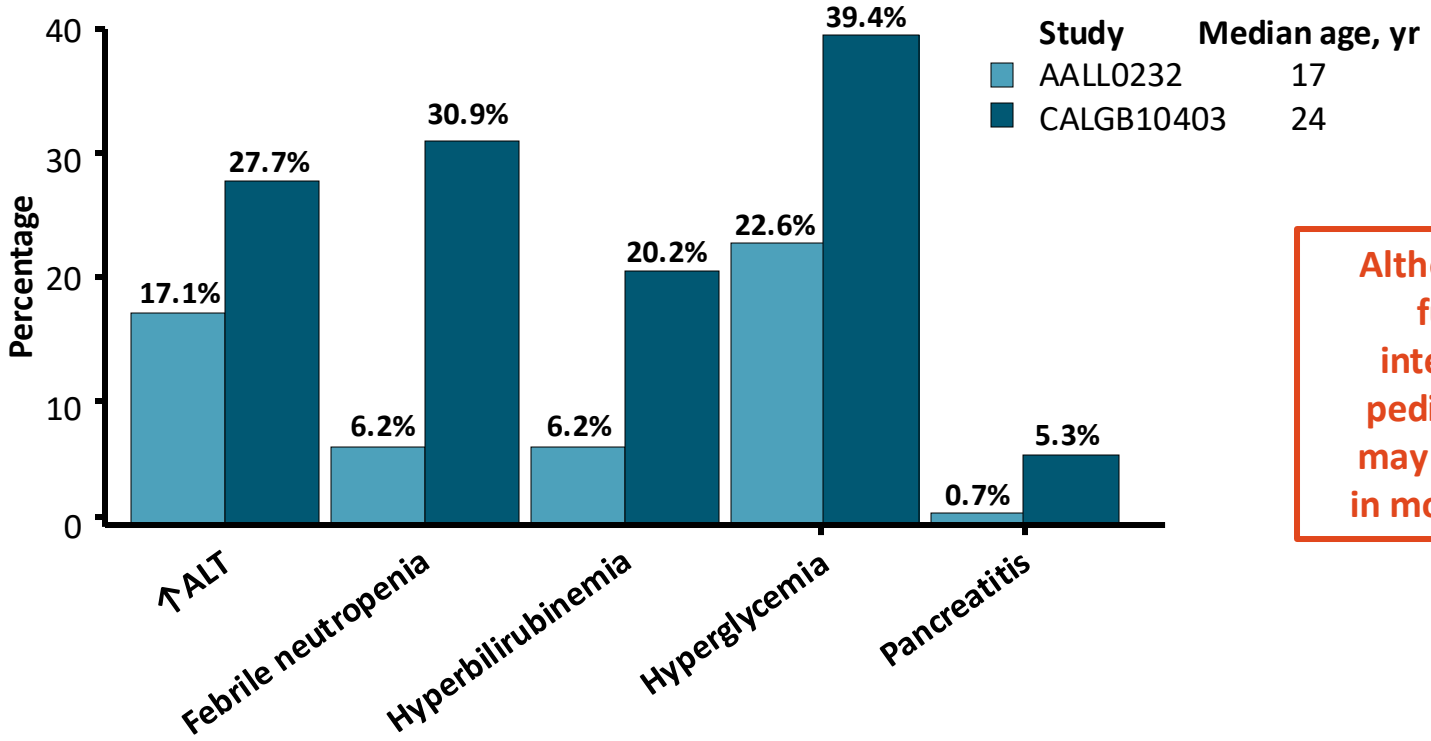




Ph-like	36-mo OS, % (95% CI)
Yes	63.3 (49.6–80.7)
No	80.5 (72.6–89.3)

1. Stock W, et al. *Blood*. 2019;133:1548-1559; 2. Stock W, et al. *Blood*. 2008;112:1646-1654.

Toxicity Profile in AYAs: Differences in “Young” vs “Old”

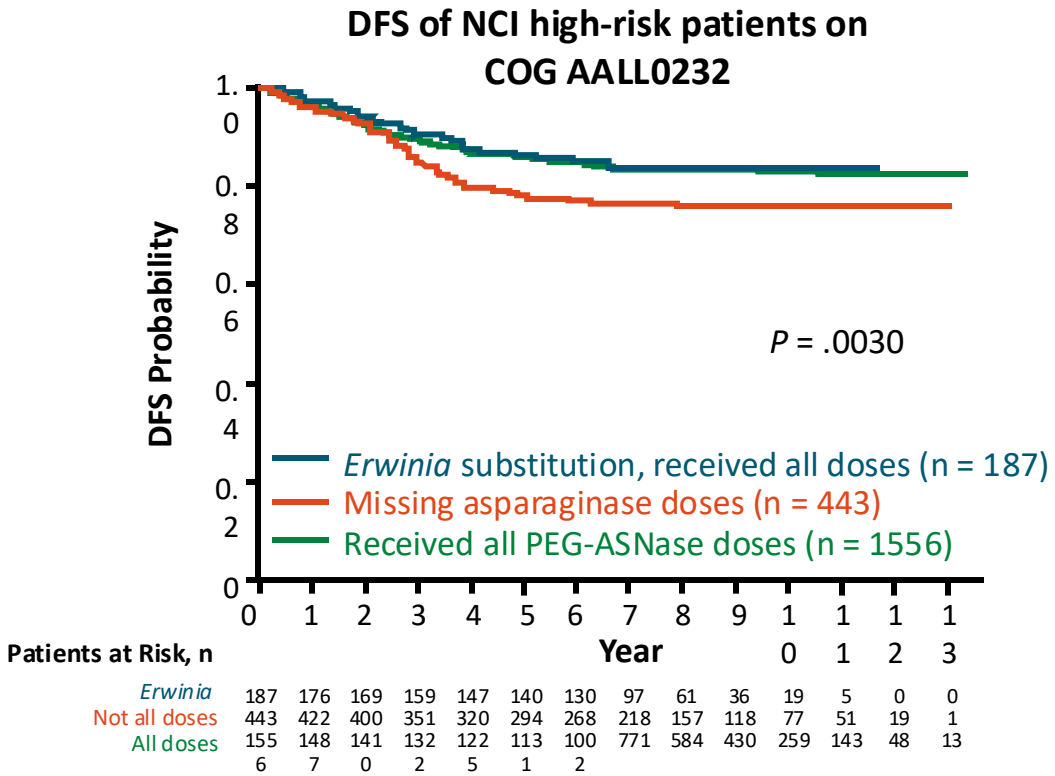


Although tolerable, further dose intensification of pediatric regimens may not be feasible in most AYA patients

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

Impact of Omitting Asparaginase Doses in ALL

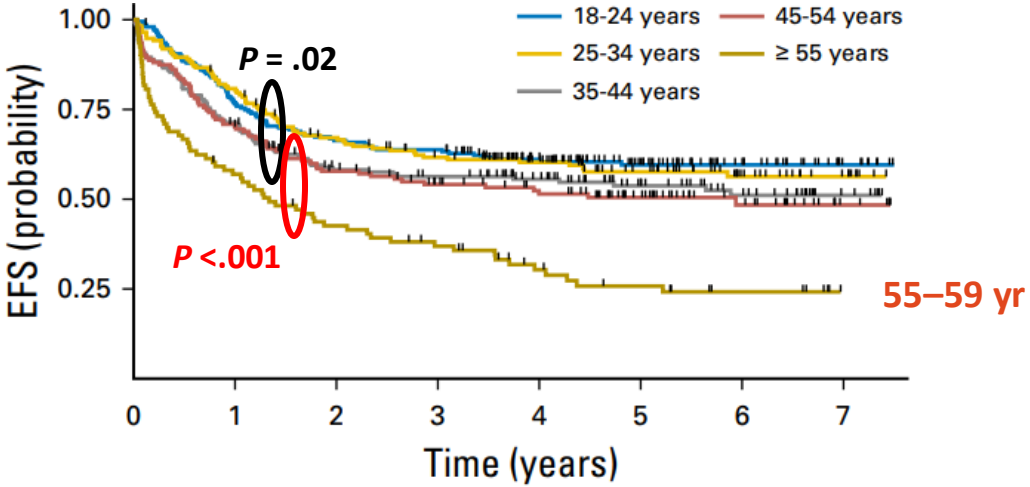
- *Erwinia* ASNase as substitution was approved in 2011 for allergic reactions
  - However, it has been intermittently unavailable because of drug supply issues
- Higher-risk patients who missed prescribed doses of ASNase altogether had 50% increased risk of relapse



Gupta S, et al. *J Clin Oncol*. 2020;38:1897-1905.

Aged Older Than 50 Years Is *Too* Old for Pediatric Regimen: Toxicities

EFS by age subsets[a]

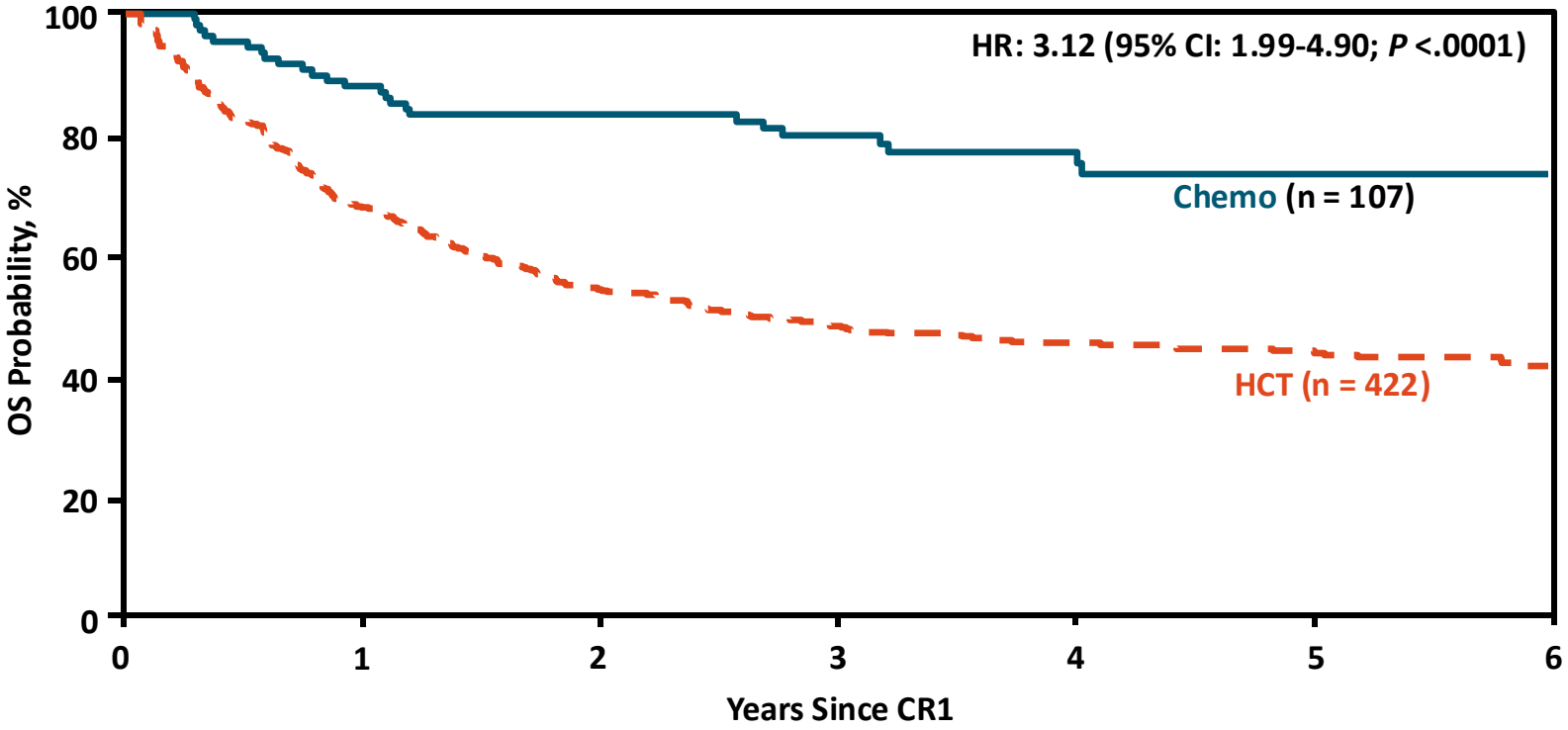


No. at risk:								
18-24 years	200	153	130	124	92	65	38	20
25-34 years	172	138	112	98	78	56	35	24
35-44 years	171	122	93	87	72	49	36	21
45-54 years	151	104	81	68	57	38	23	8
≥ 55 years	93	52	38	31	21	16	11	5

[a]GRAALL-2005: randomized trial evaluating a pediatric-inspired hyper-CVAD protocol in adults aged 18–59 yr with Ph-negative ALL.

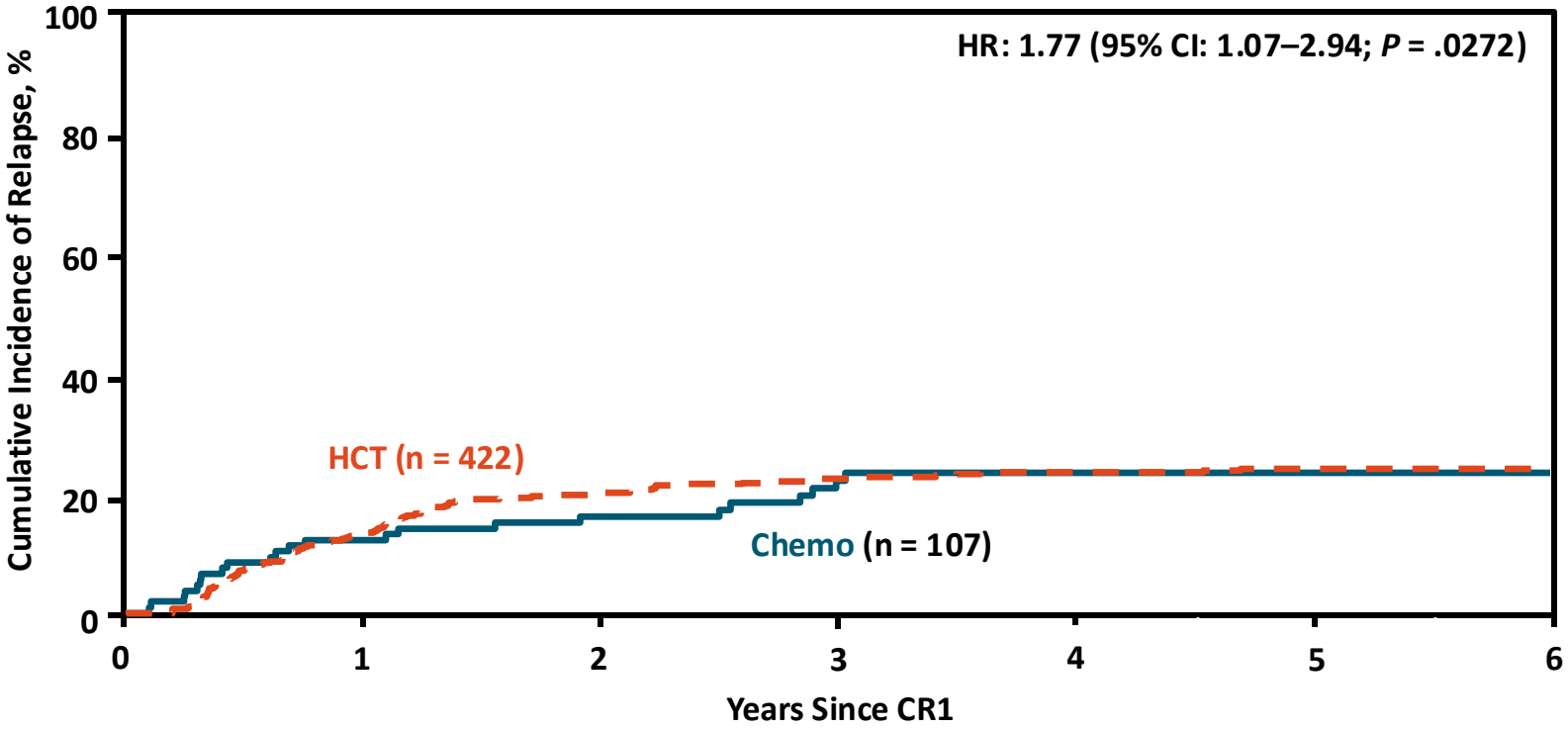
Huguet F, et al. *J Clin Oncol.* 2018;36:2514-2523.

Pediatric-Inspired Chemotherapy Regimen vs HCT: Overall Survival



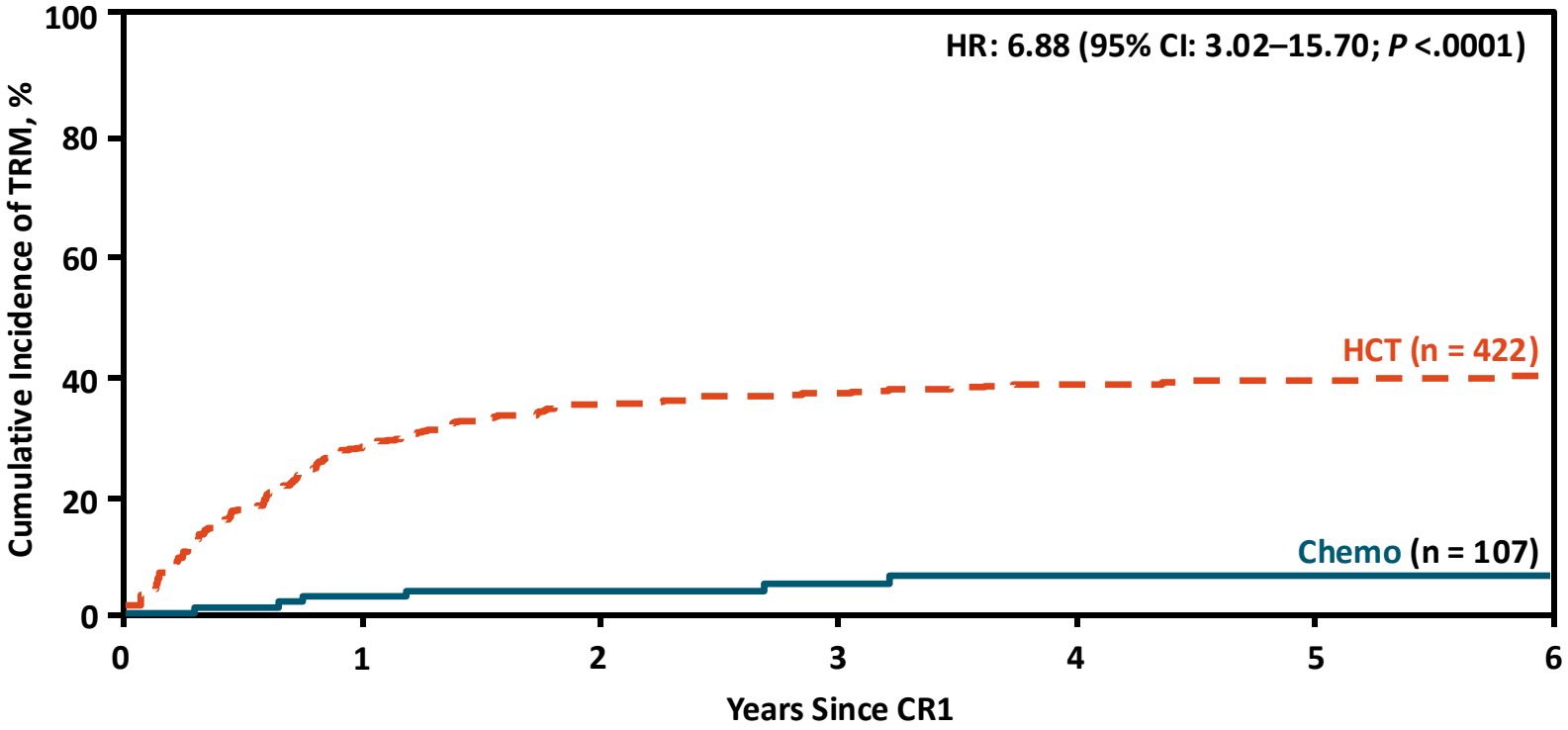
Seftel MD, et al. *Am J Hematol*. 2016;91:322-329.

Chemotherapy vs HCT: Cumulative Incidence of Relapse



Seftel MD, et al. *Am J Hematol*. 2016;91:322-329.

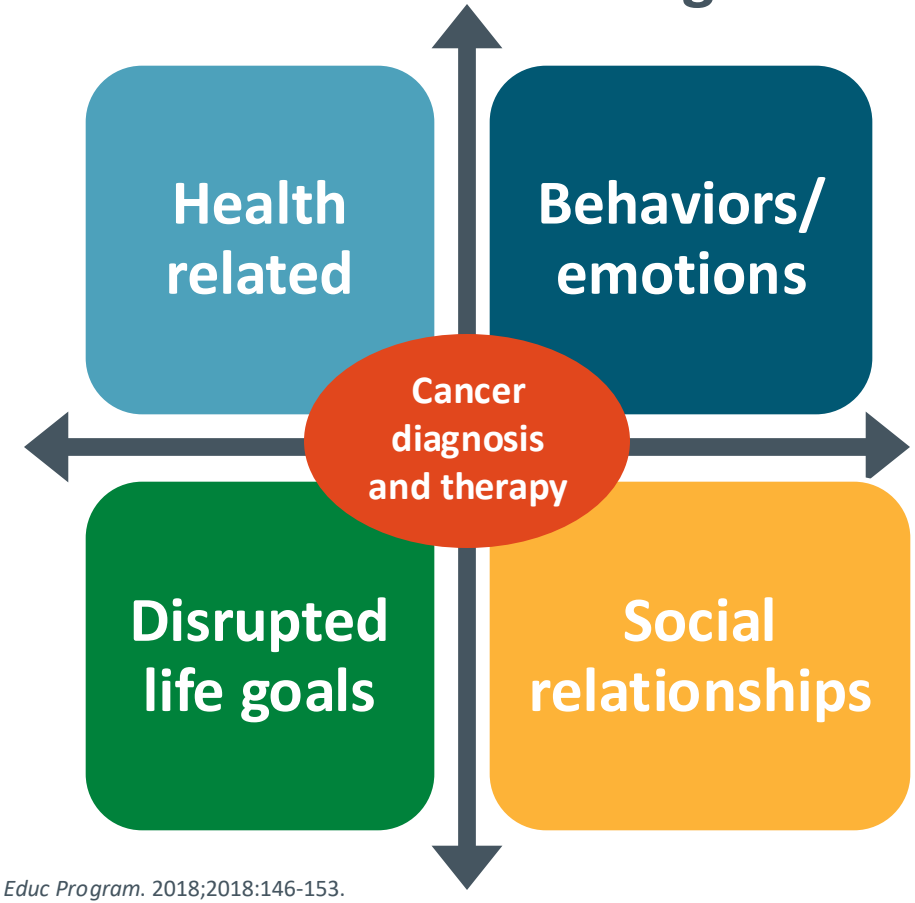
Chemotherapy vs HCT: Cumulative Incidence of Treatment-Related Mortality



Seftel MD, et al. *Am J Hematol*. 2016;91:322-329.

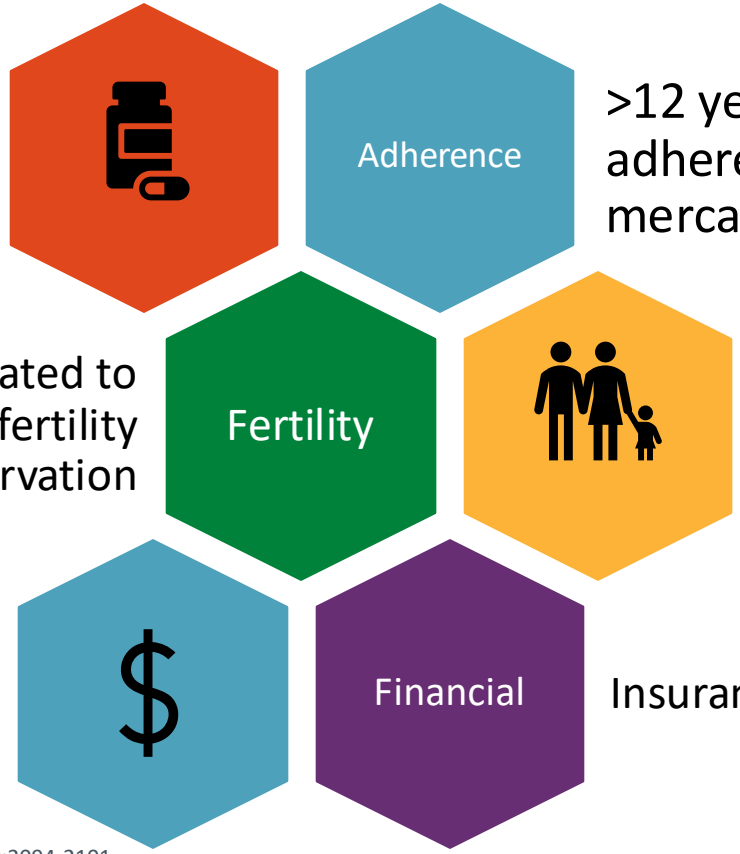
AYA Challenges and Survivorship

Major Patient-Centered Concerns Facing AYA Cancer Survivors



Baker KS, Syrjala KL. *Hematology Am Soc Hematol Educ Program*. 2018;2018:146-153.

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.

Impact of Physical and Mental Impact at Work in AYA Cancer Survivors

Variable	CT/No CT, n (%)	OR	95% CI
Interfered with physical tasks required by job			
▪ No	96/119 (44.7)	1.00	Ref
▪ Yes	187/115 (61.9)	1.97	1.22–3.11
Interfered with mental tasks required by job			
▪ No	144/189 (43.2)	1.00	Ref
▪ Yes	269/130 (67.4)	3.22	2.15–4.79
Extended paid time off from work, unpaid time off, or a change in hours, duties, or employment status			
▪ No	64/108 (37.2)	1.00	Ref
▪ Yes	352/212 (62.4)	3.56	2.31–5.47
Extended paid time off from work			
▪ No	115/63 (64.6)	1.00	Ref
▪ Yes	228/138 (62.3)	1.02	0.62–1.67
Unpaid time off from work			
▪ No	159/96 (62.4)	1.00	Ref
▪ Yes	183/103 (64.0)	1.39	0.79–2.36

Ketterl TG, et al. *Cancer*. 2019;125:1908-1917.

AYA Cancer Survivorship

Treatment Complications

- Health behaviors
  - Risky behaviors
  - Diet/exercise
- Healthcare needs
  - Chronic healthcare needs
  - Access
- Emotional adjustment
  - Fear of recurrence
  - Anxiety/PTSD
- Social relationships
- Employment/finances
  - Complete education
  - Career/debt/financial stress

Psychosocial Impact

- Cardiac
  - Cardiomyopathy
  - Obesity, HTN, dyslipidemia
  - Thrombosis
- Endocrine
  - Anterior pituitary dysfunction: GH, LH, FSH, ACTH, TSH
  - Ovarian dysfunction
  - Testicular dysfunction
- Reproductive
  - Fertility
  - Sexual dysfunction
- Musculoskeletal
  - Osteonecrosis
  - Osteopenia

Baker KS, Syrjala KL. *Hematology Am Soc Hematol Educ Program*. 2018;2018:146-153.

Pediatric Regimens Rely on Steroids and Asparaginase With Unique Toxicities

- Thrombosis and bleeding
- Pancreatitis
- Hepatic toxicity
- Metabolic syndrome (hyperglycemia, hypertriglyceridemia)
- Osteonecrosis – late toxicity, less understood

Toxicities disproportionately affect older children and adults

Mattano LA Jr, et al. *J Clin Oncol.* 2000;18:3262-3272; Patel B, et al. *Leukemia*. 2008;22:308-312; Vrooman LM, et al. *J Clin Oncol.* 2013;31:1202-1210; Albertsen BK, et al. *J Clin Oncol.* 2019;37:1638-1646; Burke PW, et al. *ESMO Open.* 2020;5:e000858.

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

as required per Section 6.2.

Course I is to begin ≤ 5 days of registration (Step 1).

COURSE I: REMISSION INDUCTION THERAPY (see Section 7.2)

Allopurinol until peripheral blasts and extramedullary disease are reduced →

IT Ara-C

Dex Days 1 -

VCR

DNR

Day	1	2	3

Allopurinol

IT-Ara-C

COURSE II: REMISSION CONSOLIDATION (see Section 7.4)

Begin Course II within 7 days after peripheral blood counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL. If counts not recovered within 4 weeks, then contact the study chairs. Therapy should be interrupted for patients who are febrile, neutropenic and proven infected, and resumed at the same point when the signs of infection have abated. Otherwise, therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 **chemotherapy until ANC** and submit specimens as re

CTX

Ara-C Days 1 - 4

6-MP on Days 1-14

IT MTX

R

Day	1	2	3

IT MTX*

VCR

PEG

Day	15	16

*Day 15 and Day 2

CTX

Ar

6-MP

R

Day	29

* HOLD

Day

CTX Cyclophosphamide

COURSE III: INTERIM MAINTENANCE (Capizzi Methotrexate) (see Section 7.5)

Begin Course III within 7 days after peripheral blood counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL. If counts not recovered within 4 weeks, then contact the study chairs.

Therapy should be interrupted for patients with severe infections and resumed when the signs of the infection have abated. VCR and IV methotrexate treatment day (See Section 8.4.3)

If patient has consented to A041

VCR

IV MTX

R

PEG

IT MTX

Day	1	2	3	4	5

PEG

Day	22	23	24	25	26

VCR Vincristine 1.5 mg/m

COURSE IV: DELAYED INTENSITIFICATION (see Section 7.6)

A bone marrow aspirate and biopsy must be obtained prior to initiation of Course IV. Begin Course IV within 7 days after peripheral blood counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL. If counts not recovered within 4 weeks, then ≥ 75,000/μL prior to starting Delayed Inte interrupted for patients with severe infecti Otherwise, therapy should not be interrupt

VCR

Dex Days 1-7 →

DOX

R

PEG

IT MTX

Day	1	2	3	4	5	6	7

Day	22	23	24	25	26	27	2

* Hold Day 29 chemotherapy until ANC > 750/μ

VCR

PEG

Day	43	44	45	46	47

Repeat Maintenance Therapy courses (12 week courses; 84 day cycles) until total duration of therapy is 2 years from start of Interim Maintenance Therapy for female patients, or 3 years for male patients (see Section 7.7). Only mercaptopurine and methotrexate will be interrupted for myelosuppression.

VCR

Dex Days 1 - 5 →

6-MP on Days 1-84 →

IT MTX

PO MTX

PO MTX

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

VCR

Dex Days 29 – 33 →

6-MP on Days 1-84 →

IT MTX*

PO MTX†

PO MTX

PO MTX

Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42

* IT MTX is given on Day 29 of the first 4 courses of maintenance therapy.

† PO MTX is held on Day 29 of the first 4 courses of maintenance therapy.

VCR

Dex Days 57-61 →

6-MP on Days 1-84 →

PO MTX

PO MTX

PO MTX

Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63

6-MP on Days 1-84 →

PO MTX

PO MTX

PO MTX

Day	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84

VCR Vincristine 1.5 mg/m^2 (maximum dose 2 mg) IV on Days 1, 29, and 57. Voriconazole and posaconazole are contraindicated with vincristine.

The AYA "Village"

- MDs with special interest/focus in ALL
- MD-NP teams
- RN infusion teams (primary nurse model)
- AYA monthly interdisciplinary meetings
- Clinical trials that cross age boundaries (b/w peds and adults)
- Clinical and scientific pediatric/adult ALL conferences
- Multidisciplinary support
  - Infectious disease, dermatology (same clinic)
  - Fertility/endocrine
  - Cardio-oncology, renal-oncology, neuro-oncology
- Social work, psychology, psychiatry
- AYA support group
- Non-English speakers paired with primary translator; consent forms translated into native language

Conclusions

- Administration of dose-intensified pediatric regimen in adults is feasible with acceptable toxicity
- This approach **translates** into better survival for adults with ALL
  - 3-yr OS: 75%; 3-yr DFS: 73% (42.2-mo f/u)[1]
  - PEG-ASNase has increased toxicity in older adult patients as well as patients with high BMI (>30)
- Many challenges remain
  - Psychosocial issues
  - Practice patterns
  - Biology (Ph-like signature)
  - MRD status

Can apply the multidisciplinary approach and survivorship clinics to adults >40 yr

1. DeAngelo DJ, et al. ASH 2015. Abstract 80.

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Q&A

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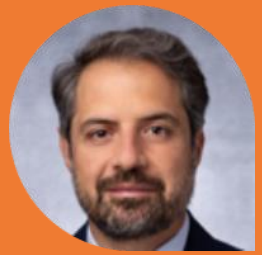
ALL case-based panel discussion



Case 1 ALL: Mridula Mokoonlall (Australia)

Case 2 ALL: Rithin Nedumannil

(Australia)

Moderator: Elias Jabbour

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Case 1

Mridula Mokoonlall

APTITUDE HEALTH

B-ALL case discussion

Mridula Mokoonlall

The Alfred Hospital, Melbourne

August 23, 2024

Mr V – 54-year-old gentleman

- Philadelphia-negative B-acute lymphoblastic leukemia
- Diagnosed on 1/02/2022
- BM: 77% blasts and PB WCC of 2.0×10^9/L
- CG: no mitosis but FISH neg for *BCR-ABL* and *KMT2A* rearrangement
  - (46,XY at relapse)
- Flow cytometry: dim CD19 and CD20 neg with aberrant expression of myeloid markers CD13 and CD33

Comorbidities

- Charlson Comorbidity Index score 1 (for age)
  - Nil significant medical history
  - Nonsmoker and minimal alcohol

- Migrant from Sri Lanka; family with 2 siblings and children
- Works in IT

- Risk stratification
- Treatment decision

Hyper-CVAD protocol

- C1A: morphologic remission with low-level MRD positivity 0.008%*
- C1B: complicated by severe AKI secondary from methotrexate, subdural hygromas due to CSF leak, and complicated by acute SDH – nil further IT therapy deliverable
  - Prophylactic cranial radiotherapy
  - Systemic chemotherapy postponed due to severe SDH
    - → Commenced on POMP protocol with 6-MP + Mtx + Pred with MRD relapse
- C2A: well enough 3 months later – morphologic remission and MRD negativity
- C2B, C3A, and C3B completed with MRD-neg CR

*MRD by multiparametric flow cytometry and IGH VH6 by RT-PCR.

Next step

Reduce-intensity conditioning allograft

- Date of transplant: 10 months post-diagnosis
- Matched sibling donor (ABO/Rh mismatched, CMV R+/D+)
- Conditioning: Flu-Mel
- GvHD prophylaxis: PTCy-CSA

Posttransplant complications

- Grade 3 GUT aGvHD by D35
  - Steroid responsive (oral prednisolone and budesonide)
- CNI induced/transplant-associated TMA
  - CSA switched to sirolimus
- BK viral reactivation with cystitis and hematuria
- Low-level CMV viremia on valganciclovir
- Significant deconditioning with ECOG down to 3
- Graft function: neutropenia and thrombocytopenia (still persistent)

Response post-AlloSCT

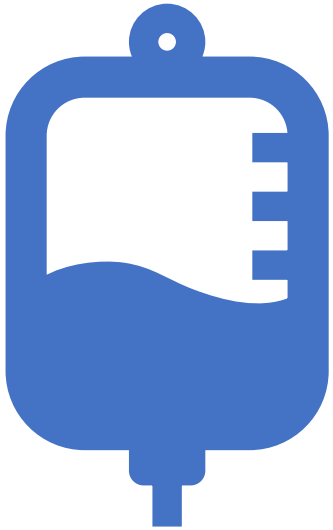
- D+30 and D+90 – BMAT: remains in MRD-neg CR

Early relapse at 8 months post-allograft

- Repeat BM at 8 months: In morphologic remission but MRD detected, FCM 0.89% and IGH VH6 1×10^{-2}
  - Was still needing intermittent GCSF doses, and Plt count between 40–65 $\times 10^{9}$/L
- 2 weeks later repeat BM – 7% blasts morphologically

At the time, functionally improved – ECOG 1

Salvage plans post-allogeneic transplant



What is the treatment of choice after relapse post-allograft at CR1?

A. IV blinatumomab
B. Inotuzumab ozogamicin
C. Repeat allogeneic transplant
D. CAR T therapy

Salvage blinatumomab as bridging therapy

- Salvage IV blinatumomab and intrathecal chemotherapy
- Cycle 1: Possible neutrophilic dermatosis (Sweet syndrome) – necessitating course of prednisolone
  - MRD detected $<1 \times 10^{-4}$ after 1 cycle of blin
- C2 complicated by grade 2 ICANS (Nadir ICE score ~6) managed with IV dexamethasone, and in setting of hypotension (no fevers) had blinatumomab interrupted
- C3 complicated by *Klebsiella oxytoca* bacteremia (EOC3 MRD neg)

CAR T

- Autologous CAR T (brexucabtagene)
- Complications: Low-grade CRS/ICANS but had parainfluenza and LRTI
- D28 BMAT – MRD negative
- MRD detected – 3 months post-brexucabtagene

- Relapsed disease with 10.5% blasts on follow-up marrow after a few weeks

Treatment options post-CAR T relapse

What is the treatment of choice after relapse post-CAR T delivered at CR2?

A. Chemotherapy
B. CD19 bispecific engager (clinical trial vs IV blinatumomab)
C. Inotuzumab ozogamicin
D. Second allogeneic transplant – same or different donor

Clinical trials option as bridging therapy

- Enrolled currently onto AMGEN Study (20180257) – Ph2a3/Ph2a4 dose expansion with SubQ blinatumomab
- Intention to bridge to second allogeneic transplant with different sibling donor

Thank you

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Case 1 – Discussion

Mridula Mokoonlall

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Case 2

Rithin Nedumannil

APTITUDE HEALTH

GLOBAL LEUKEMIA ACADEMY

ALL (AYA) Clinical Case
August 23, 2024

Rithin Nedumannil,
MBBS, MPH, FRACP, FRCPA
Peter MacCallum Cancer Centre, Victoria, Australia
Email: rithin.nedumannil@petermac.org

Initial diagnosis

29 yo female constitutional trisomy 21 (Down syndrome)

- Very active, independent ADLs, lives with parents, perineal lichen planus

CD19+ CD20+ CD22+ positive, Ph-like (*CRLF2* rearranged) pre–B-ALL

Presented unwell with leukocytosis

- WCC 641 × 10^9/L, Hb 50 g/L, PLT 36 × 10^9/L; Film 99% blasts
- Flow: **CD19+,** 10+bright, **20+, 22+,** 24+, 34+, 38+dim, 58+, 9+, cyt79a+, MPO–
- CG: 21+; FISH for *BCR-ABL1, KMT2A, ETV6/RUNX1* negative
- *BCR*::*ABL1* qualitative PCR not detected
- WGS: ***IGH*::*CRLF2*** rearrangement
- NGS (amplicon panel)
  - ***JAK2*** c.2044A>T; p.(Ile682Phe)
  - ***NRAS*** c.35G>A; p.(Gly12Asp)
  - ***ATM*** c.4618G>T;p(Asp1540Tyr) VUS

AYA induction

- Commenced pre-phase steroids and vincristine
- Required emergency leukapheresis and intubation to facilitate management and insertion of lines
- Ommaya inserted, CSF not involved by flow cytometry or cytology
- Commenced AYA (COG AALL0232) induction with rituximab: May 2022
- Slow early response: BMAT D14: 20% blasts on aspirate; 40%–50% blasts by CD19/CD34 IHC, flow 53% blasts with immunophenotypic switch CD45dim, 34+, **19+**, 10+ bright, **20–, 22–**, 24+, 38-, 58+
- Post-induction BMAT D27: 3.3% blasts on aspirate, CD19/34/PAX5 IHC **5%–10% blasts**; flow 3.8% MRD CD45+dim, 34+, **19+** (with a dim tail of 30%), 10+, 20–, **22 partial (20% positive)**, 24+, 38–, 58+

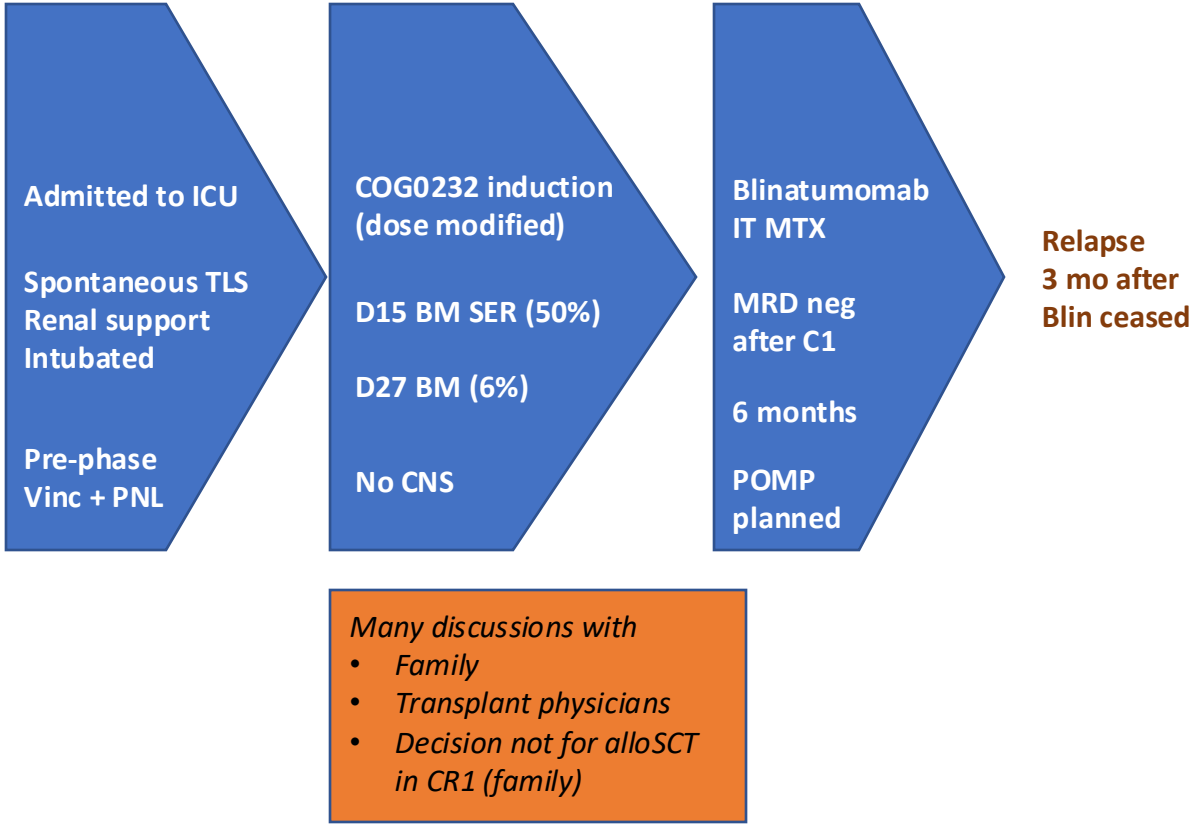
Salvage blinatumomab

- Commenced salvage blinatumomab for refractory disease post-AYA induction
- BMAT post-cycle 1: morphologic remission (CR1), no immunophenotypic evidence of MRD by flow
- Discussion regarding transplant: high risk of toxicity and poor tolerance of toxicities/procedures required, supported by mother's preferences, case discussed at allograft MDM
- Completed total 5 cycles of blinatumomab + IT MTX
- BMAT post-cycle 5: ongoing morphologic remission, no immunophenotypic evidence of MRD by flow (sensitivity 10^{-4} to 10^{-5})
- Planned for POMP maintenance: delayed due to GI issues

First relapse

- Relapse 3 months post-completion of fifth cycle of blinatumomab
- FBE Hb 140 g/L WCC 26 × 10^9/L PLT 341 × 10^9/L with 28% circulating blasts
- BMAT: blasts 72% on aspirate, crushed trephine
- Flow cytometry: CD45+, **19**+, 10+ (bright), 20–, **22+**, 24+, 34+, 38–, 58+
- CG: constitutional trisomy 21
- FISH: *CRLF2* rearrangement (using CRLF2 BA probe)
- NGS: *JAK2* c.2044A>T; p.(Ile682Phe), *NRAS* c.35G>A; p.(Gly12Asp), ***NRAS* c.34G>A; p.(Gly12Ser)**, *ATM* c.4618G>T;p(Asp1540Tyr) VUS
- CSF not involved by flow or cytology

Summary of treatment course



Q

How would you treat this patient?

1. Chemotherapy
2. Inotuzumab
3. CD19-targeted CAR T
4. Inotuzumab then CAR T
5. Inotuzumab then allograft

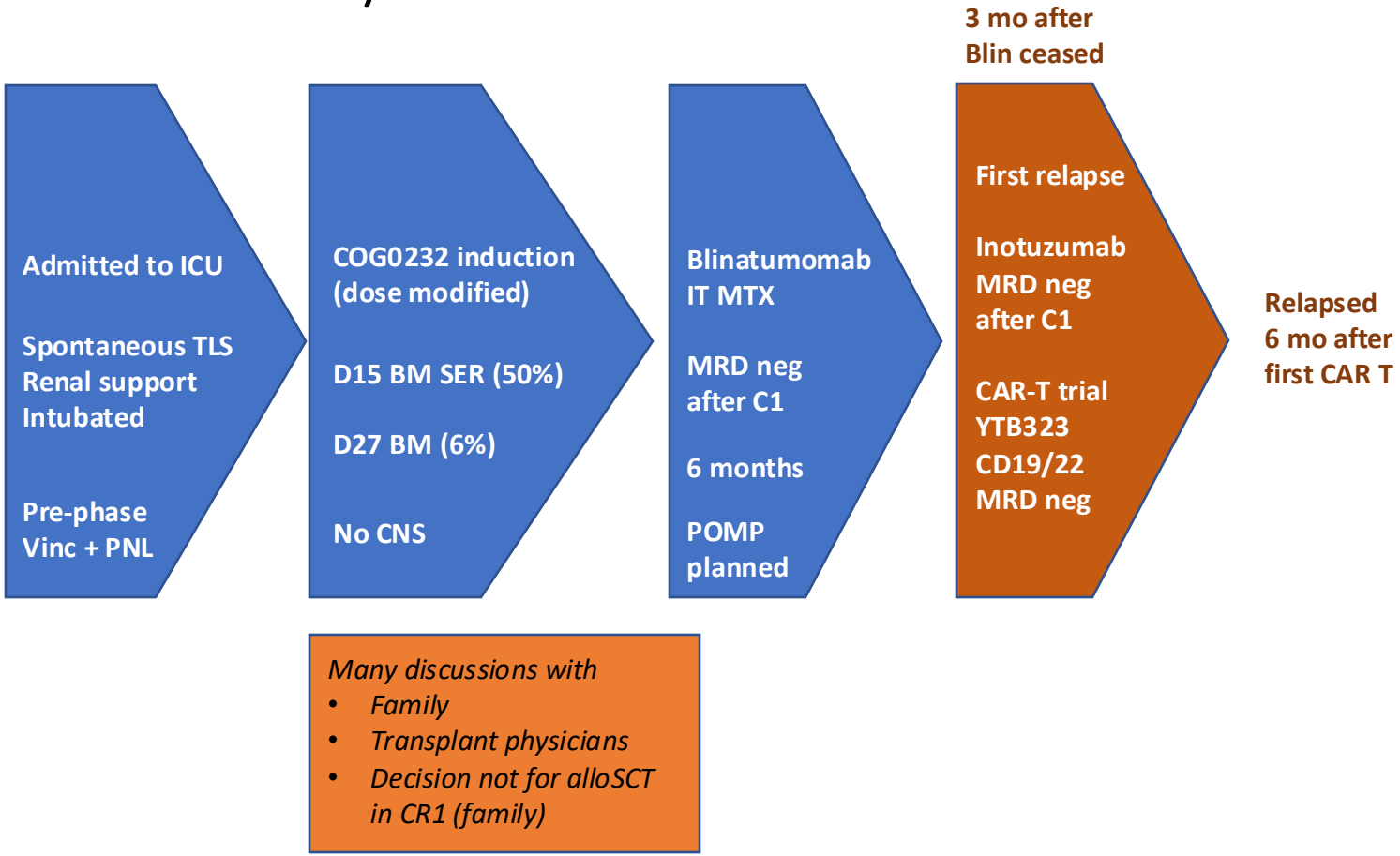
Salvage inotuzumab and CAR T

- Salvage inotuzumab: Achieved morphologic remission (CR2) with no immunophenotypic evidence of MRD by flow (sensitivity 10^{-3}) post-cycle 1 inotuzumab
- Enrolled YTB323 CAR T (trial) CD19/CD22 ALL arm
- Commenced FC LD chemotherapy 1/12 post-completion of inotuzumab followed by infusion of YTB CAR T
- No CRS/ICANS
- BMAT D28 post-CAR T: ongoing morphologic remission, no immunophenotypic evidence of MRD by flow (sensitivity 10^{-4} to 10^{-5}); NGS no *KRAS/JAK2* variants detected
- BMAT 3 months post-CAR T: ongoing morphologic remission, no immunophenotypic evidence of MRD by flow (sensitivity 10^{-3} to 10^{-4})

Second relapse – more CAR T

- Relapse 6 months post-YTB CAR T: incidental finding on 6-month BMAT
- FBE Hb 143 WCC 3.0 ANC 1.8 PLT 121
- BMAT: aspirate 5% blasts, CD34/19 IHC 10%, flow 2.6% blasts CD45+, 19+, 10+ (bright), 20–, 22+, 24+, 34+, 38–, 58+
- CSF not involved by flow or cytology
- Bridging prednisolone and vincristine
- Second YTB323 CAR T infusion (compassionate access) following FC LD
- Grade 2 CRS treated with tocilizumab and dex, no ICANS
- Circulating blasts D23 post-second CAR T infusion with rising LDH and uric acid
- PB flow confirmed B-lymphoblasts, CD45+ (dim), **19+**, 10+ (bright), **20 bimodal** (positive and dim in 50%), **22+**, 24+, 34+, 38–, 58+
- BMAT D28: frank refractory B-ALL, 99% blasts on aspirate
- Discussed allogeneic SCT, declined in view of toxicities, higher TRM risk. Main goals are to optimize QOL and minimize time in hospital

Summary of treatment course



Q

How would you treat this patient?

1. Chemotherapy
2. Chemotherapy + ruxolitinib
3. Blinatumomab
4. Inotuzumab
5. Inotuzumab then allograft

Salvage inotuzumab

- Recommenced inotuzumab
- BMAT post-cycle 1 inotuzumab: hypocellular (0%–30%), morphologic remission (CR3 with incomplete count recovery), no immunophenotypic evidence of MRD by flow (sensitivity $<10^{-3}$)
- Persistent pancytopenia post-cycle 1, cycle 2 inotuzumab delayed by 1/12
- Further discussions regarding trial options and allogeneic stem cell transplantation – parents not keen for allograft due to toxicities and high risk of TRM
- BMAT post-cycle 2 inotuzumab: hypocellular (20%) with ongoing morphologic remission, no immunophenotypic evidence of MRD by flow (sensitivity $<10^{-3}$)
- Persistent cytopenias, unable to proceed with cycle 3 inotuzumab

Third relapse

- 3/12 post-cycle 2 inotuzumab presented with headaches, vomiting, and reduced mobility; recent L eye hyphema
- MRI brain and orbits: abnormal FLAIR signal within vitreous tumor of the left globe c/w known hyphema, otherwise normal intracranial examination
- MRI spine: diffusely enlarged enhancing nerve roots of the cauda equina and leptomeningeal enhancement of the lower spinal cord
- FBE Hb 120 g/L WCC 3.2×10^9/L, ANC 2.6×10^9/L, PLT 44×10^9/L
- CSF total protein 0.30 g/L, glucose 7.0 mmol/L, **lymphocyte count 6000×10^6/L**
- CSF flow cytometry: 99% blasts – **CD19+** (bright), CD45+ CD10+ (bright), **20+, 22+**, 34–, 38+ (dim), 58+, CD9 (partial)
- CSF cytology: highly cellular CSF with sheets of leukemic blasts

Summary of treatment course

Admitted to ICU

Spontaneous TLS
Renal support
Intubated

Pre-phase
Vinc + PNL

COG0232 induction (dose modified)

D15 BM SER (50%)

D27 BM (6%)

No CNS

Blinatumomab
IT MTX

MRD neg after C1

6 months

POMP planned

3 mo after Blin ceased

First relapse

Inotuzumab
MRD neg after C1

CAR-T trial
YTB323
CD19/22
MRD neg

6 mo after first CAR T

Second relapse

Compassionate CAR T trial
YTB323
CRS grade 2
Toci + Dex

D28 BMAT refractory

Inotuzumab
MRD neg after C1 ($<10^{-3}$)

Inotuzumab
C2: cytopenias

Rising PB blast

CNS disease

Many discussions with
- *Family*
- *Transplant physicians*
- *Decision not for alloSCT in CR1 (family)*

Further discussions
- *Family*
- *Declined alloSCT in CR3*

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Case 2 – Discussion

Rithin Nedumannil

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Discussion

To ponder on. . .

- Where to go from here?
- Deliverability of chemotherapy
  - Dose adjustments in constitutional trisomy 21
- AlloSCT in Down syndrome
  - Outcomes
  - Transplant-related mortality
- Role of targeted therapies (ruxolitinib)
- Immunotherapy (antibody/CAR T)
  - Meaning of MRD-negative status

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BREAK

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

Naval Daver

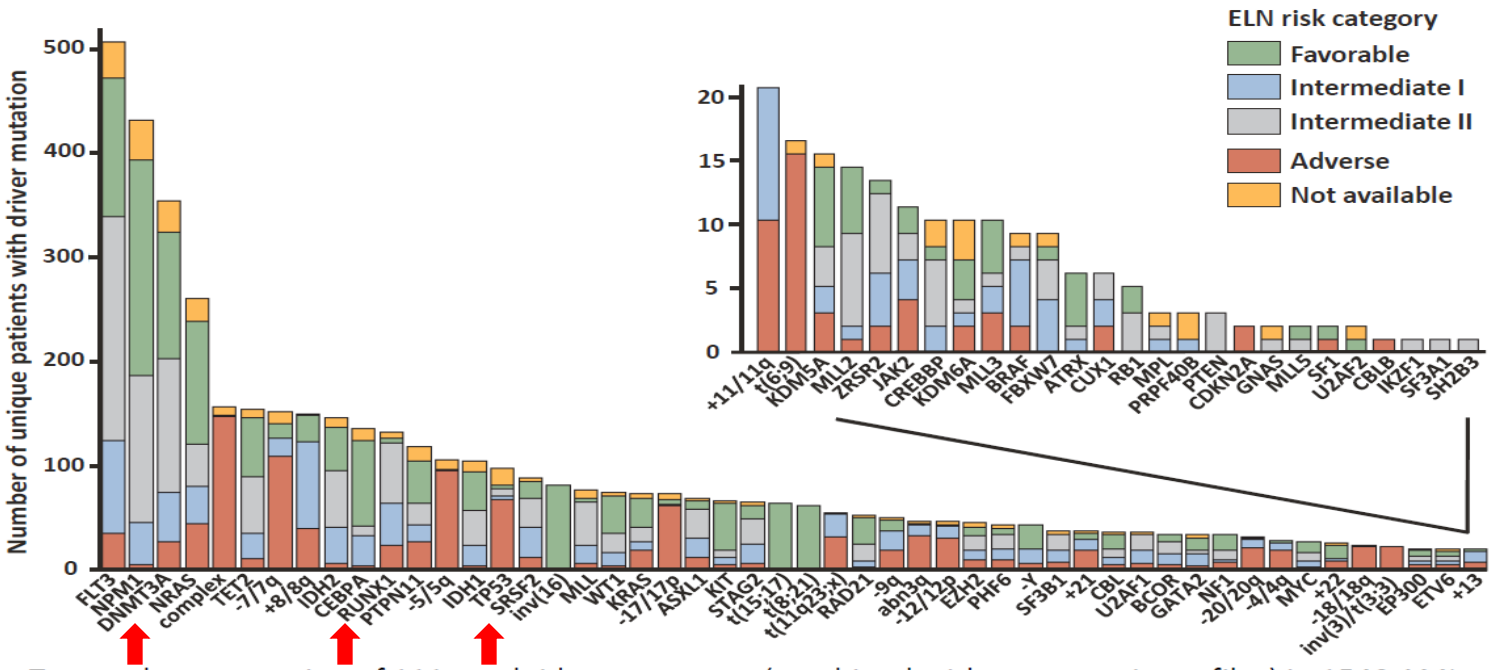
APTITUDE HEALTH®

Optimizing the Incorporation of Targeted Therapies in the Treatment of AML

GLA JAPAC August 2024

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

Major advances in understanding the cytogenetic and mutational landscape of AML



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

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

Using genomics to improve AML prognostication and AlloSCT decisions

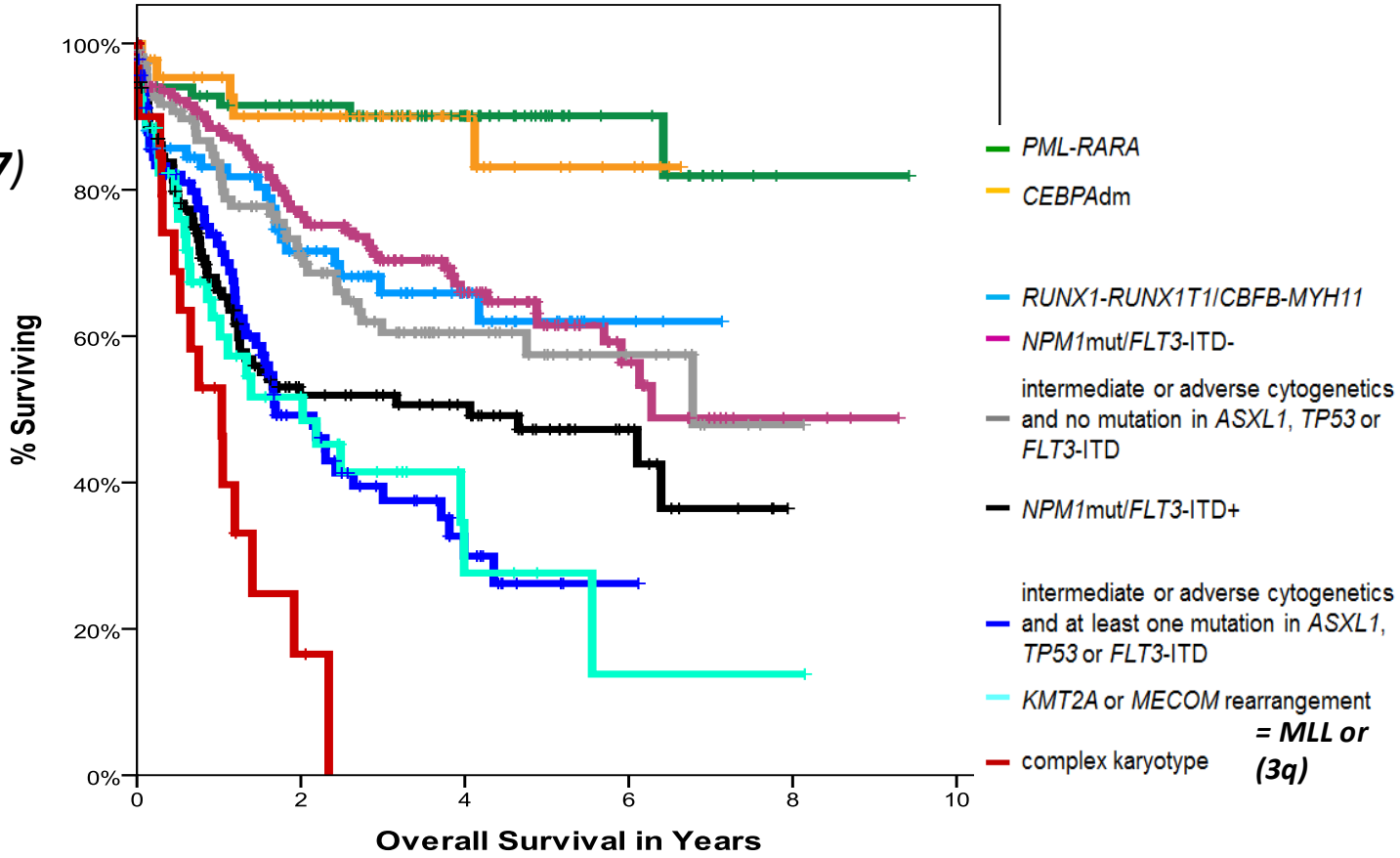
APL:

PML-RARA = t(15;17)

Core-binding factor (CBF) leukemias:

RUNX1-RUNX1T1 = t(8;21)

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



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

Using genomics to improve AML therapy

- ***FLT3* mutations** – add FLT3 inhibitor (midostaurin, sorafenib, quizartinib, gilteritinib), consider allo-SCT

- ***IDH1/2* mutations** – add IDH inhibitor: enasidenib (AG-221/IDH2 inhibitor), ivosidenib or olutasidenib (IDH1 inhibitors)

- ***MLL*r (*KMT2A*r)** – Menin inhibitors (Syndax, Kura, Sumitomo, J&J, BMF, and others)

- ***NPM1* mutation in diploid CG** – Menin inhibitors, Ara-C sensitivity, VEN sensitivity

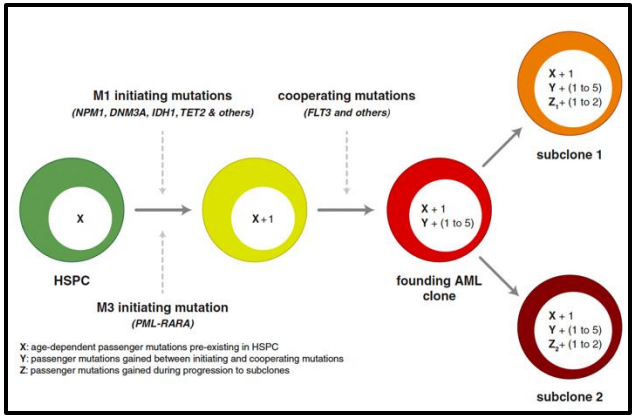
- ***TP53* mutation** – consider decitabine 10 days, new agents (APR, CD47), IO therapies, early referral to allo-SCT

- ***RAS* mutations** – no targetable therapies in AML, common resistance pathway to VEN, FLT3i, IDHi therapies; consider clinical trials

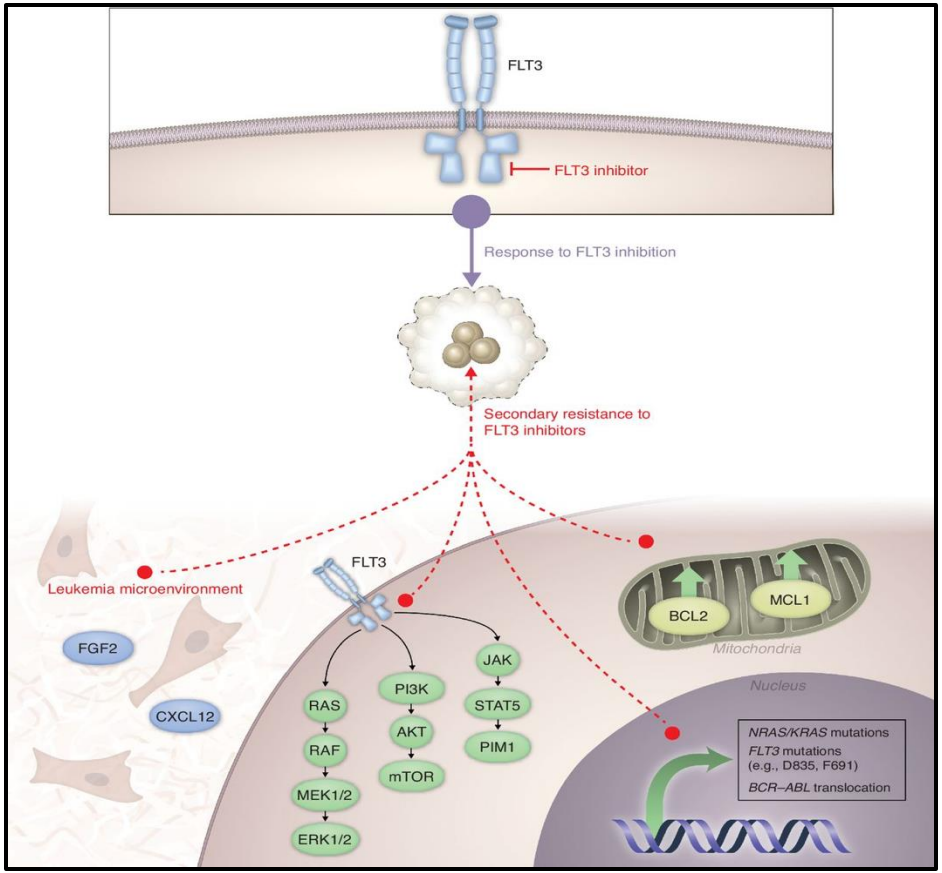
1. Targeting *FLT3* Mutations

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

PTPN11
NPM1
DNMT3A
WT1



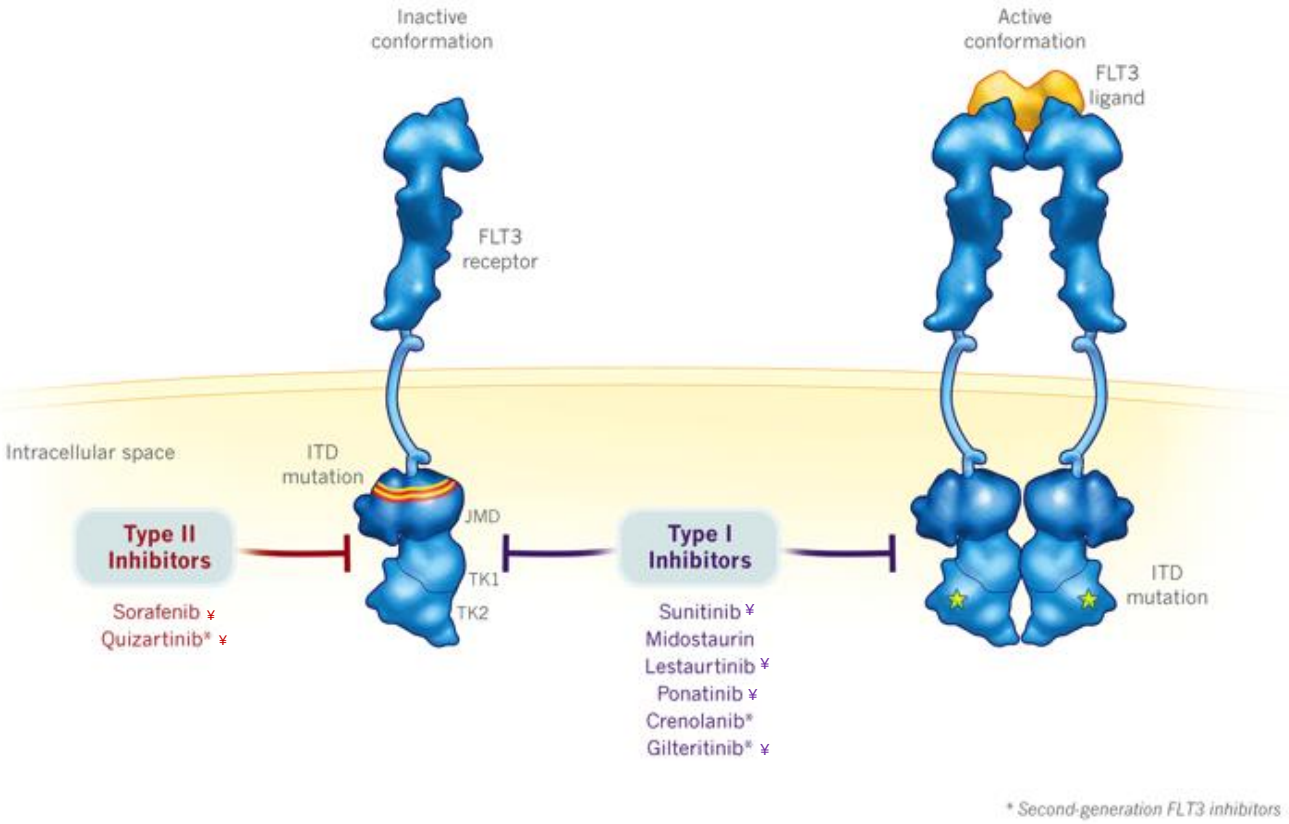
FLT3-ITD
NPM1
DNMT3A
WT1



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

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

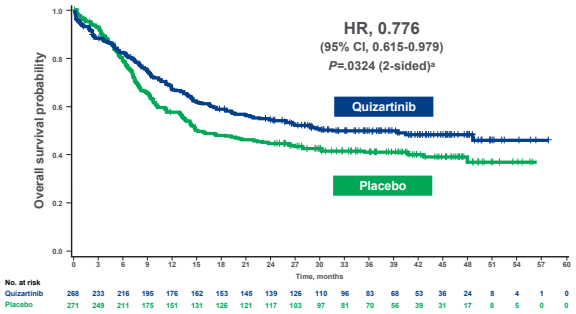
Type 1: Bind receptor "active" conformation near ATP pocket or activation loop: ITD and TKD
Type 2: Bind receptor "inactive" conformation near ATP pocket – ITD only

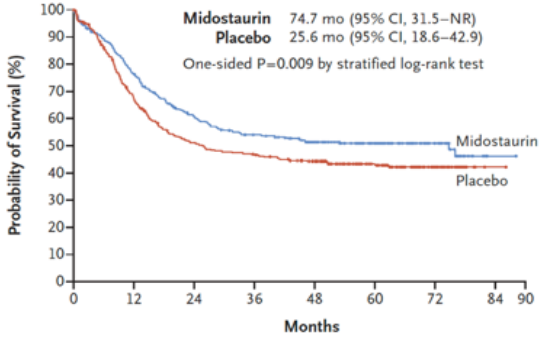


Daver N et al, Leukemia. 2019 Feb;33(2):299-312

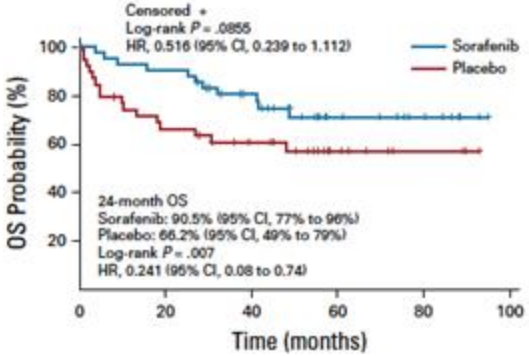
FLT3 inhibition improves survival in fit patients across the treatment spectrum

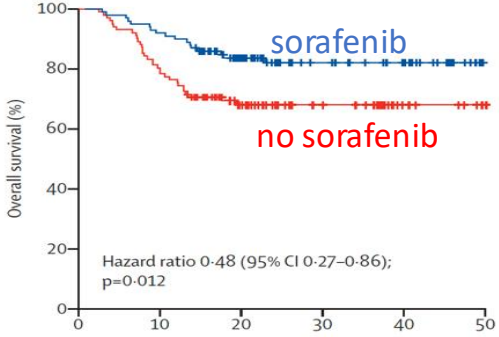
Newly diagnosed, intensive chemotherapy + TKI/placebo



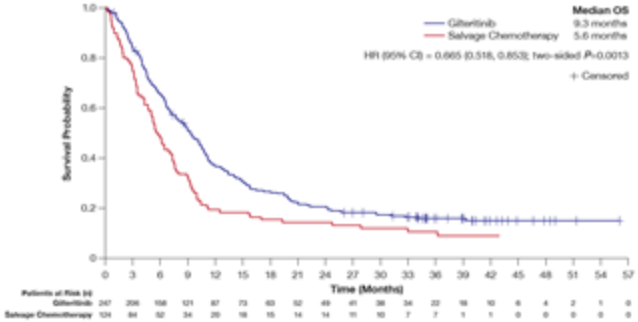


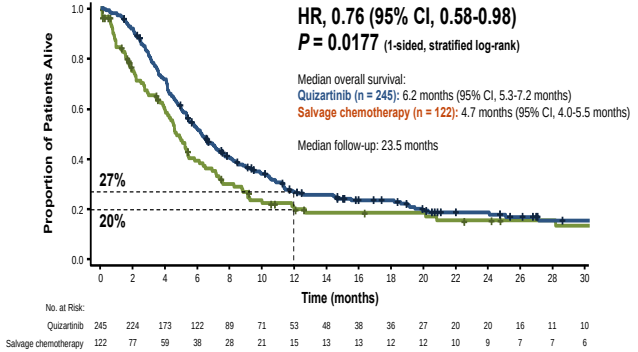
TKI maintenance after alloHSCT (sorafenib 2 studies)





Relapsed/Refractory single agent TKI vs chemotherapy

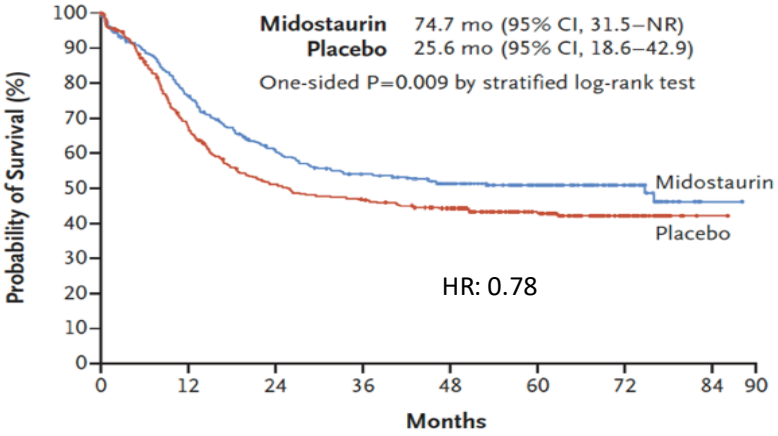




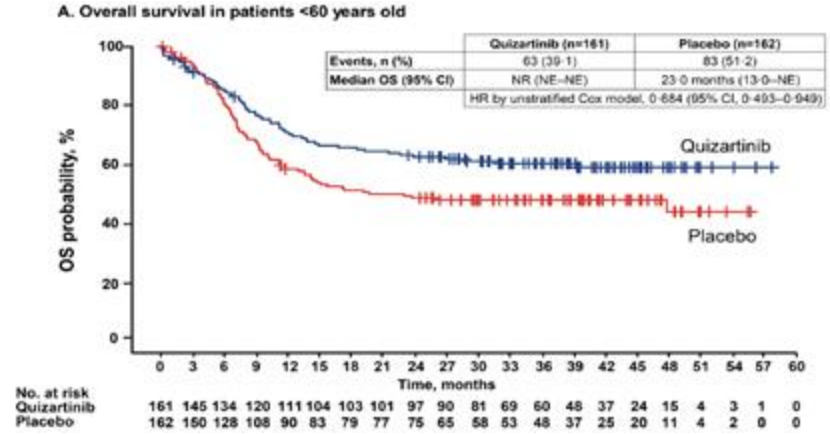
Erba HP, et al. EHA 2022, abstract S100;Stone RM, et al. N Engl J Med. 2017;377(5):454-464; Burchert A, et al. J Clin Oncol. 2020;38(26):2993-3002; Xuan Y, et al. Lancet Oncol. 2020;21(9):1201-1212; Perl AE, et al. Blood. 2022;139(23):3366-3375; Cortes JE, et al. Lancet Oncol. 2019;20(7):984-997.

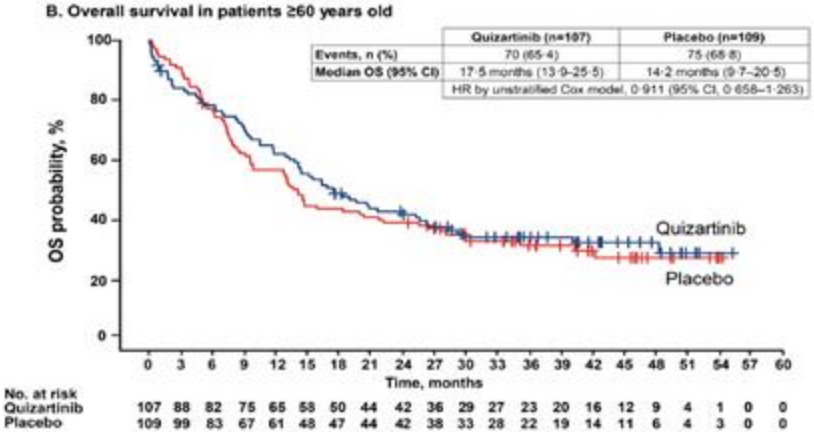
Younger patients (<60 years) particularly benefit from quizartinib

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



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

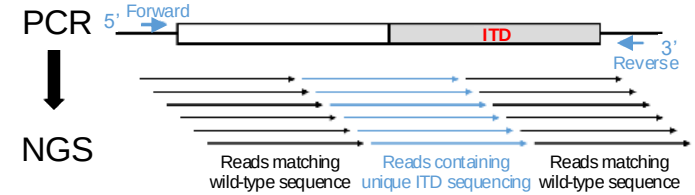


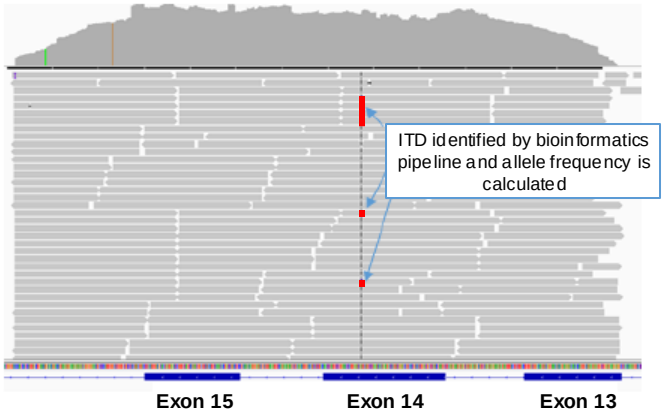


Measurable residual disease (MRD) and QuANTUM-First

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

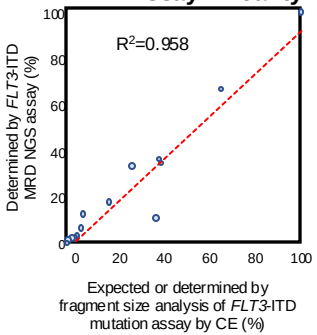
Schema for *FLT3*-ITD MRD Assay





Ultra-deep sequencing of the region (Illumina SBS)

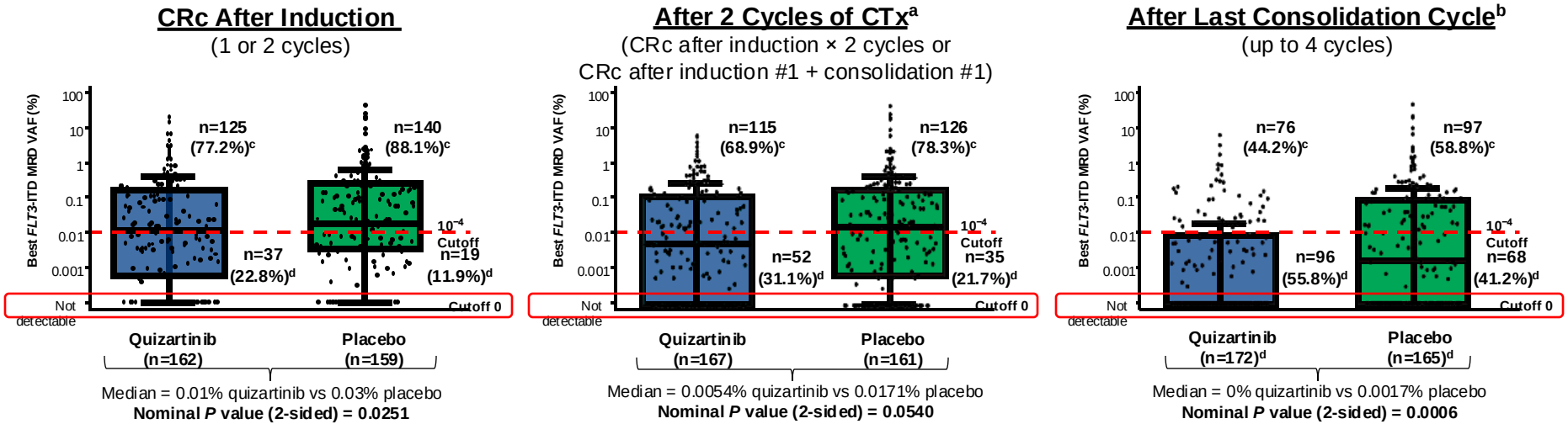
MRD Assay Linearity

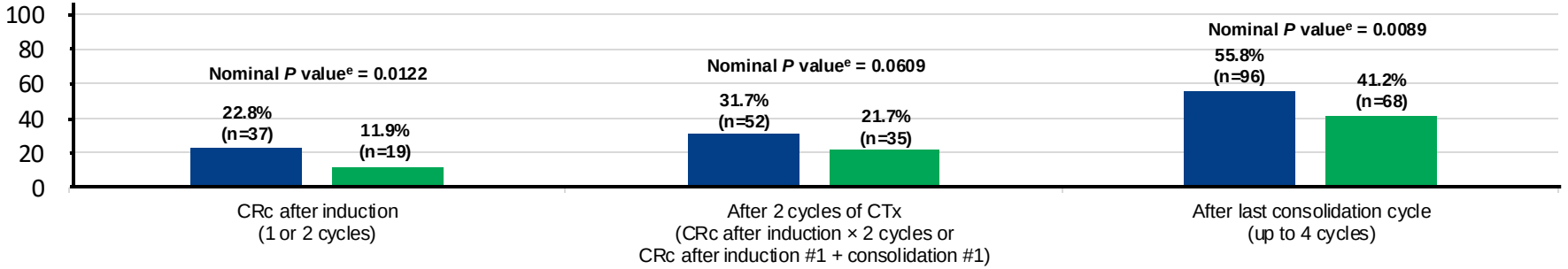


AML, acute myeloid leukemia; CE, capillary electrophoresis; CR, complete remission; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITD, internal tandem duplication; LLOD, lower limit of detection; LLOQ, lower limit of quantification; MRD, measurable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

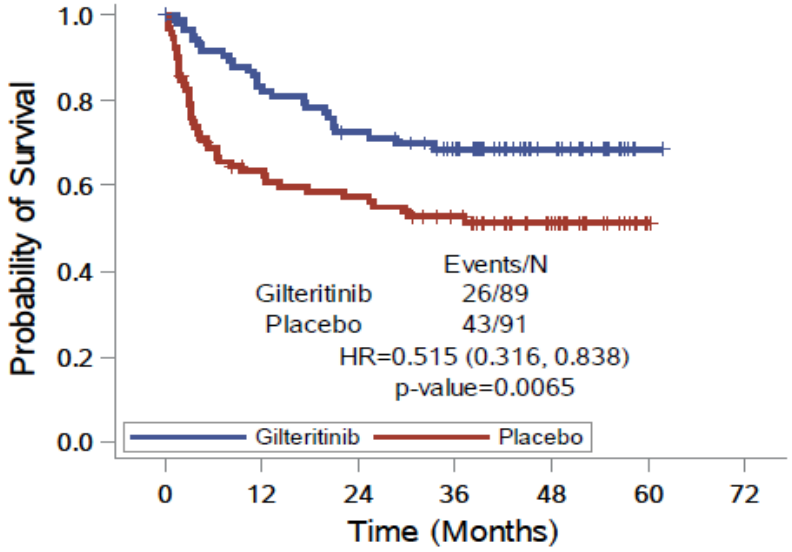




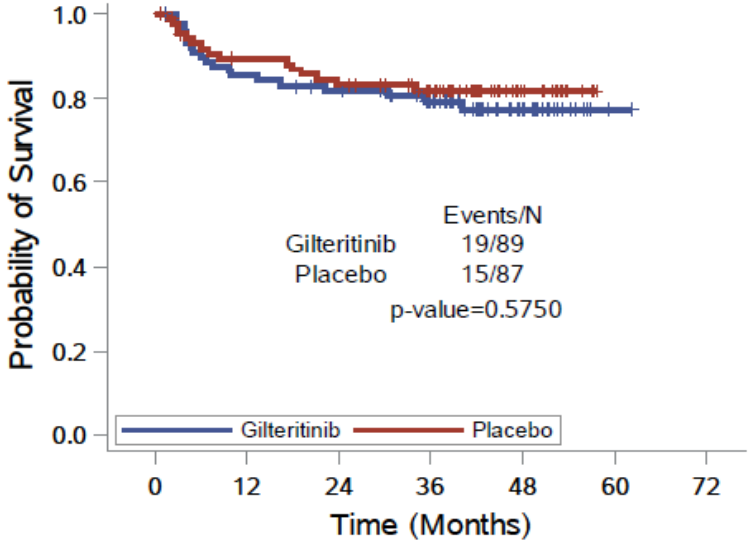
Post hoc analysis. [a]Defined as 2 cycles of induction CTx or 1 cycle of induction CTx + 1 cycle of consolidation CTx. [b]Include samples up to end of consolidation, including from induction. [c]Percentage of patients with *FLT3*-ITD MRD VAF>0 among CRc patients with MRD data. [d]Percentage of patients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



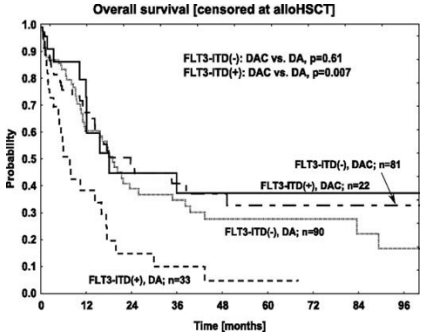
RFS
MRD-



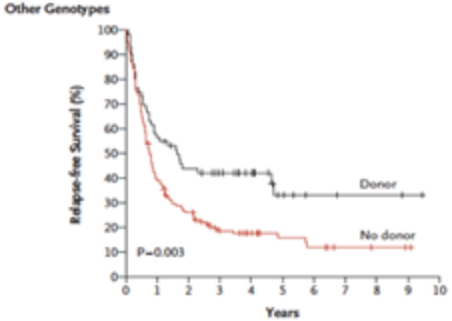
Levis M et al, LBA EHA 2023

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%

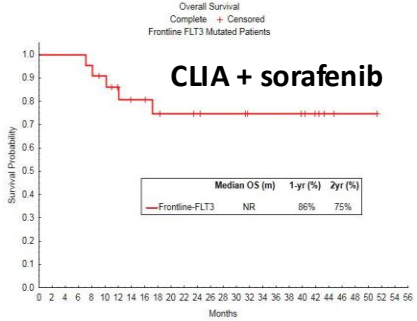
Adding purine analogue to DA (DAC)



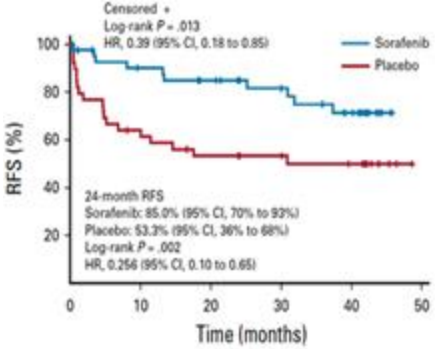
First remission AlloHSCT



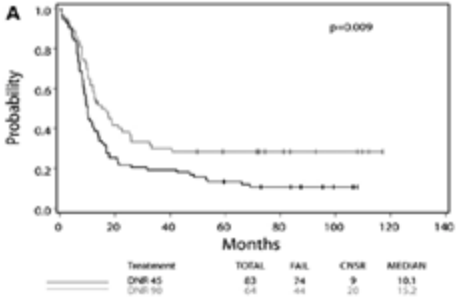
FLT3 inhibitors

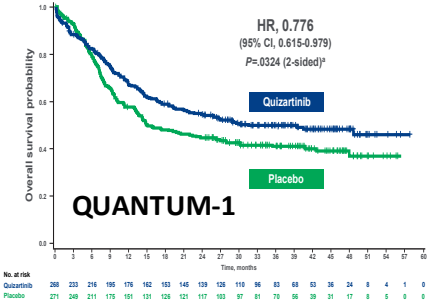


Post-AlloSCT sorafenib

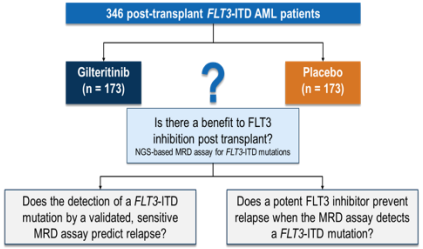


High-dose daunorubicin





GILT maintenance Ph III



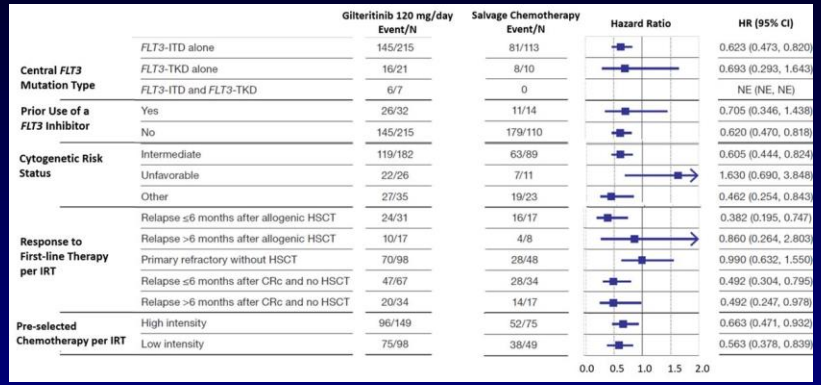
Would AZA+GILT be better?

R/R AML

ADMIRAL trial: Gilteritinib vs salvage chemo in relapsed AML

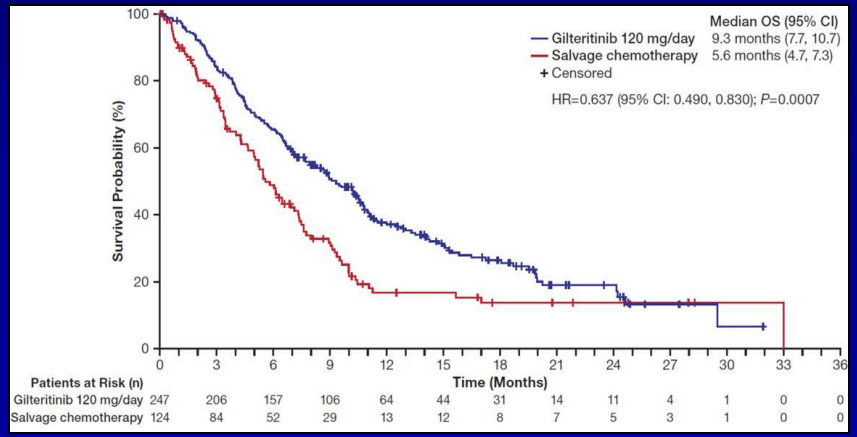
- 371 patients with relapsed *FLT3*-mutated AML randomized to
  - Gilteritinib 120 mg/day (N = 247)
  - Salvage chemotherapy (N = 124)

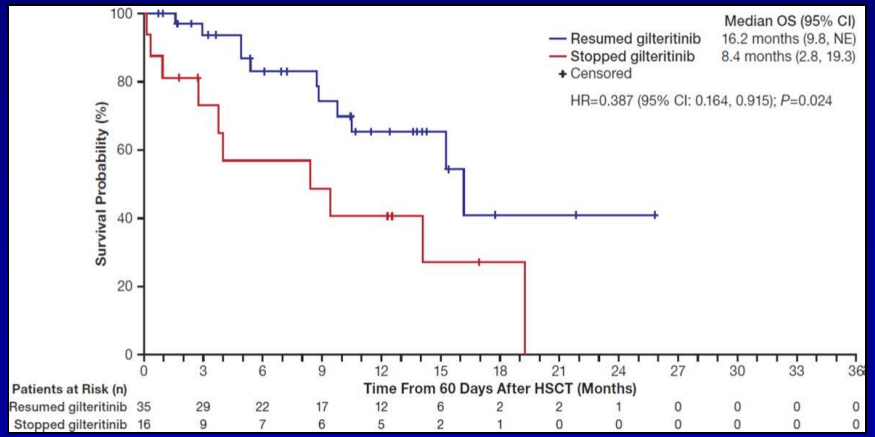
Response	Gilteritinib	Salvage Chemotherapy
CR, n (%)	52 (21)	13 (11)
CRc [CR, CRi, CRp], n (%)	134 (**54**)	27 (**22**)
CR/CRh, n(%)	84 (**34**)	19 (**15**)



		Gilteritinib 120 mg/day Event/N	Salvage Chemotherapy Event/N	HR (95% CI)
Central *FLT3* Mutation Type	*FLT3*-ITD alone	145/215	81/113	0.623 (0.473, 0.820)
	FLT3-TKD alone	16/21	8/10	0.693 (0.293, 1.643)
	FLT3-ITD and *FLT3*-TKD	6/7	0	NE (NE, NE)
Prior Use of a *FLT3* Inhibitor	Yes	26/32	11/14	0.705 (0.346, 1.438)
	No	145/215	179/110	0.620 (0.470, 0.818)
Cytogenetic Risk Status	Intermediate	119/182	63/89	0.605 (0.444, 0.824)
	Unfavorable	22/26	7/11	1.630 (0.690, 3.848)
	Other	27/35	19/23	0.462 (0.254, 0.843)
Response to First-line Therapy per IRT	Relapse ≤6 months after allogenic HSCT	24/31	16/17	0.382 (0.195, 0.747)
	Relapse >6 months after allogenic HSCT	10/17	4/8	0.860 (0.264, 2.803)
	Primary refractory without HSCT	70/98	28/48	0.990 (0.632, 1.550)
	Relapse ≤6 months after CRc and no HSCT	47/67	28/34	0.492 (0.304, 0.795)
	Relapse >6 months after CRc and no HSCT	20/34	14/17	0.492 (0.247, 0.978)
Pre-selected Chemotherapy per IRT	High intensity	96/149	52/75	0.663 (0.471, 0.932)
	Low intensity	75/98	38/49	0.563 (0.378, 0.839)

Hazard Ratio: 0.0, 0.5, 1.0, 1.5, 2.0





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)	

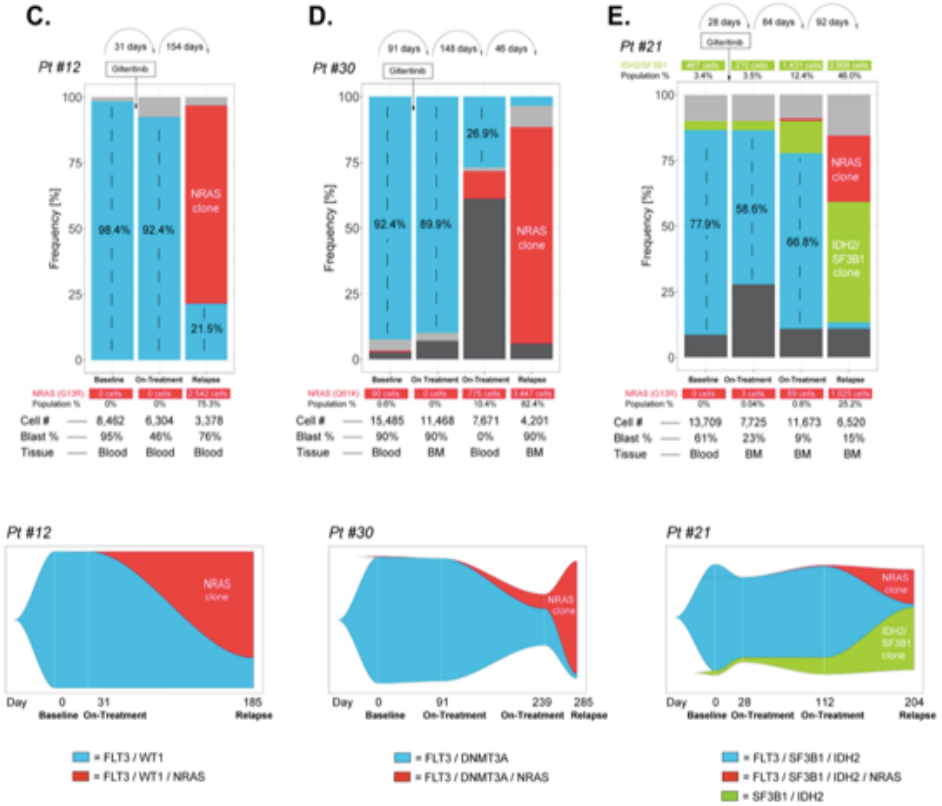
[a]Defined as the sum of the patients who achieved CR, Cri, and CRp

- **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.

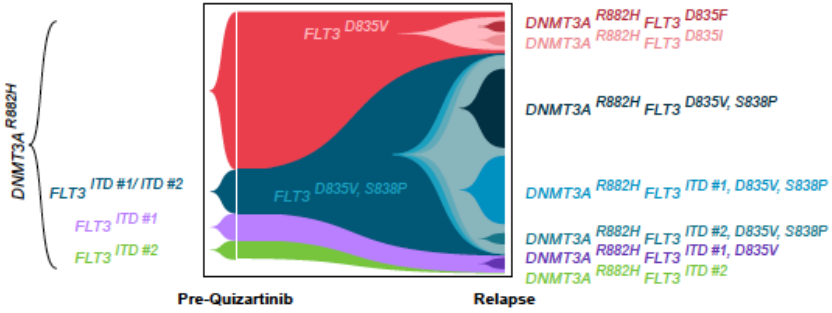
Resistance to second-generation FLT3 TKIs is highly polyclonal: Single-agent FLT3is, no matter how potent, are unlikely to be curative

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

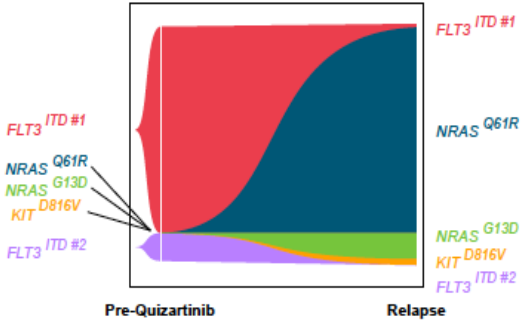


Quizartinib (Type II): On target resistance through acquisition of *FLT3*-TKD

Patient 15

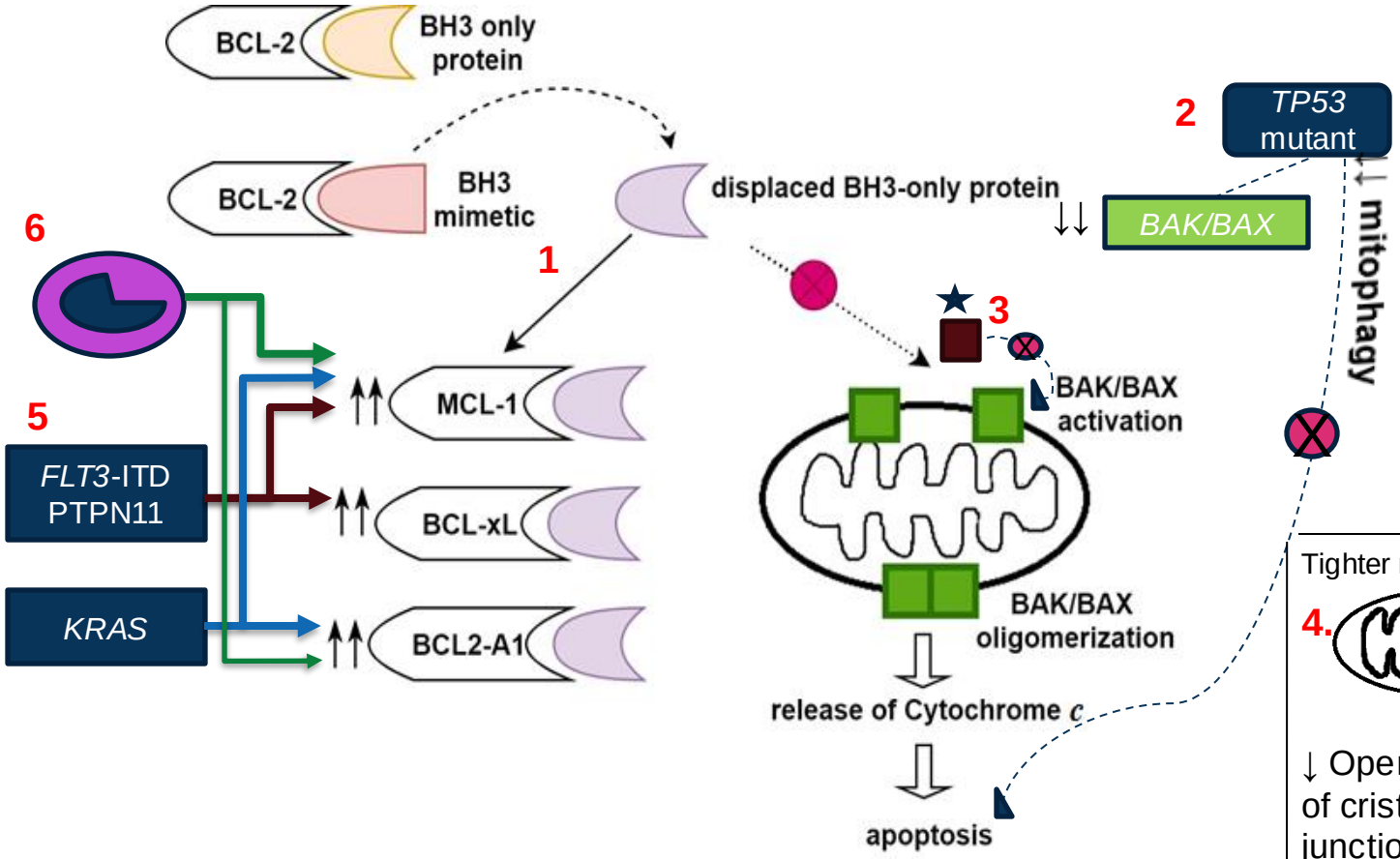


Patient 16



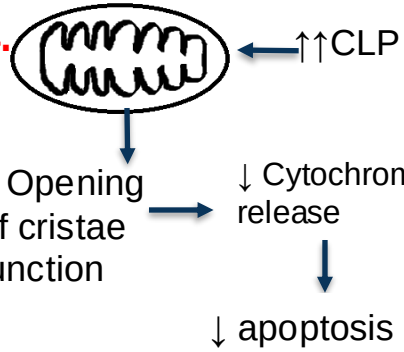
McMahon CM, et al. Cancer Discov. 2019 Aug;9(8):1050-1063; Peretz C, Catherine Smith, et al. Blood Adv. 2021 Mar 9;5(5):1437-1441

Venetoclax resistance: Road to "triplets"



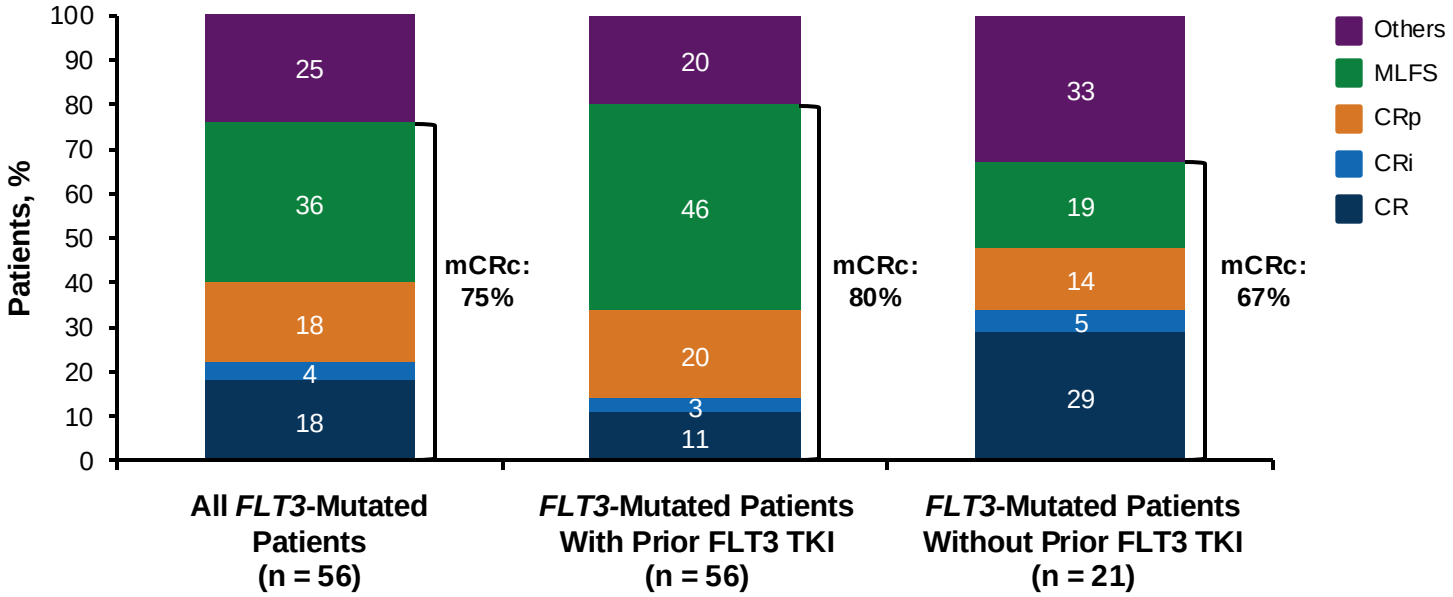
1. Other anti-apoptotic BCL-2 family proteins
2. *TP53* mutation?
3. *BAX* mutation?
4. Mitochondrial aberration?
5. Mutations in activating kinases
6. Monocytic differentiation

Tighter mitochondrial cristae lumen



Modified from Ong et al. Cancer Drug Resistance 2022

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



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

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

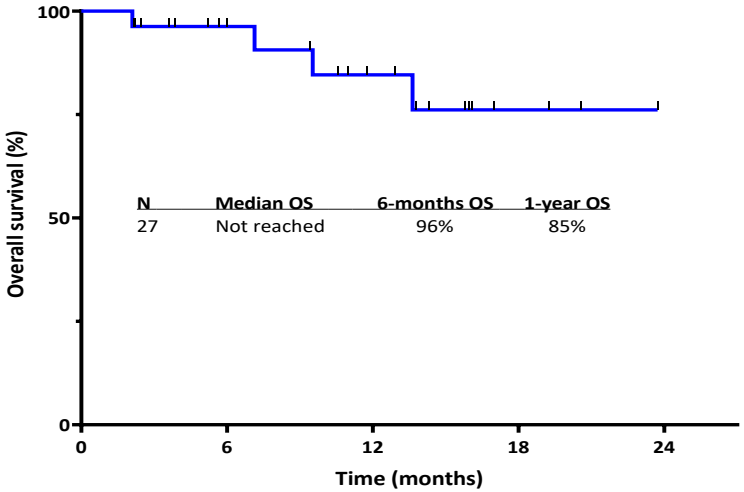
Aza + Ven + Gilteritinib in frontline *FLT3*-mutated AML: Healthier marrow, potentially more curative, and better tolerated

Induction

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

Consolidation (up to 24 cycles)

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

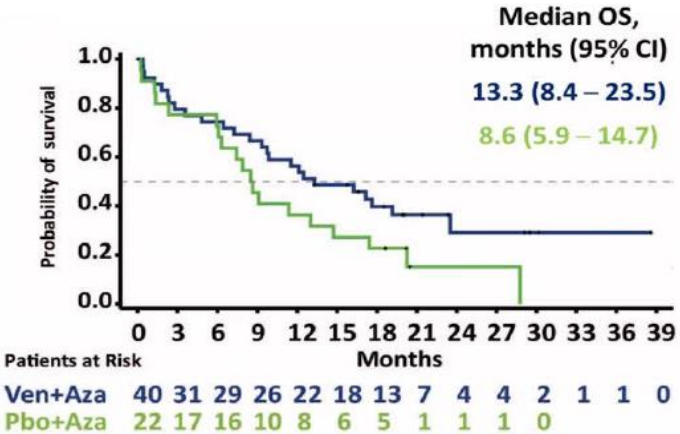


N=30

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

Recovery:
ANC ≥0.5 37d
Plt ≥50 25d

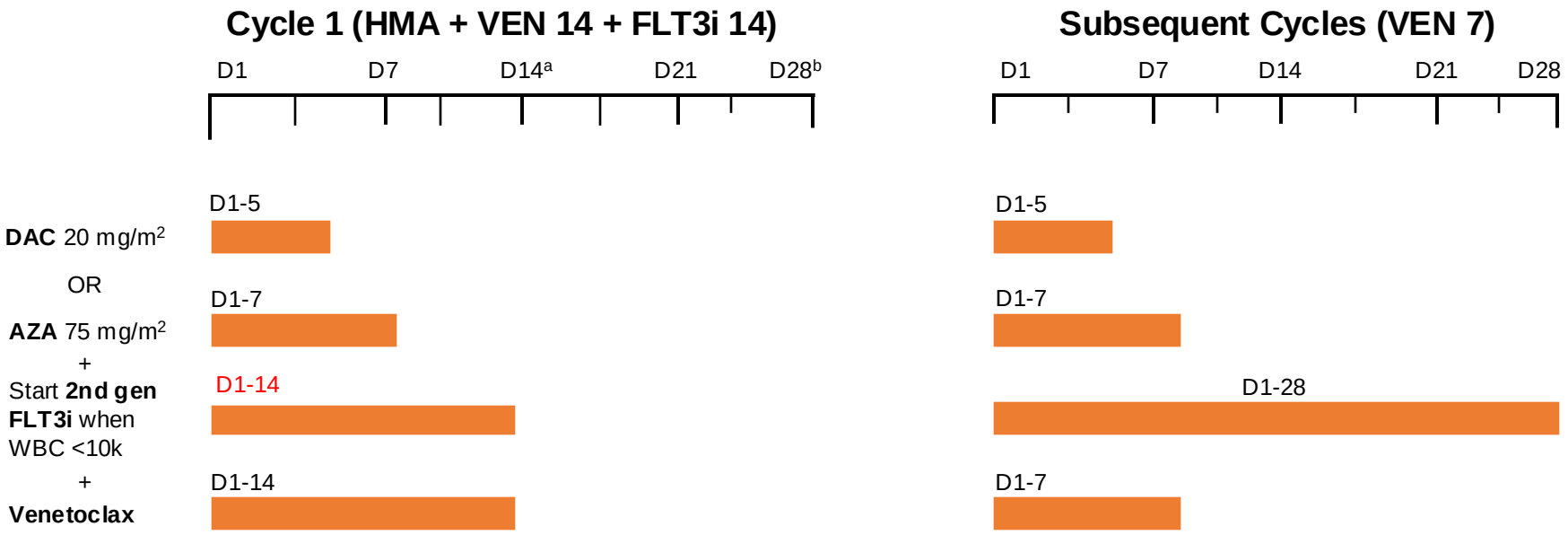
Historical perspective (Konopleva M et al CCR 2023)
AZA+VEN in FLT3m frontline AML (N=40)



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

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

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

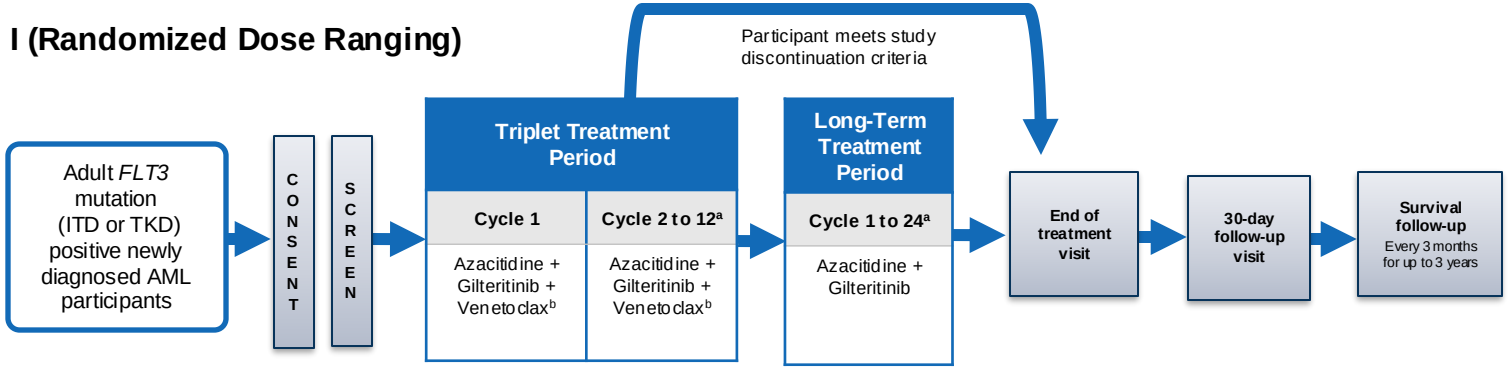


[a] C1 D14: Perform bone marrow biopsy; if bone marrow shows <5% blasts and/or <5% cellularity/insufficient sample → stop venetoclax on D14. [b] Repeat a C1 D28 bone marrow on all patients to confirm remission. If C1 D28 bone marrow confirms remission and ANC <0.5 and/or platelet <50K, consider interrupting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

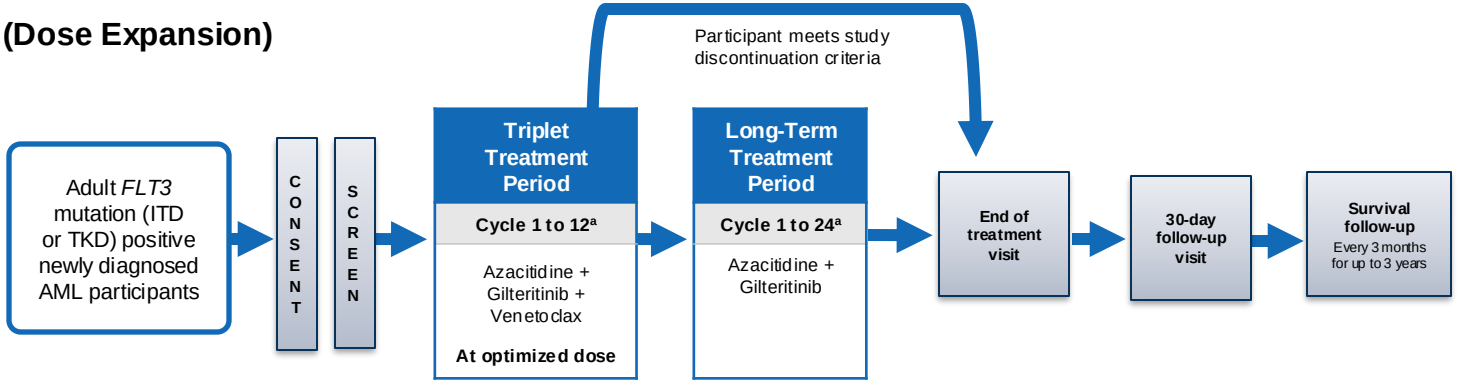
Daver N et al. Blood Cancer J. 2021;11:104.

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

Phase I (Randomized Dose Ranging)



Phase II (Dose Expansion)



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

PIs : J Altman and N Daver

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

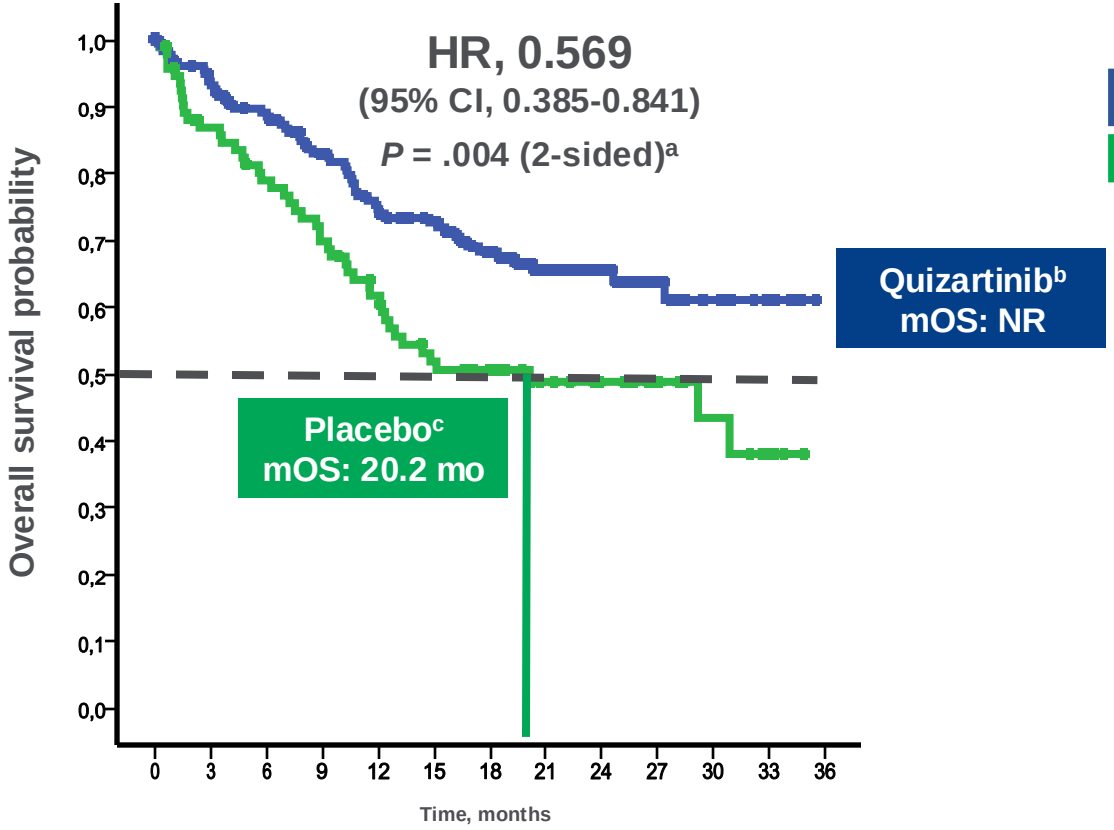
Montesinos P[1], Rodríguez-Veiga R[1], Bergua JM[2], Algarra Algarra JL[3], Botella C[4], Pérez-Simón JA[5], Bernal T[6], Tormo M[7], Calbacho M[8], Salamero O[9], Serrano J[10], Noriega V[11], López-López JA[12], Vives S[13], Colorado M[14], López-Lorenzo JL[15], Vidriales MB[16], García-Boyero R[17],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

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

PETHEMA

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

Secondary endpoint (interim analysis): Overall survival



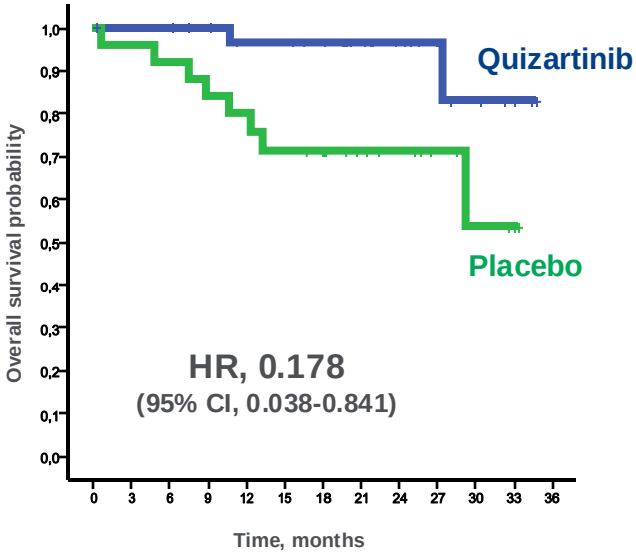
Number of Events

Quizartinib	56/180
Placebo	46/93

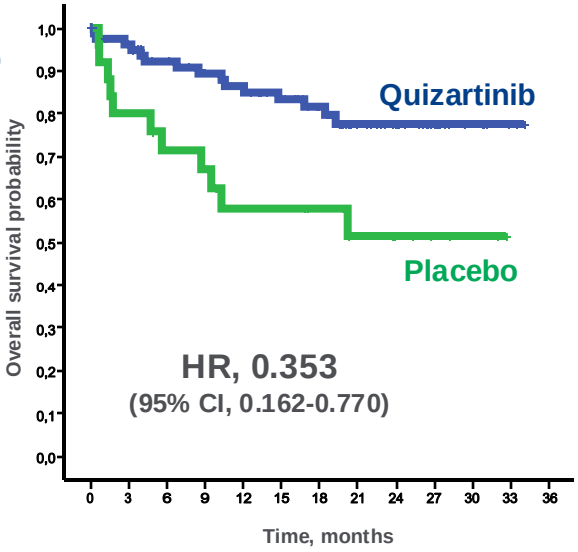
HR, hazard ratio; mOS, median overall survival; NR, not reached.
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 21.5 months. [c] Median follow-up time for placebo arm, 20.3 months.

Sensitivity analysis: Overall survival according to ELN2017 risk

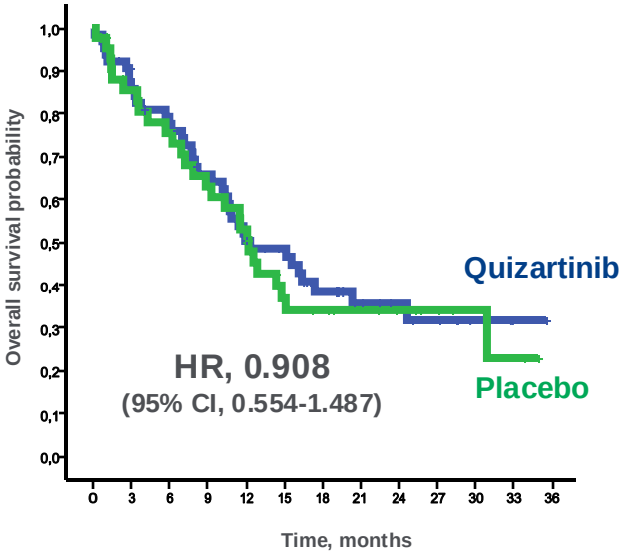
OS – ELN2017 Favorable



OS – ELN2017 Intermediate



OS – ELN2017 Adverse



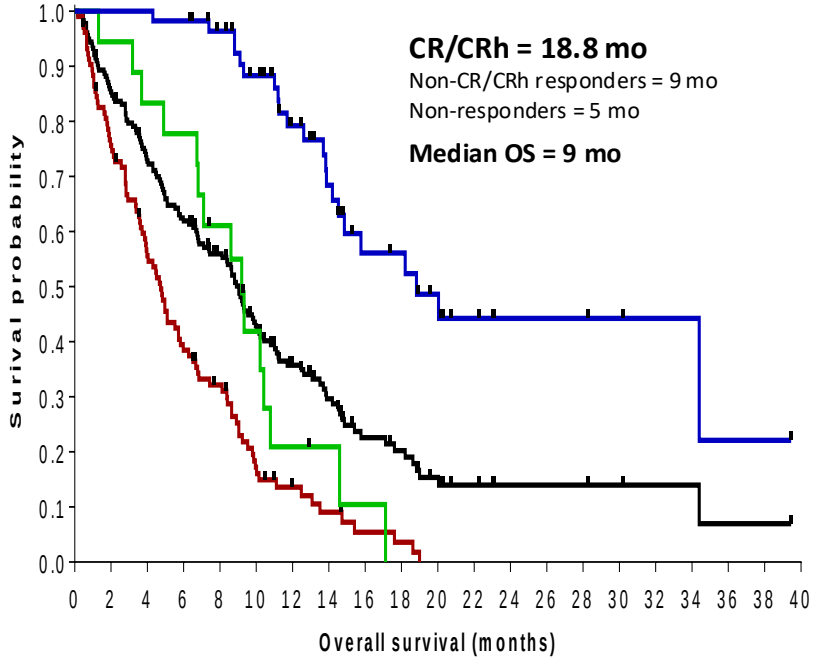
ELN, European LeukemiaNet; HR, hazard ratio

2. Targeting *IDH1* and *IDH2*

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

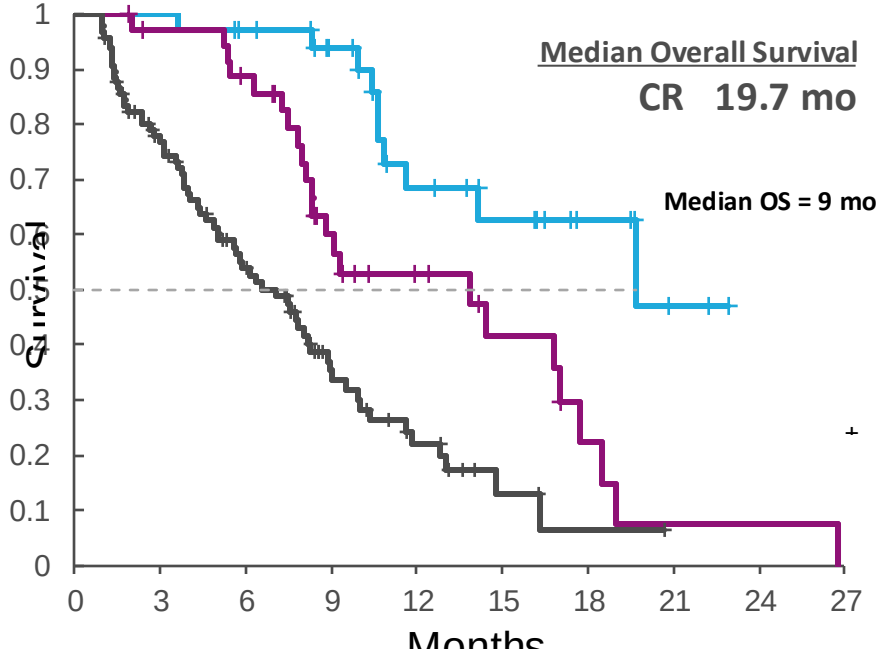
CR rate ~20%
CR/CRh rate ~30%
ORR ~40%

Ivosidenib (IDH1 inhibitor)



DiNardo CD et al, NEJM 2018

Enasidenib (IDH2 inhibitor)



Stein EM et al, Blood 2017

OLUTA R/R monotherapy response rates

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

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

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

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

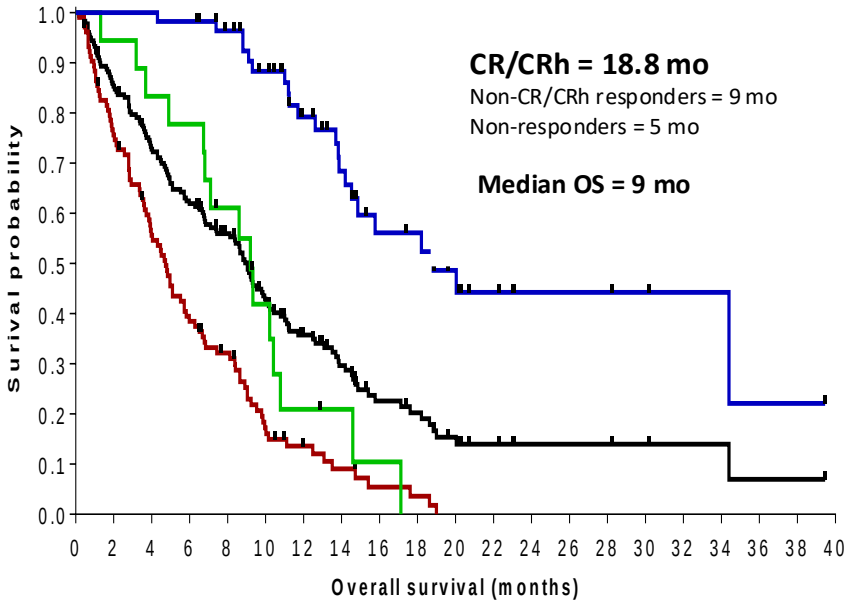
Median Duration of Response ~12 mo
(compared to ~6.5 mo w/ IVO)

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

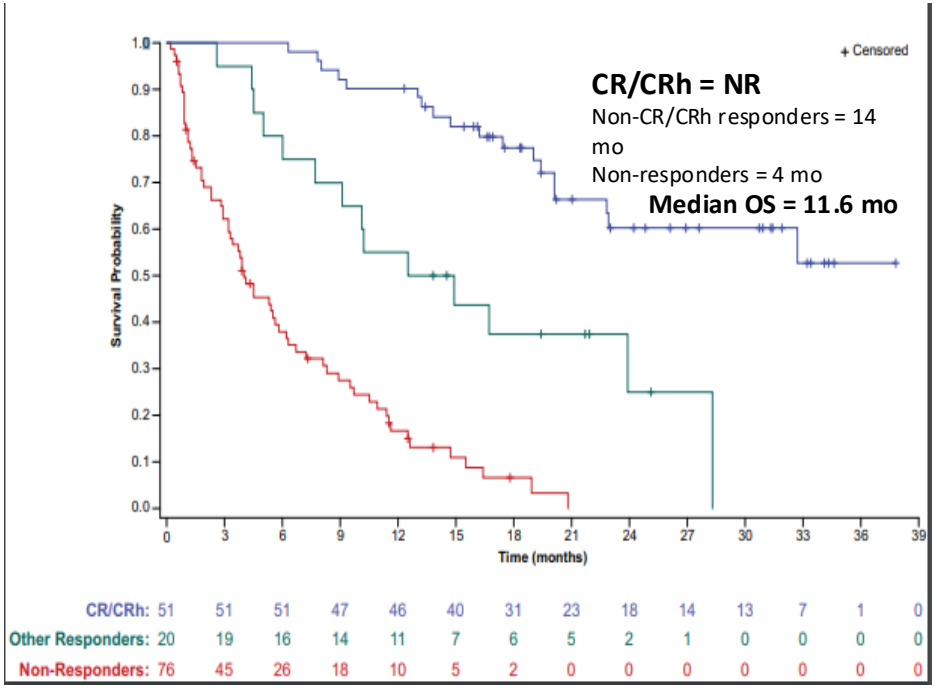
De Botton S et al, Blood Adv 2023

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

Ivosidenib (IDH1 inhibitor)



Olutasidenib (IDH1 inhibitor)



DiNardo CD et al, NEJM 2018

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)**

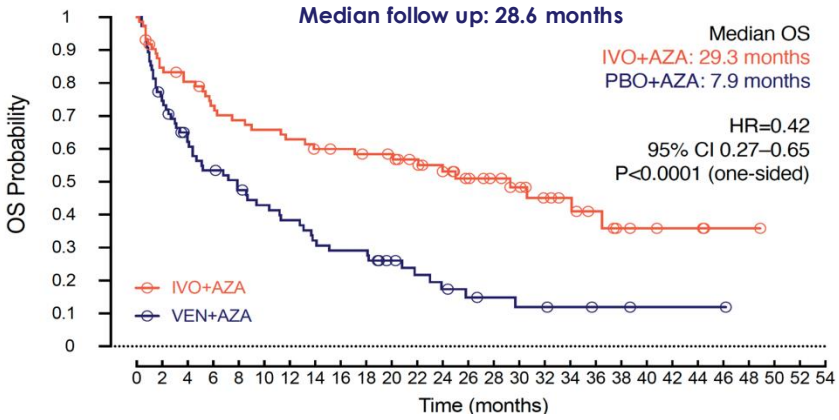
DS manifestations typically include

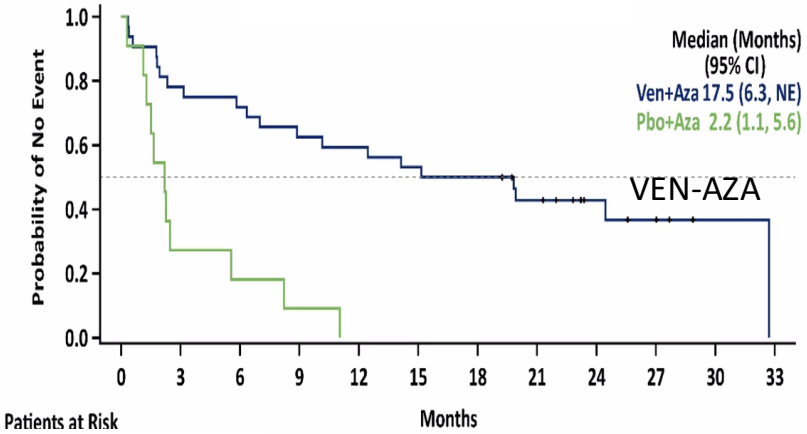
- Fever
- Dyspnea
- Pulmonary infiltrates
- Hypoxia
- Rash
- Edema

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





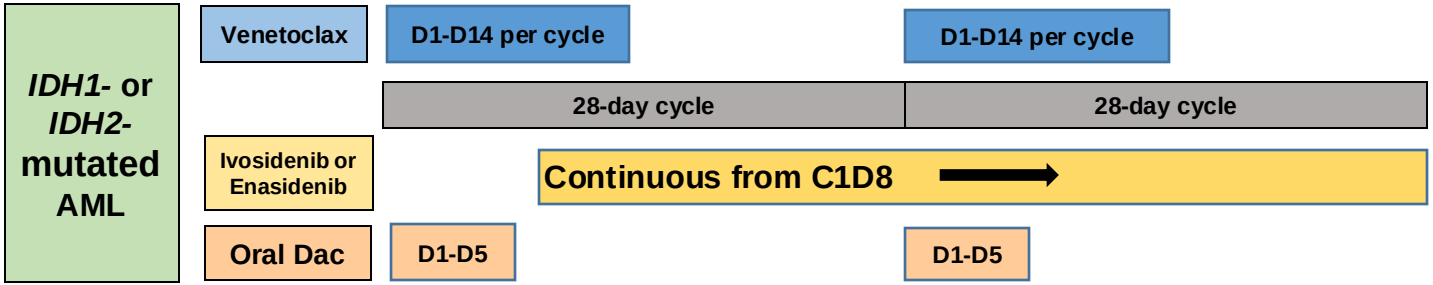
Montesinos et al, NEJM 2022, 386; 1519-31
De Botton et al. P142 , ASCO 2023

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)



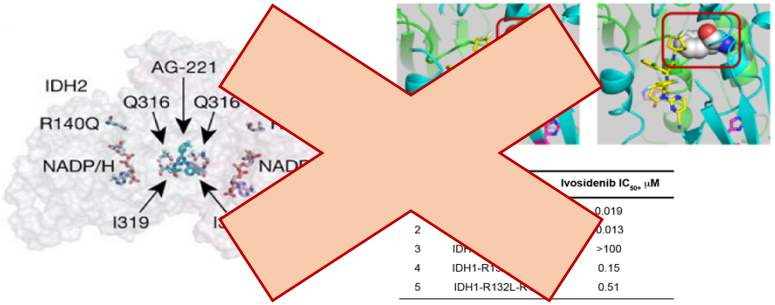
Response, %	Newly Dx *IDH1* (n = 10)	Newly Dx *IDH2* (n = 14)	R/R (n = 26) *IDH1*	R/R (n = 26) *IDH2*
CRc	90	100	50	44
MRD neg	80	93	50	19

***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.

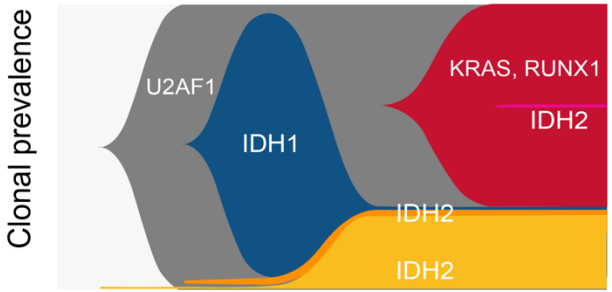
How does this compare with IDH inhibitor monotx resistance?

2HG Related



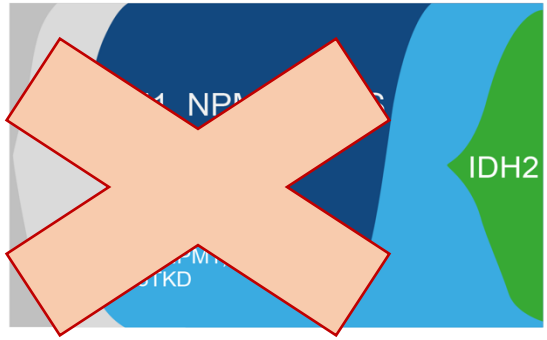
"Second Site Mutations"

Non-2HG Related

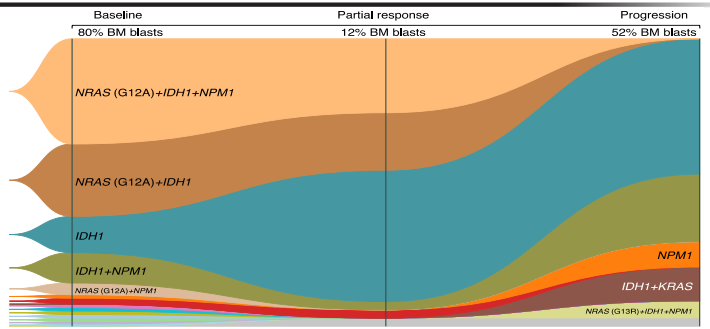


Reinstitution of Differentiation Block
(CEBPα, RUNX1, GATA2)

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



"Isoform Switching"

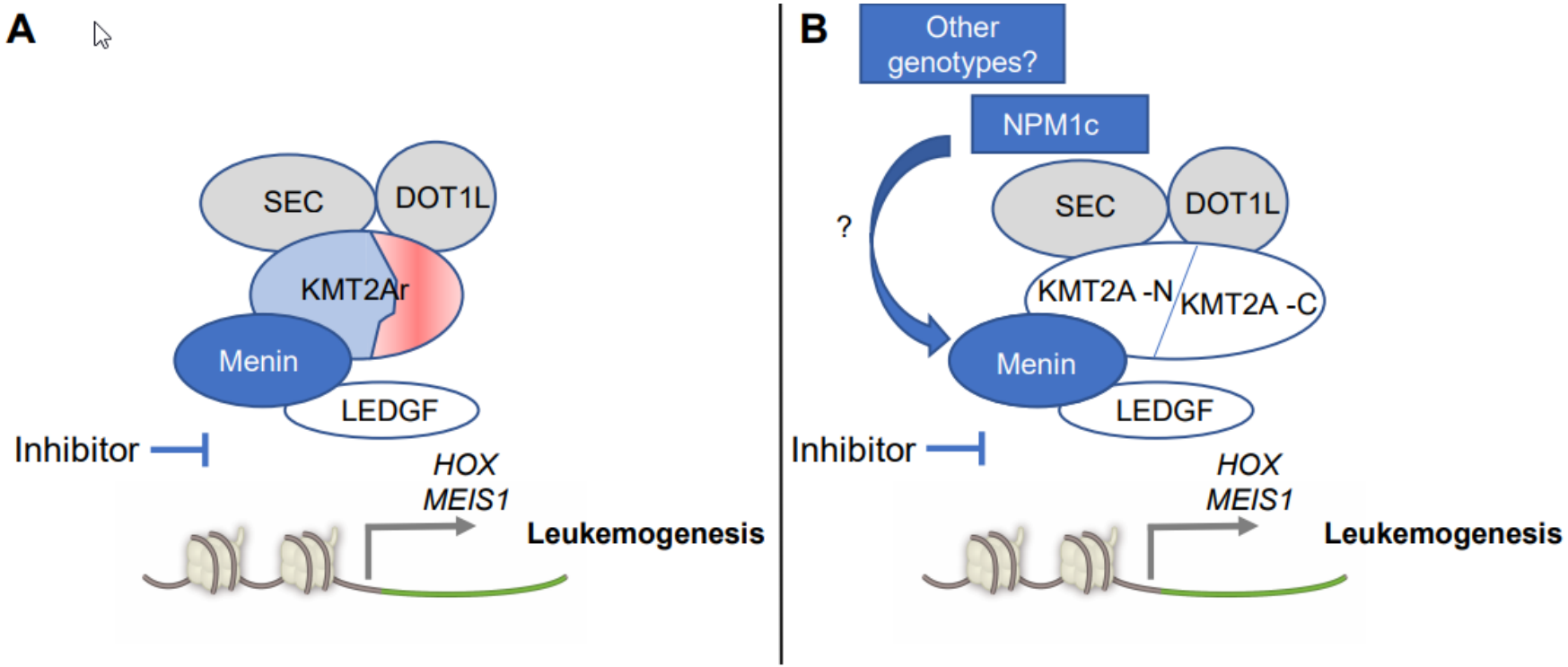


Activated Signaling / Proliferation Pathways
(FLT3-ITD, K/NRAS, PTPN11)

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

Patients aged ≥30 days with R/R acute leukemia

Revumenib RP2D

163 mg (95 mg/m^2 if body weight <40 kg) q12h oral + a strong CYP3A4i in 28-day cycles

→ ***KMT2A*r acute leukemia**

→ ***NPM1*m AML**

Still enrolling, not included in this analysis

- **Primary endpoint**
  - CR+CRh rate*
- **Key secondary efficacy endpoints**
  - CRc
  - ORR

A planned interim analysis of patients with *KMT2Ar* acute leukemia was conducted

*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)

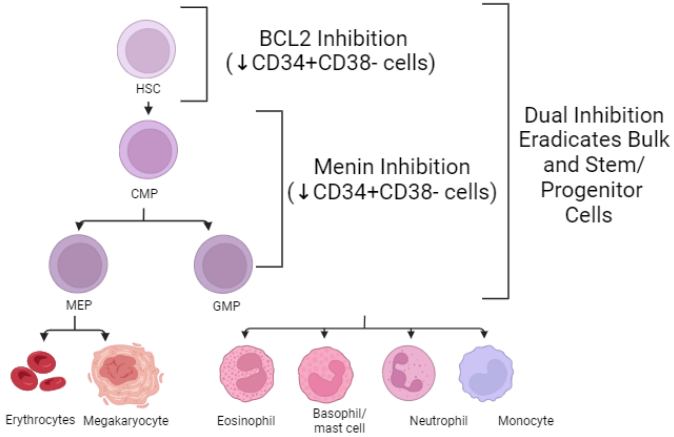
CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR);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

Rationale for SAVE combination

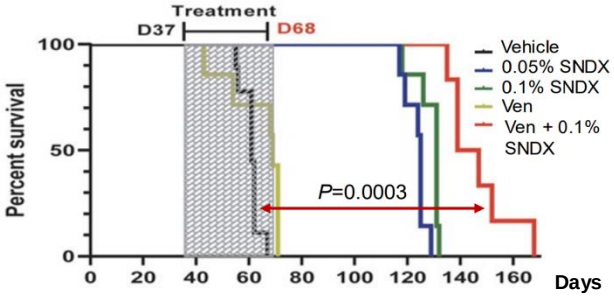
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

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

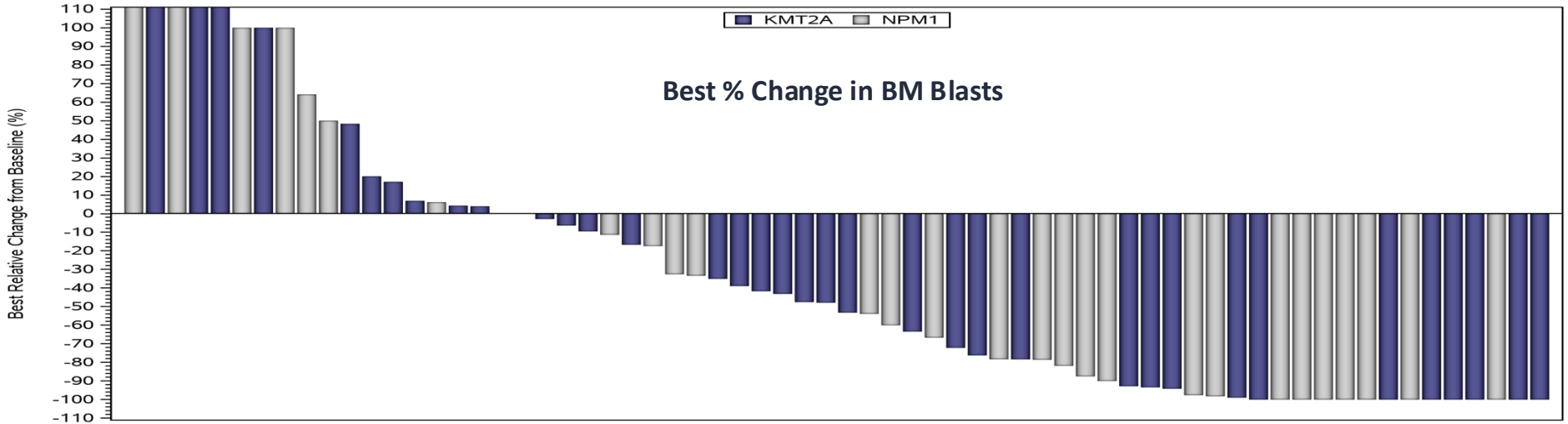
SAVE (SNDX-5613+ASTX727 +Ven) in R/R AML

- 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

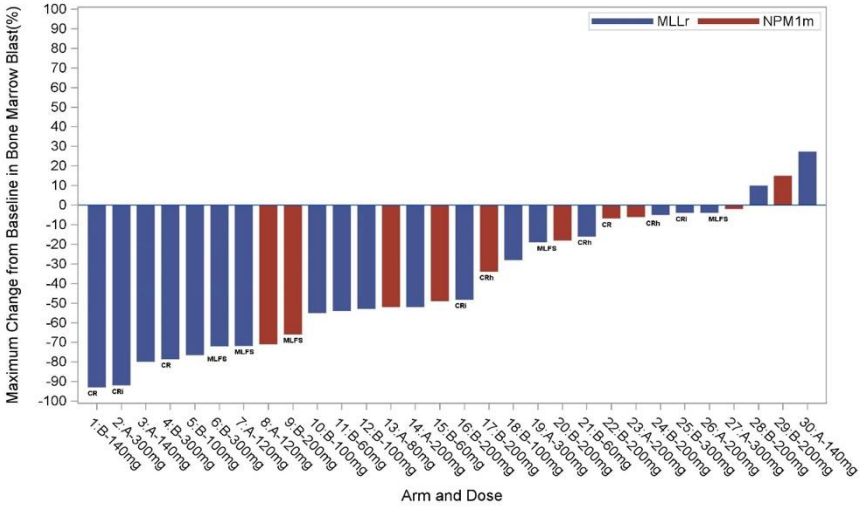


Jabbour. Blood 142: abst 57; 2023

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)

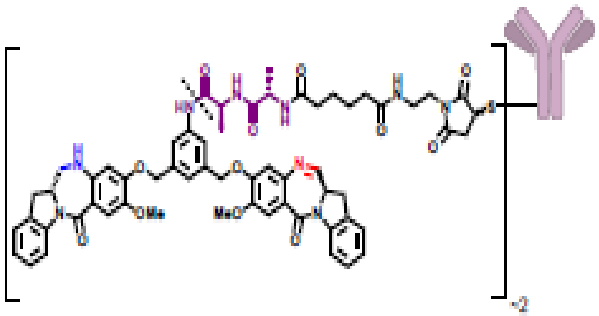
Daver N. EHA 2024 Abst S411

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%**

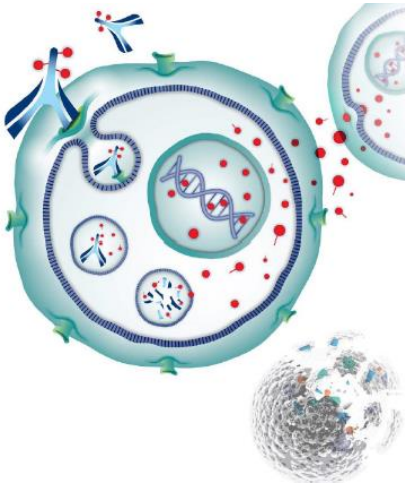


Red: imine (site of DNA alkylation)

Blue: amine (non-covalently binds DNA)

Purple: peptide linker

Dashed line: Site of catabolism

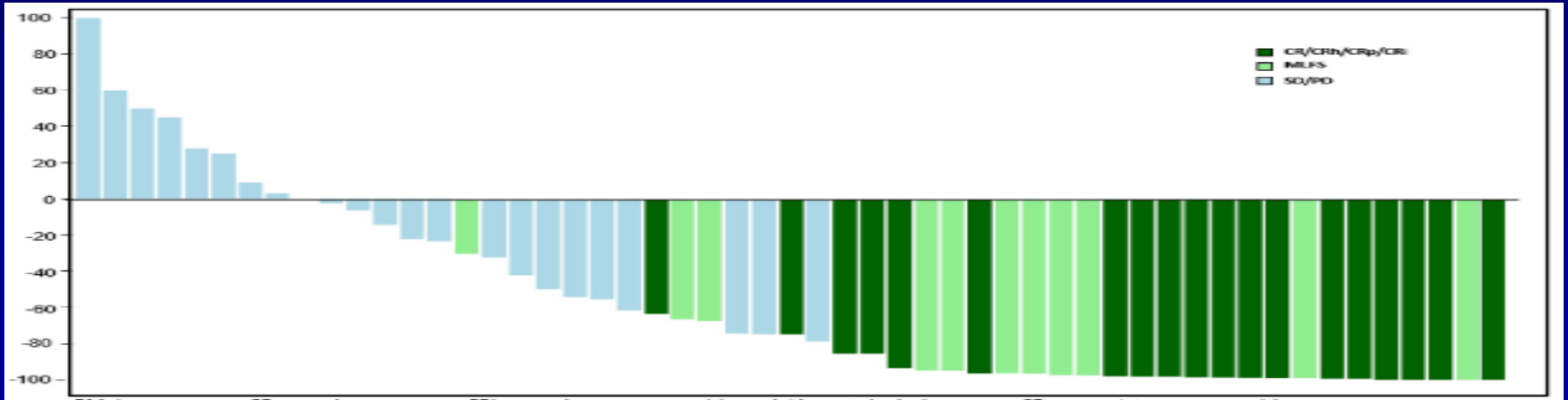


Daver N et al Lancet Oncology March 2024

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



BM=bone marrow; CR=complete response; CRh=complete response with partial hematological recovery; CRp=complete response with incomplete platelet recovery; MLFS=morphological leukemia-free state; SD=stable disease; PD=progressive disease

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

Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Therapeutic approaches in high-risk and frail patients with AML

Shaun Fleming

APTITUDE HEALTH®

Therapeutic approaches in frail and high-risk AML patients

A/Prof Shaun Fleming MBBS(Hons), PhD, FRACP, FRCPA
Head of Myeloid Diseases Service

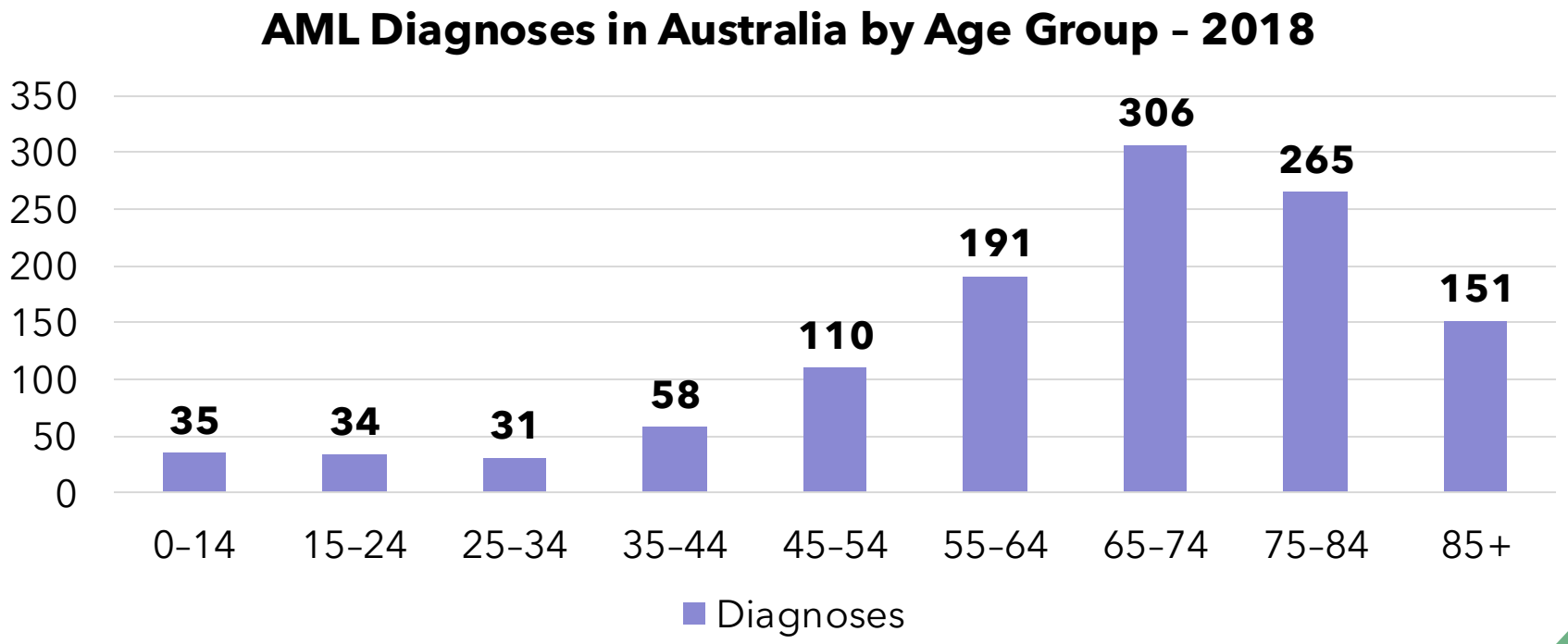
Alfred Hospital, Melbourne, Australia

Conjoint Associate Professor, Monash University

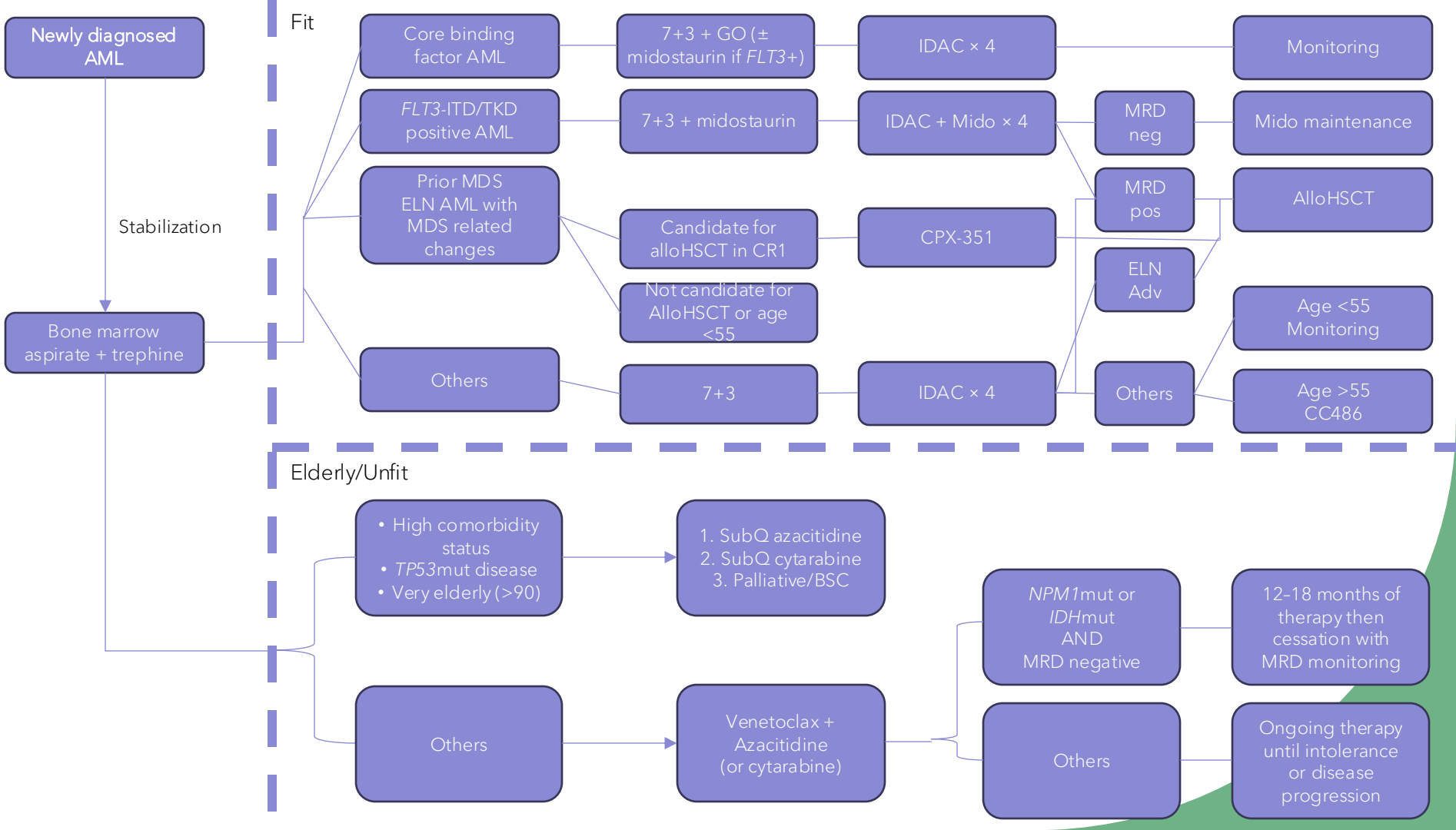
Disclosures

- Amgen – advisory board membership, research funding, speakers honoraria
- Pfizer – advisory board membership, speakers honoraria
- BMS – advisory board membership, speakers honoraria
- Astellas – advisory board membership
- Novartis – speakers honoraria
- AbbVie – advisory board membership, speakers honoraria
- Gilead – advisory board membership
- Jazz – speakers honoraria

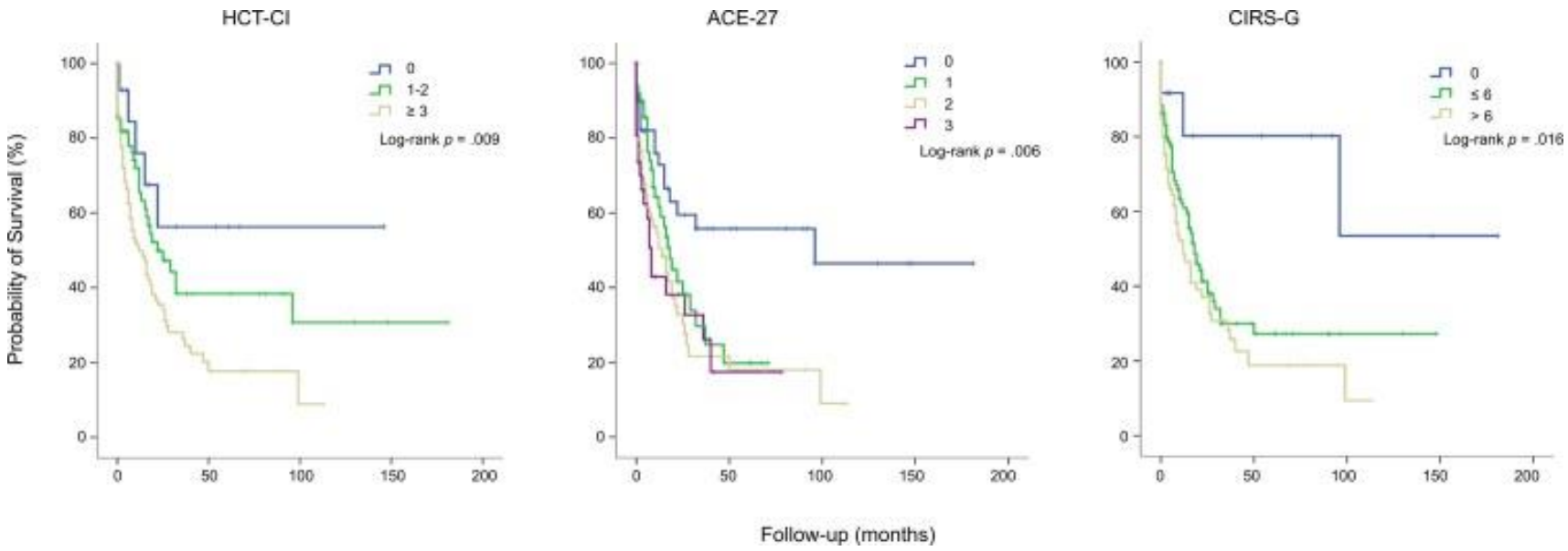
AML is predominately a disease of the elderly



Data from AIHW.


Newly diagnosed AML
Stabilization
Bone marrow aspirate + trephine
Fit
Core binding factor AML
7+3 + GO (± midostaurin if FLT3+)
IDAC × 4
Monitoring
FLT3-ITD/TKD positive AML
7+3 + midostaurin
IDAC + Mido × 4
MRD neg
Mido maintenance
Prior MDS ELN AML with MDS related changes
Candidate for alloHSCT in CR1
CPX-351
MRD pos
AlloHSCT
Not candidate for AlloHSCT or age <55
ELN Adv
Age <55 Monitoring
Others
7+3
IDAC × 4
Others
Age >55 CC486
Elderly/Unfit
• High comorbidity status
• TP53mut disease
• Very elderly (>90)
1. SubQ azacitidine
2. SubQ cytarabine
3. Palliative/BSC
Others
Venetoclax + Azacitidine (or cytarabine)
NPM1mut or IDHmut AND MRD negative
12–18 months of therapy then cessation with MRD monitoring
Others
Ongoing therapy until intolerance or disease progression

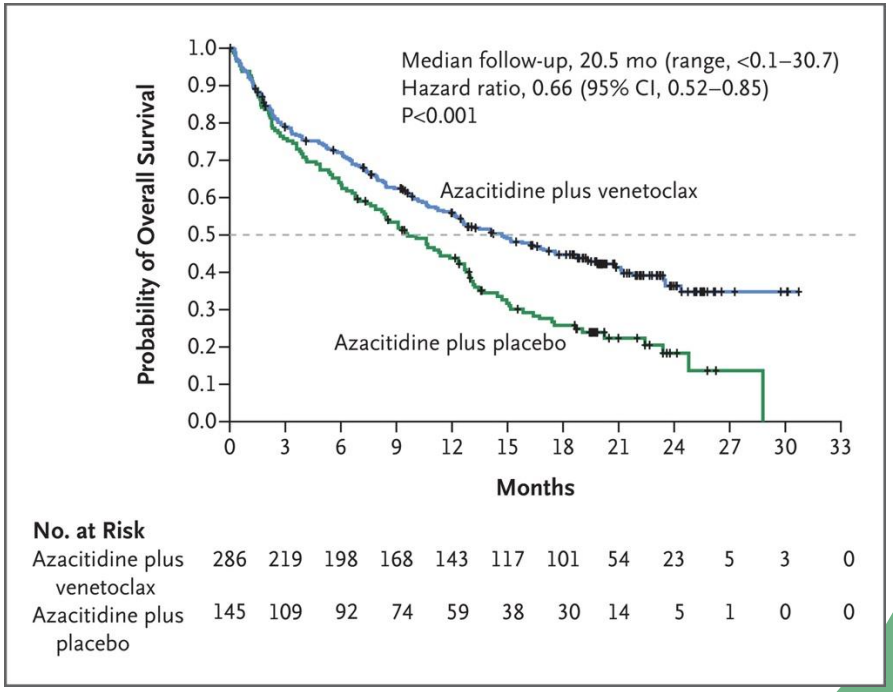
Comorbidity status in intensively treated patients



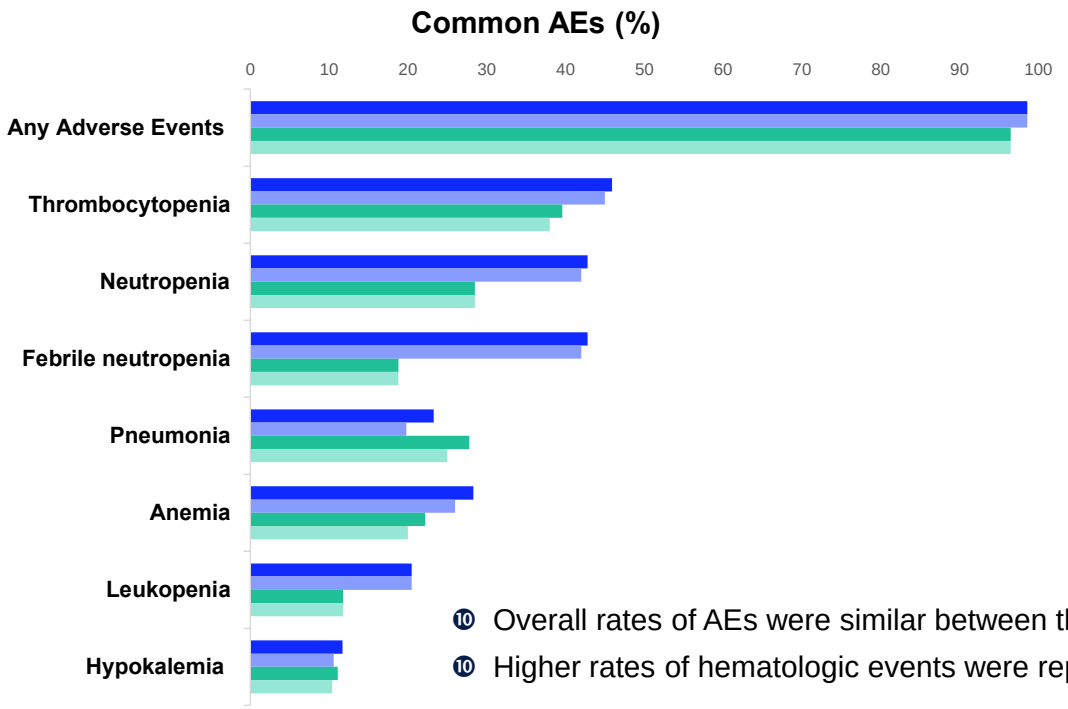
Wass M, et al. *PLoS One*. 2016;11(10):e0164587.

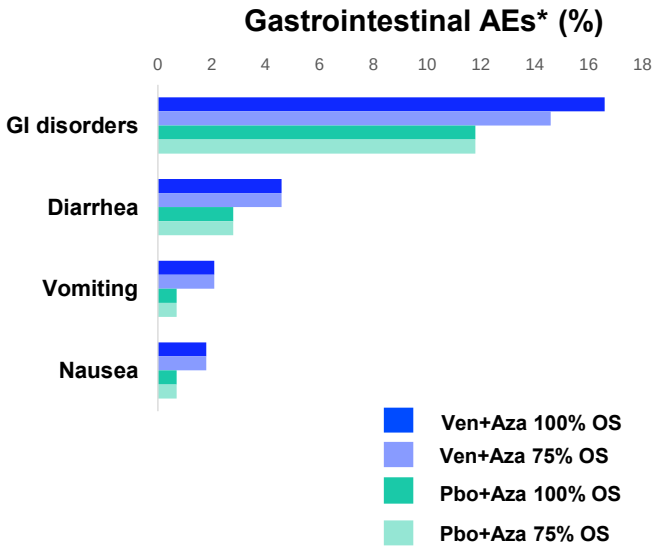
Venetoclax-azacitidine in AML

- Prior therapies for elderly AML patients have been disappointing
  - Very limited improvement in survival outcomes compared with palliative therapies alone
- Venetoclax (a BCL-2 inhibitor) in combination demonstrated a clear survival improvement in older/unfit adults with newly diagnosed AML
- Composite CR rate of 66.4% vs 28.3%
- Toxicity profile warrants consideration
  - More neutropenia – 42% vs 28%
  - More febrile neutropenia – 42% vs 19%
  - Infections overall – 84% vs 73%



DiNardo CD, et al. *N Engl J Med*. 2020;383(7):617-629.



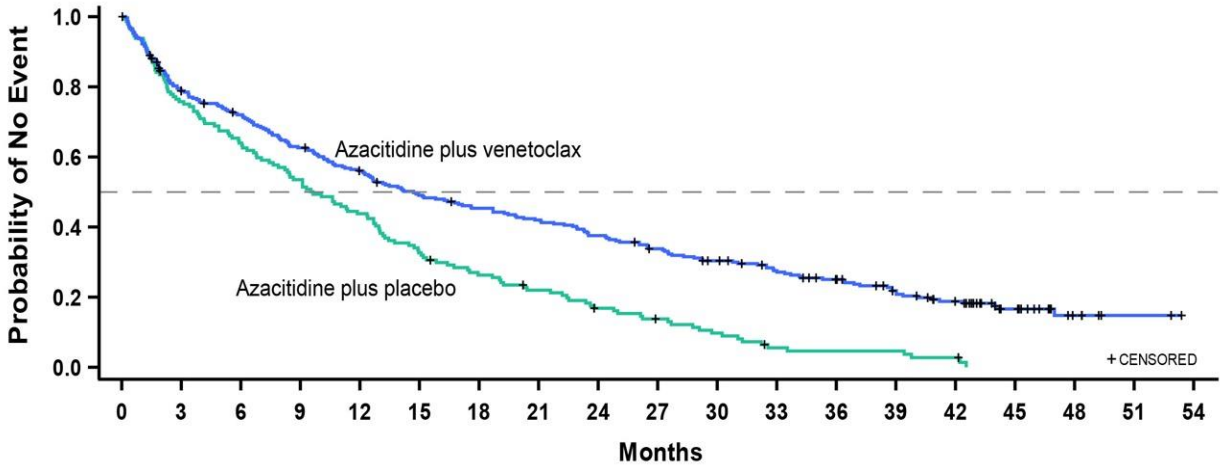


- Overall rates of AEs were similar between the two arms
- Higher rates of hematologic events were reported in the Ven+Aza arm

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

Very few patients will be cured by Ven-Aza

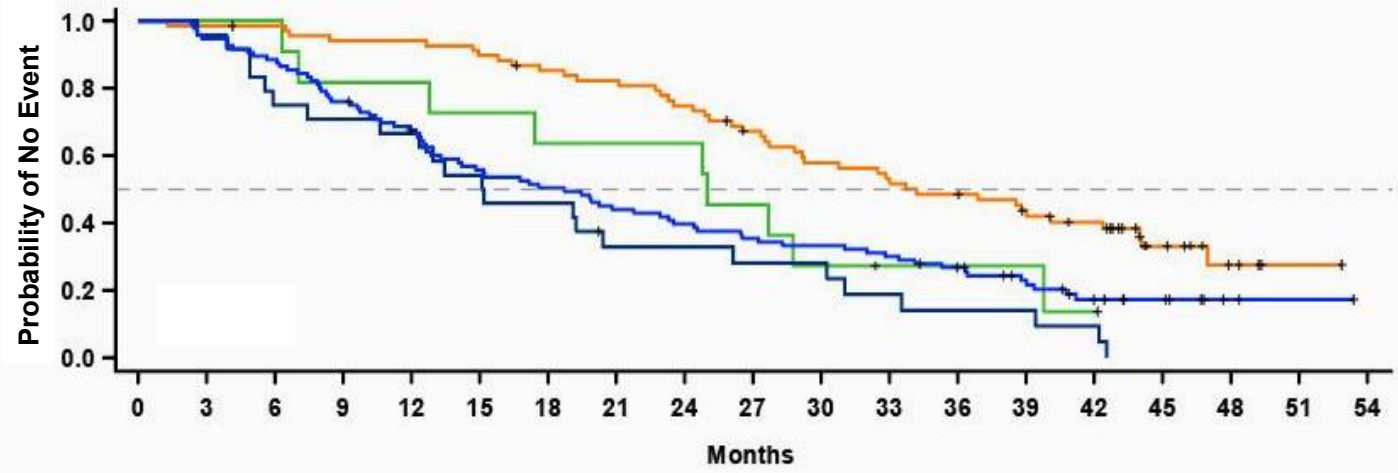
Figure 1. Overall Survival



Patients at Risk

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

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



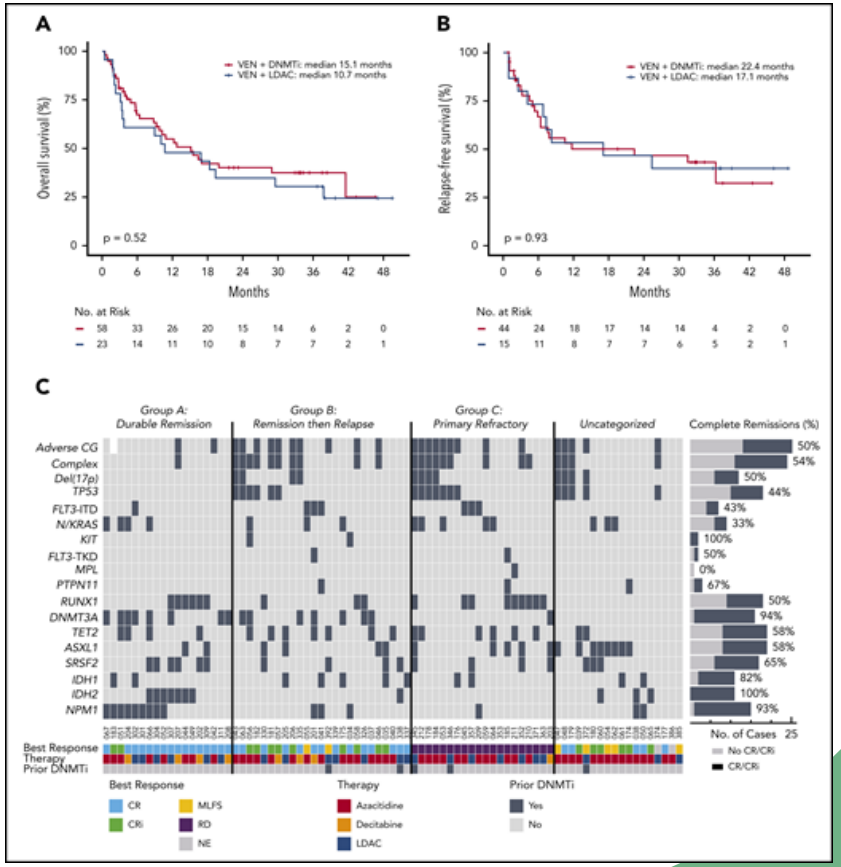
Patients at Risk

Ven + Aza MRD <10^{-3}	69	68	67	64	64	61	57	55	50	43	37	34	31	26	22	10	4	1	0
Ven + Aza MRD ≥10^{-3}	96	91	85	73	63	52	47	41	37	33	31	28	23	17	10	7	2	1	0
Pbo + Aza MRD <10^{-3}	11	11	11	9	9	8	7	7	7	5	3	2	2	2	1	0			
Pbo + Aza MRD ≥10^{-3}	24	23	18	17	16	13	11	7	7	6	6	4	3	3	2	0			

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

Molecular factors can predict response to venetoclax combinations

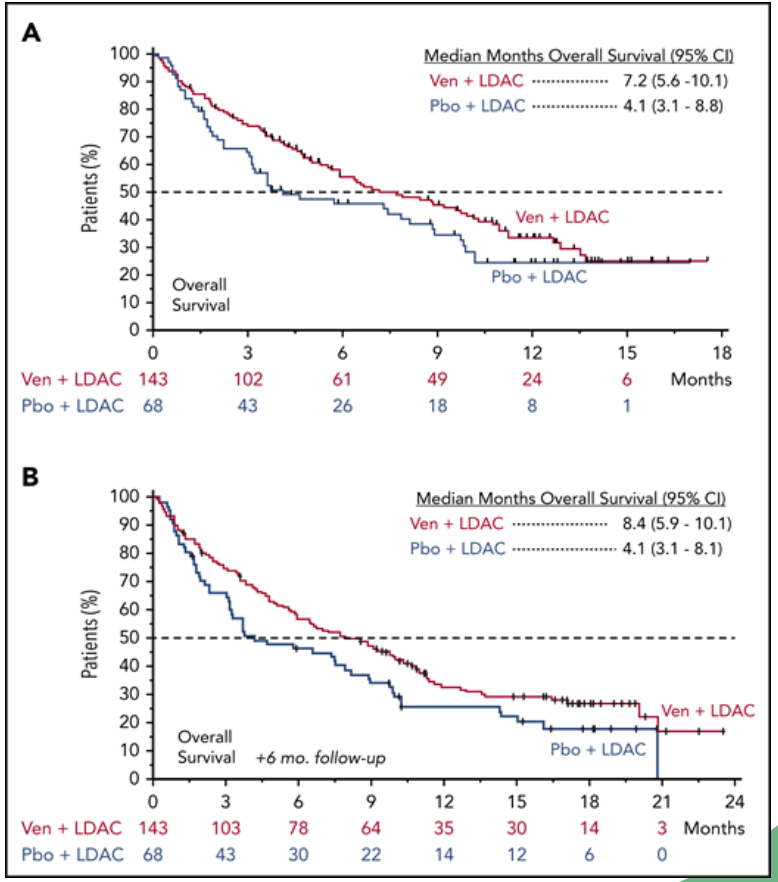
- Complete remission and long-term survival more common in patients with *NPM1* and *IDH2* mutations
- *TP53* and *FLT3*-ITD mutations were associated with poor responses and were enriched at treatment failure



DiNardo CD, et al. *Blood*. 2020;135(11):791-803.

Cytarabine + venetoclax represents an alternative in older adults with AML

CR/CRi of 43% vs 13%



Wei AH, et al. *Blood*. 2020;135(24):2137-2145.

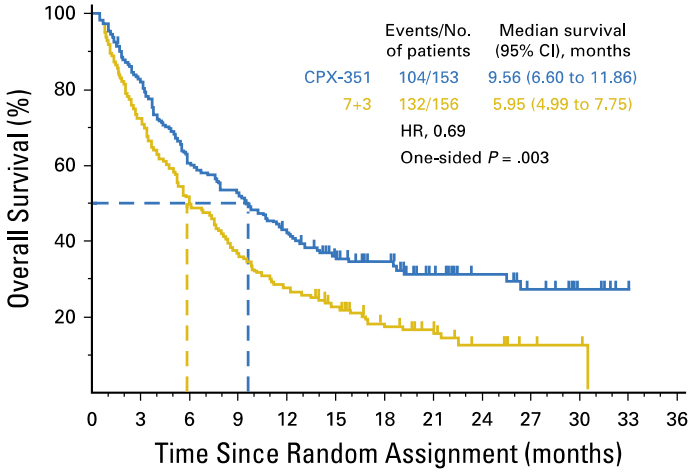
Risk stratification for adults receiving non-intensive therapies

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

Döhner H, et al. *Blood*. Published online August 12, 2024. doi:10.1182/blood.2024025409

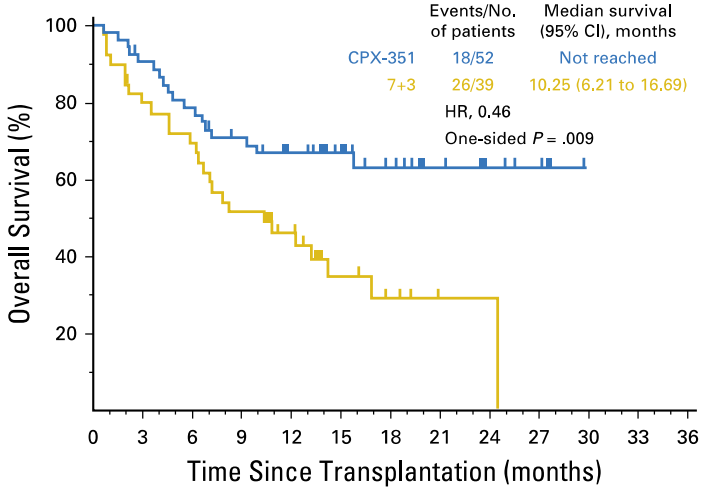
Daunorubicin and cytarabine (CPX-351) in sAML

- Randomized study comparing against 7+3
  - Followed by 5+2 consolidation in control arm
- CR+CRi of 47.7% vs 33.3%



No. at risk

CPX-351	153	122	92	79	62	46	34	21	16	11	5	1
7+3	156	110	77	56	43	31	20	12	7	3	2	0

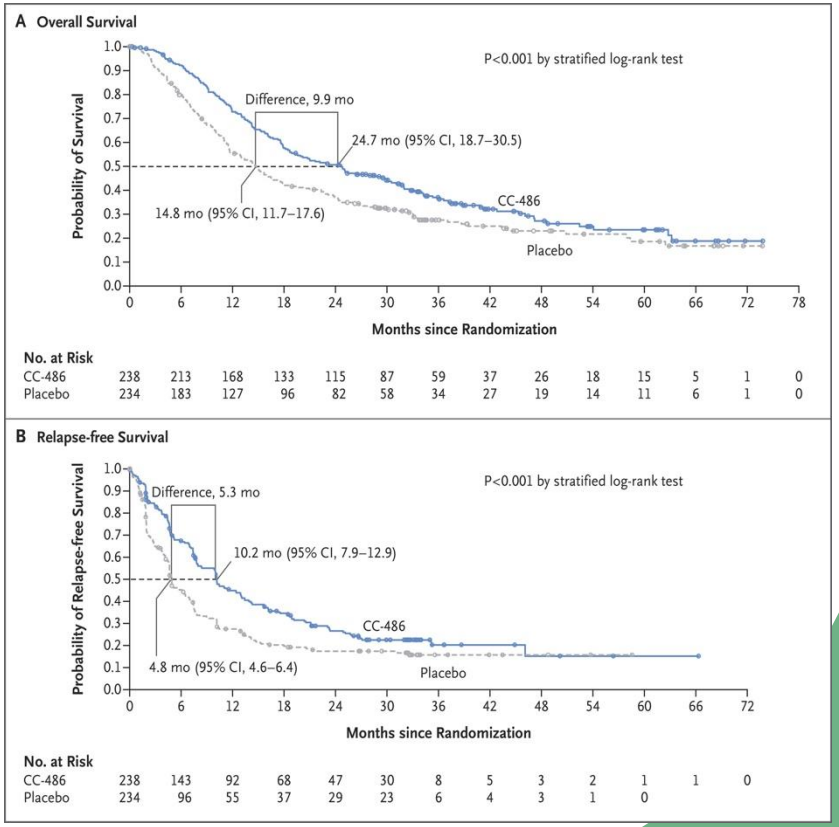


No. at risk

CPX-351	52	46	40	34	27	20	15	9	6	3	0	0
7+3	39	31	27	20	15	7	4	1	1	0	0	0

Maintenance therapy in AML

- Maintenance chemotherapy utilized in several studies
  - Clearly established role in ALL
  - No clear evidence that it was useful in AML
  - Other therapies such as IL-2 maintenance used
    - Toxic with relatively limited improvement in survival outcomes
- Phase II studies suggested a possible role for azacitidine as maintenance therapy
- The QUAZAR CC-486 study explored oral azacitidine for maintenance therapy in patients aged ≥55 with AML in CR1
- Demonstrated an improvement in OS and RFS
- Major toxicities were low-grade GI toxicities and higher-grade hematologic toxicities



Wei AH, et al. *N Engl J Med*. 2020;383(26):2526-2537.

A lot of older/comorbid patients seem to be admitted and not survive to discharge

Anecdotal observation

Definitions

- Patient population
  - Patients aged over 65 years with newly diagnosed AML
- Intensive treatment
  - Remission induction-type chemotherapy (either an anthracycline + cytarabine combination such as 7+3 or a high-dose cytarabine-based regimen such as FLAG)
- Non-intensive treatment
  - Subcutaneous cytarabine or azacitidine as a single agent or in combination with venetoclax
  - Thioguanine + subcutaneous cytarabine
  - IV azacitidine + venetoclax

AML composite model

- Multicenter analysis to test and validate
  - The prognostic impact of comorbidities on 1-year mortality after initial therapy of AML
  - A novel, risk-stratifying composite model incorporating comorbidities, age, and cytogenetic and molecular risks
- 1100 patients, ages 20 to 89 years, were treated for AML between January 1, 2008, and December 31, 2012, at 5 institutions specialized in treating AML
- Composite model comprising augmented HCT-CI, age, and cytogenetic/molecular risks had the best C statistic and AUC predictive estimates of 0.72 and 0.76, respectively

Sorror ML, et al. *JAMA Oncol.* 2017;3(12):1675-1682.

AML composite model

The Augmented HCT-CI = all the above + the following		
Comorbidity	**Definition**	**Score**
Hypoalbuminemia	Value of <3.5 g/dL; using the closest value before start of treatment.	1
Thrombocytopenia	Value of <20,000 cells/μL; using the closest value before start of treatment	1
Elevated LDH	Values of >200-1000 U/L; using the closest value before start of treatment.	1
Elevated LDH	Value of >1000 U/L; using the closest value before start of treatment.	2
The AML-CM = all the above + the following		
Component	**Definition**	**Score**
Age	50-59 years old	1
Age	≥60 years old	2
ELN cytogenetic/molecular risk groups	Intermediate	1
ELN cytogenetic/molecular risk groups	Adverse	2

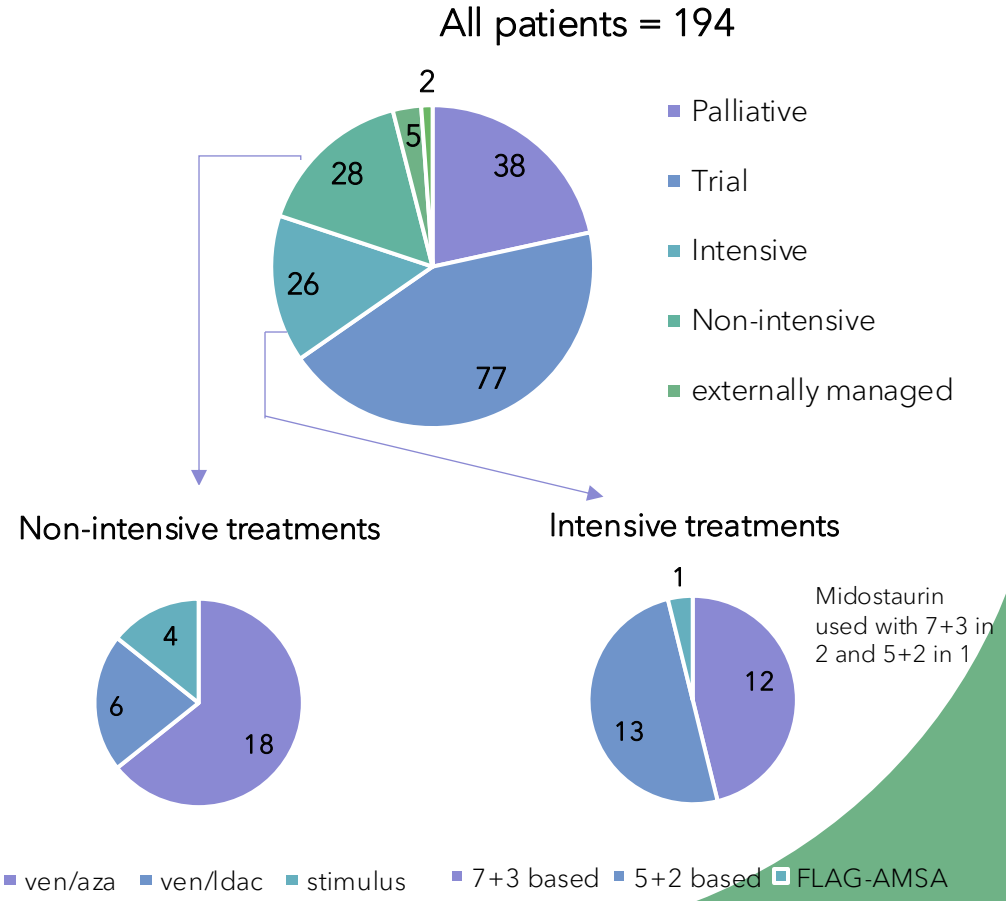
Sorror ML, et al. *JAMA Oncol.* 2017;3(12):1675-1682.

Methods

- Retrospective review of hospital records of patients diagnosed with AML age ≥70 years from January 2016–January 2023 and treated as standard of care as first line of therapy at Alfred Health, Melbourne, Victoria. Descriptive statistics were used, and Kaplan-Meier estimate for survival

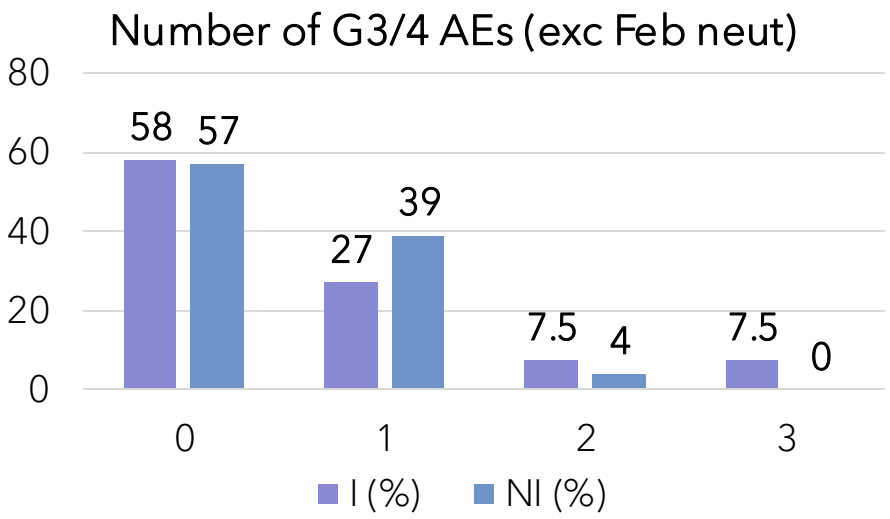
Our results: demographics and treatment

Baseline Demographics	Intensive (n = 26)	Non-Intensive (n = 28)
Age, median (range)	72 (70-78)	76 (70-91)
ELN criteria		
Not available	0	2 (7%)
Favorable	10 (38%)	4 (14%)
Intermediate	8 (31%)	7 (25%)
Adverse	8 (31%)	15 (54%)
Molecular		
FLT3-ITD	4/25 (1 NA)	4/22 (6 NA)
NPM1	8/25 (1 NA)	5/22 (6 NA)
TP53	4/22 (4 NA)	2/22 (6 NA)
IDH1/2	3/23 (3 NA)	4/22 (6 NA)
Primary AML	21 (81%)	15 (54%)
Secondary AML	5 (19%)	10 (36%)
Therapy related	0	3 (10%)
Baseline counts, median (range)		
Hb	93 (50-129)	87.5 (52-124)
WCC	14.25 (0.9-57.15)	4.2 (0.8-120.8)
Plt	60.5 (7-486)	54 (18-135)
Blast count BM	52 (7-99)	49 (20-97)
AML-CM, median (range)	6.5 (3-11)	8 (3-14)

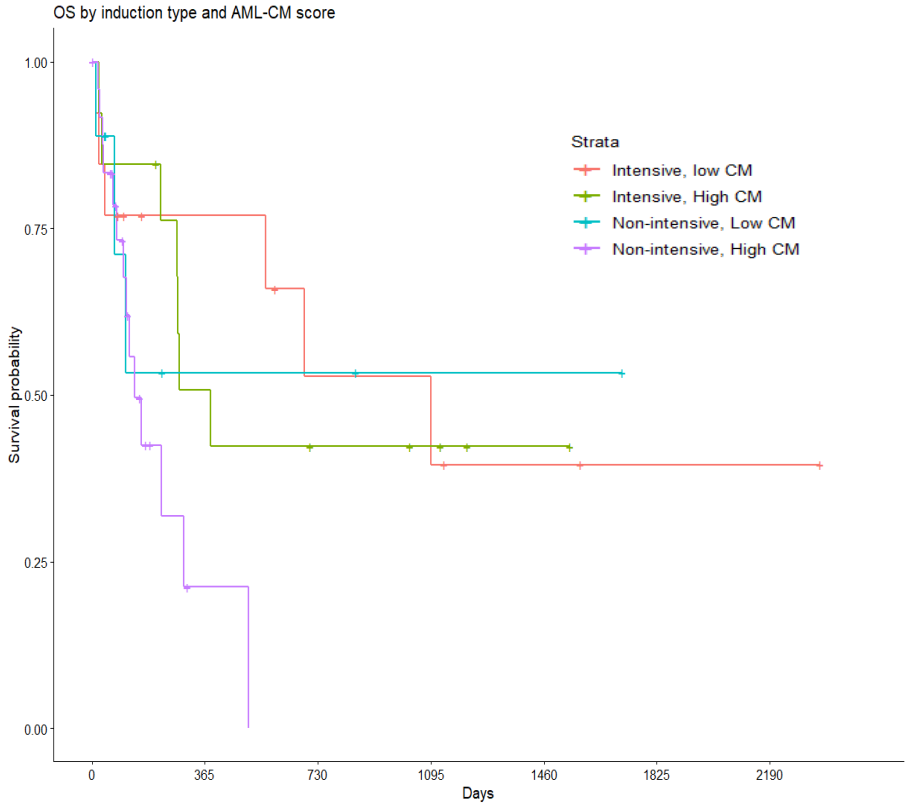


Results: toxicity + hospital burden

Toxicity	Intensive (n = 26)	Non-Intensive (n = 28)
C1 G3/4 neutropenia duration, days median (range)	27 (19-49)	31.5 (2-53)
C1 G3/4 thrombocytopenia, days median (range)	22.5 (0-61)	18 (0-36)
Febrile neutropenia	24/26 (92%)	15/28 (54%)
Number of admissions, median (range)	3.5 (1-10)	2 (1-27)
Length of stay, median (range)	66 (23-137)	38 (1-100)
Admitted to ICU	4/26 (15%)	2/28 (7%)
RBC transfusions, median (range)	16.5 (5-62)	10 (0-35)
PLT transfusions, median (range)	13 (4-47)	4 (0-39)
Death <60 days from dx	5/26 (19%)	6/28 (21%)



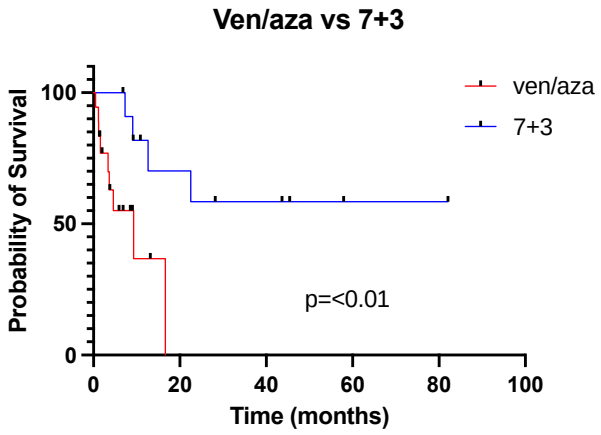
OS by induction type and CM

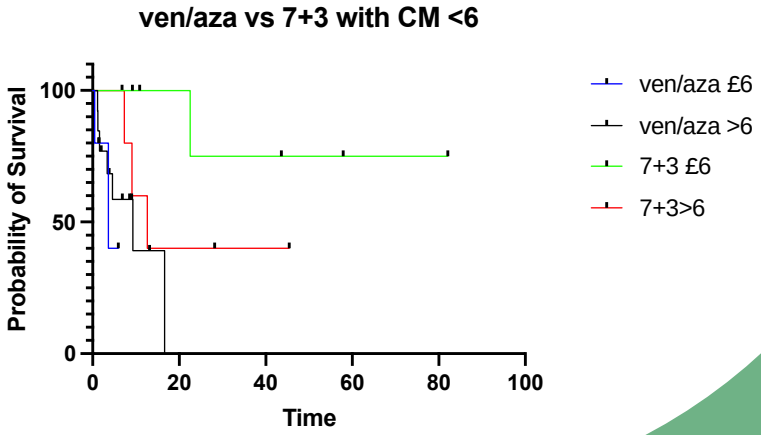


Outcomes	Intensive (n = 26)	Non-Intensive (n = 28)
Response rate after C1		
CR/Cri	14 (54%)	12 (35%)
Not CR/CRi (SD, MLFS, PR)	4 (15.3%)	9 (26%)
Progressive disease	4 (15.3%)	4 (12%)
Not assessed	4 (15.3%)	9 (26%)
Relapse after response	7/18 (39%)	4/21 (19%)
Transplant	3/26 (11.5%)	0
Deaths	14/26 (54%)	16/28 (57%)
Median OS months (range)	22.55 (0.4-77)	5.23 (0.1-56)
Median follow up	37.05	6.18

Ven-Aza vs 7+3

	Ven-Aza (n = 18)	7+3 (n = 12)
ELN		
Fav	1 (5%)	7 (58%)
Int	5 (28%)	1 (8%)
Adv	12 (67%)	4 (33%)
CM <6	4 (22%)	5 (42%)
CM >6	14 (78%)	7 (58%)
Response after C1		
CR/CRi	8 (44%)	10 (83%)
MLFS	3 (17%)	
SD/PR	2 (11%)	
Refractory	2 (11%)	2 (17%)
Not assessed	3 (17%)	
Deaths <60 days	4 (22%)	0
Deaths total	9 (50%)	4 (33%)
Median OS (months)	9.3 (0.4-16)	NR (6.8-82)





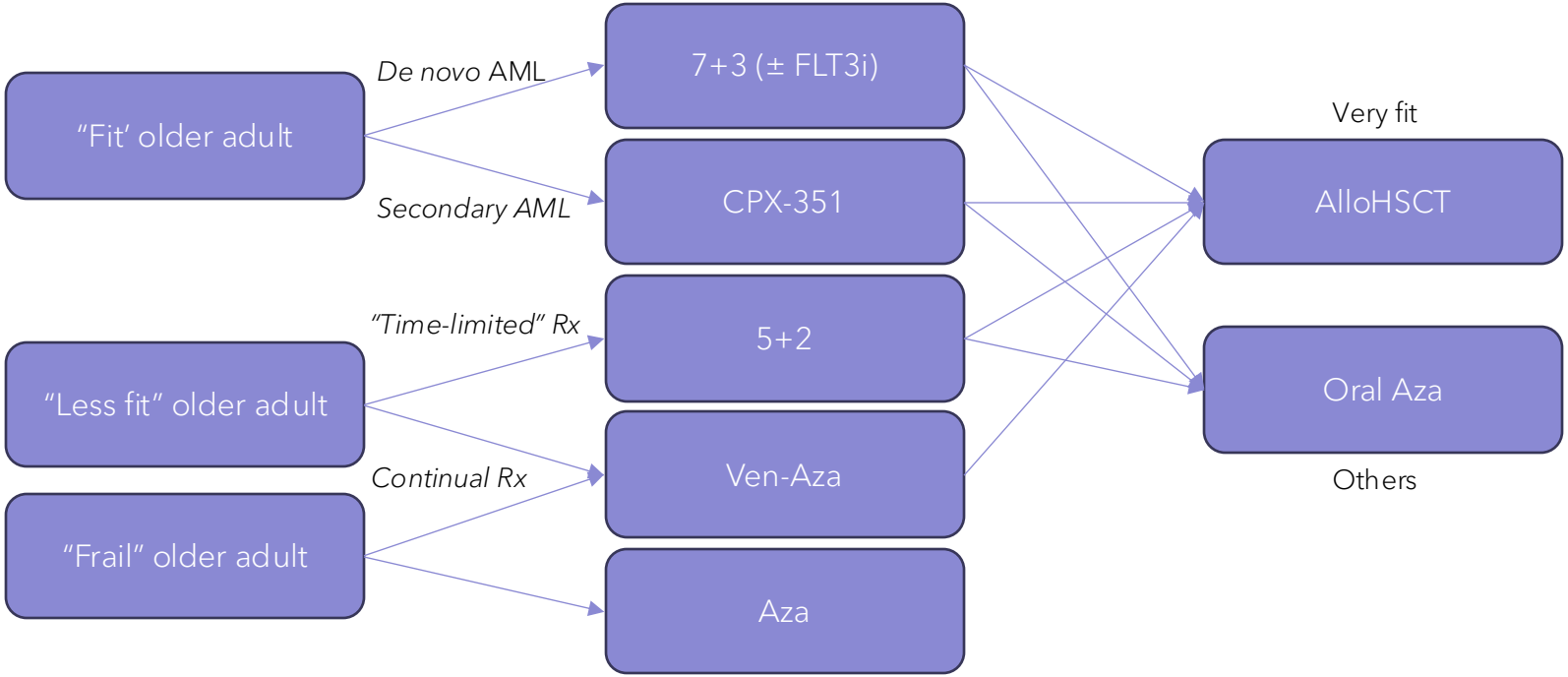
Ven-Aza vs 7+3

- Data reflect patient population and physician choice of treatment
  - Eg, 7+3 much higher favorable ELN and lower CM, as this is what we use to decide on treatment – remembering CM incorporates ELN anyway

Outcomes: all

- Survival outcome trended toward superiority for patients receiving remission induction chemotherapy (2-year OS of 47% vs 21%, $P = .054$)
- 2-year survival outcomes were similar among patients with a low AML-CM (6 or less) irrespective of therapy received (53% in both groups)
- Significantly improved within the group with a higher AML-CM (over 6) receiving intensive chemotherapy (2-year OS of 42.3% vs 0%, $P = .037$)
- Similarity in outcomes in both intensive and non-intensive therapy, both appear reasonable options for the treatment of fit older adults

So how do we approach the older AML patient in 2024?



The challenges that remain

- How best can we assess frailty of older AML patients?
  - Clinician "gestalt"
  - AML Composite model
  - Comprehensive geriatric assessment
- Ven-Aza as a bridge to alloHSCT in AML
  - Is a remission on Ven-Aza the same as a remission post-intensive chemoRx?
- Approaches to "time-limited" therapy for frailer adults with AML

THANK YOU

Global Leukemia Academy

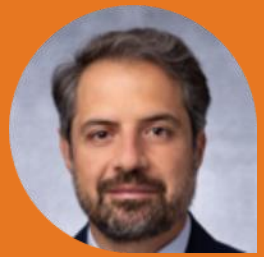
Q&A

APTITUDE HEALTH®

Global Leukemia Academy

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

Elias Jabbour, Junichiro Yuda
and all faculty



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Panel discussion

APTITUDE HEALTH®

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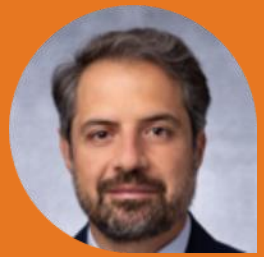
Session close

Elias Jabbour



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Question 3 [REPEATED]

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

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

Question 4 [REPEATED]

Which of the following is NOT true for treating ALL?

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

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

C. MRD– CR does not correlate strongly with outcome

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

Agenda: Day 2

Time (UTC +8)	Title	Speaker
8.00 AM – 8.10 AM	Welcome to Day 2	Naval Daver
8.10 AM – 8.30 AM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
8.30 AM – 8.50 AM	Long-term safety considerations for leukemias (focus on ALL)	Jae Park
8.50 AM – 9.10 AM	Current and future role of transplantation in acute leukemias in Asia-Pacific	Shaun Fleming
9.10 AM – 9.20 AM	Break	
9.20 AM – 9.40 AM	Current treatment options for relapsed AML in adult and elderly patients	Junichiro Yuda
9.40 AM – 10.10 AM	AML case-based panel discussion • Case 1 AML: Ane Veu (Fiji) • Case 2 AML: Feng-Ming Tien (Taiwan)	Naval Daver and Patient case presenters And all faculty
10.10 AM – 10.50 AM	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 Asia-Pacific	Naval Daver and all faculty
10.50 AM – 11.00 AM	Session close	Naval Daver

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SEE YOU TOMORROW!

August 22/23 and 23/24, 2024 – Asia-Pacific

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