Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

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

October 19–20, 2023 – Latin America

Meeting sponsors AMGEN astellas

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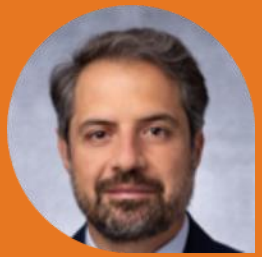
Welcome and meeting overview

Elias Jabbour



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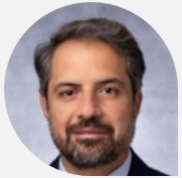
Meet the Faculty

CHAIR



Elias Jabbour, MD
MD Anderson Cancer Center,
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CO-CHAIR

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

FACULTY

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

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

Wellington Silva, MD, PhD
Hospital das Clínicas, University of São Paulo, Brazil

Objectives of the program

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

Day 1: Virtual Plenary Sessions

Thursday, Oct 19, 2023
5.00 PM – 8.00 PM UTC -5 (Houston time)
7.00 PM – 10.00 PM UTC -3 (Brasilia/Buenos Aires)

Time	Title	Speaker
7.00 PM – 7.10 PM	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
7.10 PM – 7.25 PM	Review of prognostic value of MRD in ALL and AML	Phillip Scheinberg
7.25 PM – 7.40 PM	Latest achievements and developments in ALL and AML	Elias Jabbour
7.40 PM – 7.50 PM	Best practices for first-line treatment in ALL	Josep-Maria Ribera
7.50 PM – 8.05 PM	AYA ALL patients: What is the current treatment approach for this diverse patient population? Special considerations for adolescents and young adults and how we can use this experience in adult patients	Wellington Silva
8.05 PM – 8.35 PM	ALL case-based panel discussion • Case ALL: elderly/frail (10 min) • Case ALL: AYA (10 min) • Discussion (10 min) – panelists: all faculty	Roberta Demichelis and Juan Luis Ontiveros Austria All faculty
8.35 PM – 8.45 PM	Break	
8.45 PM – 9.10 PM	Genetic characterization and risk stratification of AML; role of *FLT3* and *IDH* in AML and special considerations for young and fit patients	Naval Daver
9:10 PM – 9.25 PM	Therapeutic approaches in high-risk and frail AML patients	Phillip Scheinberg
9.25 PM – 9.50 PM	Panel discussion: Open questions in ALL and AML – regional challenges (transplant, CAR T, studies, and other)	Elias Jabbour and all faculty
9.50 PM – 10.00 PM	Session close	Elias Jabbour

Day 2: Virtual Plenary Sessions

Friday, Oct 20, 2023
5.00 PM – 8.00 PM UTC -5 (Houston time)
7.00 PM – 10.00 PM UTC -3 (Brasilia/Buenos Aires)

Time	Title	Speaker
7.00 PM – 7.10 PM	Welcome to Day 2	Naval Daver
7.10 PM – 7.30 PM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
7.30 PM – 7.50 PM	Current treatment options for relapsed AML in adult and elderly patients	Naval Daver
7.50 PM – 8.20 PM	AML case-based panel discussion • Case AML: young high-risk (10 min) • Case AML: elderly (10 min) – fellow (TBD) • Discussion (10 min) – panelists: all senior faculty	Roberta Demichelis and Sergio Rodriguez Centre All faculty
8.20 PM – 8.30 PM	Break	
8.30 PM – 8.50 PM	Long-term safety considerations for leukemias (focus on ALL)	Josep-Maria Ribera
8.50 PM – 9.10 PM	Current and future role of transplantation in acute leukemias in Latin America	Wellington Silva
9.10 PM – 9.50 PM	Panel discussion: How treatment in first line influences further therapy approaches in ALL and AML • Will CAR T and bispecifics change the treatment landscape? • Role of HSCT – is it still necessary? • What does the future look like? Adoption of therapies and evolving standards of care in LATAM	Elias Jabbour, Naval Daver, and all faculty
9.50 PM – 10.00 PM	Session close	Elias Jabbour

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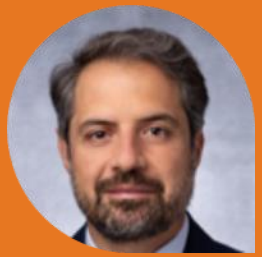
Introduction to the voting system

Elias Jabbour



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Question 1

In which country do you currently practice?

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

Question 2

Which leukemias do you primarily treat?

A. AML

B. ALL

C. Both

Question 3

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

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

Question 4

Which of the following is NOT true for treating ALL?

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

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

C. MRD– CR does not correlate strongly with outcome

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

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Review of prognostic value of MRD in ALL and AML

Phillip Scheinberg

Head, Division of Hematology

Hospital A Beneficência Portuguesa

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Disclosures

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

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

Classificação da Organização Mundial de Saúde: 2022 (5ª Edição)

Duas famílias: LMA com anormalidades genéticas definidas e LMA definida por diferenciação
A classificação de LMA NOS não é mais aplicável

Leucemia Mieloide Aguda

A maioria das LMAs com anormalidades genéticas definidas pode ser diagnosticada com <20% de mieloblastos

A LMA com mutação somática *RUNX1* não é reconhecida como um tipo distinto da doença

As LMAs com fusões raras são incorporadas como subtipos da LMA com outras alterações genéticas definidas

LMA com alterações genéticas definidas

- LPA com fusão *PML::RARA*
- LMA com fusão *RUNX1::RUNX1T1*
- LMA com fusão *CBFB::MYH11*
- LMA com fusão *DEK::NUP214*
- LMA com fusão *RBM15::MRTFA*
- LMA com fusão *BCR::ABL1*
- LMA com rearranjo *KMT2A*
- LMA com rearranjo *MECOM*
- LMA com rearranjo *NUP98*
- LMA com mutação *NPM1*
- LMA com mutação *CEBPA*
- LMA relacionada à mielodisplasia
- LMA com outras alterações genéticas definidas

LMA definida por diferenciação

- LMA com diferenciação mínima
- LMA sem maturação
- LMA com maturação
- Leucemia basofílica aguda
- Leucemia mielomonocítica aguda
- Leucemia monocítica aguda
- Leucemia eritroide aguda
- Leucemia megacarioblástica aguda

A LMA-RM substitui o termo anterior LMA "com alterações relacionadas à mielodisplasia"
A transformação da SMD e SMD/NMP continua a ser definida junto com a LMA-RM devido a suas amplas características biológicas similares

Anormalidades citogenéticas e moleculares que definem a LMA relacionada à mielodisplasia (LMA-RM)

Anormalidades citogenéticas definidoras

- Cariótipo complexo (≥3 anormalidades)
- Deleção de 5q ou perda de 5q por translocação desequilibrada
- Monossomia do 7, deleção de 7q ou perda de 7q por translocação desequilibrada
- deleção de 11q
- deleção de 12p ou perda de 12p por translocação desequilibrada
- Monossomia do 13 ou deleção de 13q
- deleção de 17p ou perda de 17p por translocação desequilibrada
- Isocromossomo 17q
- cromossomo X isodicêntrico, idic(X)(q13)

Mutações somáticas definidoras

- *ASXL1*
- *BCOR*
- *EZH2*
- *SF3B1*
- *SRSF2*
- *STAG2*
- *U2AF1*
- *ZRSR2*

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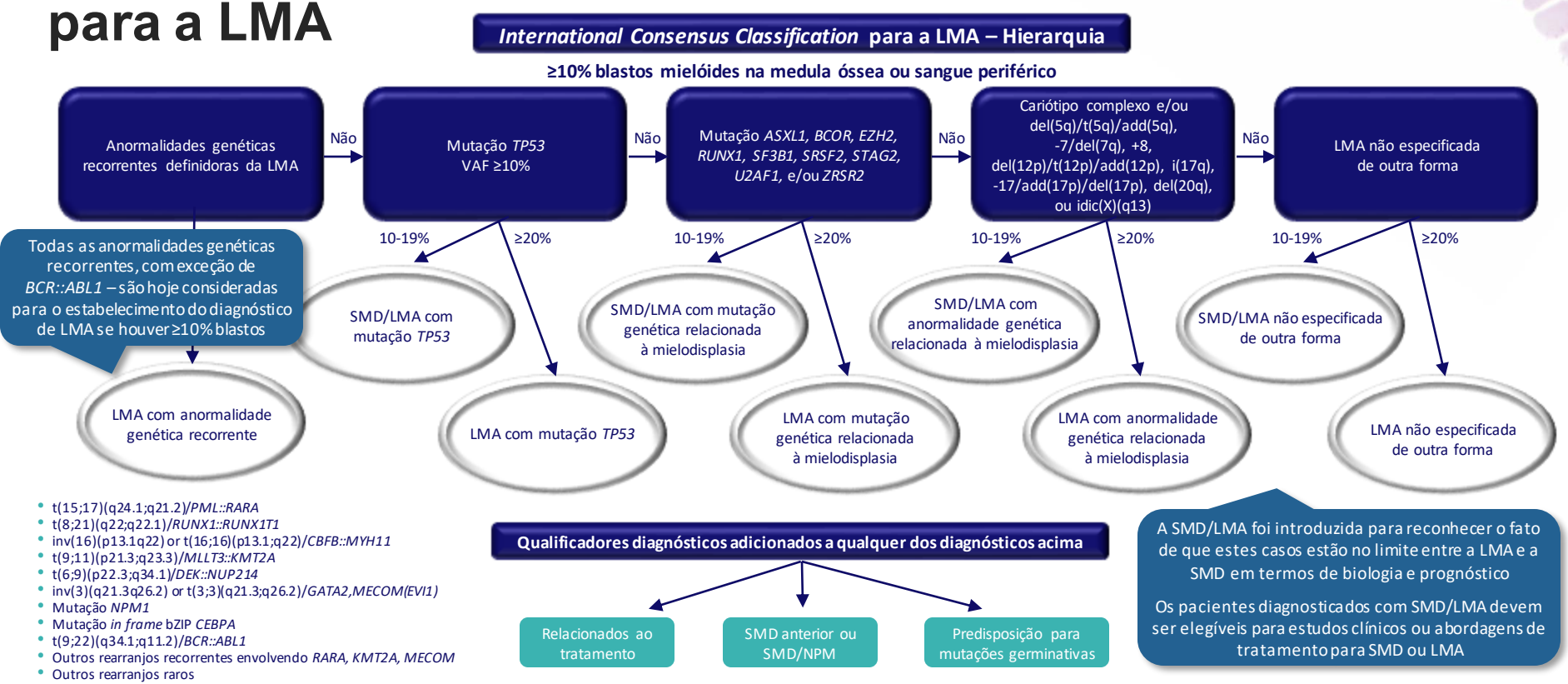
LMA: Leucemia Mieloide Aguda; **SMD:** Síndrome mielodisplásica; **NMP:** neoplasia mieloproliferativa; **NOS:** não especificada de outra forma; **LPA:** leucemia promielocítica aguda; **LMA-RM:** leucemia relacionada à mielodisplasia; Khoury JD, et al. Leukemia. 2022;36(7):1703-1719.

Hierarquia do *International Consensus Classification* (ICC) para a LMA



- t(15;17)(q24.1;q21.2)/*PML::RARA*
- t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*
- t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*
- t(6;9)(p22.3;q34.1)/*DEK::NUP214*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)*
- Mutação *NPM1*
- Mutação *in frame* bZIP *CEBPA*
- t(9;22)(q34.1;q11.2)/*BCR::ABL1*
- Outros rearranjos recorrentes envolvendo *RARA, KMT2A, MECOM*
- Outros rearranjos raros

Qualificadores diagnósticos adicionados a qualquer dos diagnósticos acima

- Relacionados ao tratamento
- SMD anterior ou SMD/NPM
- Predisposição para mutações germinativas

A SMD/LMA foi introduzida para reconhecer o fato de que estes casos estão no limite entre a LMA e a SMD em termos de biologia e prognóstico

Os pacientes diagnosticados com SMD/LMA devem ser elegíveis para estudos clínicos ou abordagens de tratamento para SMD ou LMA

LMA: Leucemia Mieloide Aguda; **SMD:** Síndrome mielodisplásica; **NMP:** neoplasia mieloproliferativa; **VAF:** frequência de variants dos alelos.

1. Arber DA, et al. Blood. 2022 Jun 29;blood.2022015850. doi: 10.1182/blood.2022015850. Online ahead of print.
2. Döhner H, et al. Blood. 2022 Jul 7;blood.2022016867. doi: 10.1182/blood.2022016867. Online ahead of print.

Classificação de risco da ELN: 2022 vs 2017

Categoria de risco	ELN 2022
Favorável	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) ou t(16;16)(p13.1q22)/*CBFB::MYH11* • Mutação *NPM1* sem *FLT3*-ITD • Mutação *inframe* bZIP *CEBPA*
Intermediário	• Mutação *NPM1* com *FLT3*-ITD • *NPM1* tipo selvagem com *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Anormalidades citogenéticas e/ou moleculares não classificadas como favoráveis ou adversas
Adverso	• t(6;9)(p23;q34.1)/*DEK::NUP214* • Rearranjo t(v;11q23.3)/*KMT2A* • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11:p13)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) ou t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)* • Rearranjo t(3q26.2;v)/*MECOM(EVI1)* • -5 ou del(5q); -7; -17/abn(17p) • Cariótipo complexo ou monossomia • Mutação *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* ou *ZRSR2* • Mutação *TP53*

Favorável independentemente de ser mono ou bialélica

A proporção alélica de FLT3-ITD não é mais considerada na classificação de risco

A LMA com mutação *NPM1* e anormalidades citogenéticas de risco adverso é classificada como risco adverso

Anromalidades genéticas adicionais

Excluídos cariótipos hiperdiploides com ≥3 trissomias (ou polissomias) sem anormalidades estruturais

LMA com mutações genéticas relacionadas à mielodisplasia agora é classificada como risco adverso

NOTA:

- A classificação e risco da ELN para a LMA foi desenvolvida com base em dados de pacientes tratados intensivamente e pode necessitar de modificações para pacientes recebendo terapias menos intensivas
- A classificação inicial de risco pode ser alterada durante o curso de tratamento com base nos resultados de análise de DRM

LMA: Leucemia Mieloide Aguda; ELN: European Leukemia Net; DRM: doença residual mínima.

Döhner H, et al. *Blood*. blood.2022016867.

MRD Monitoring

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

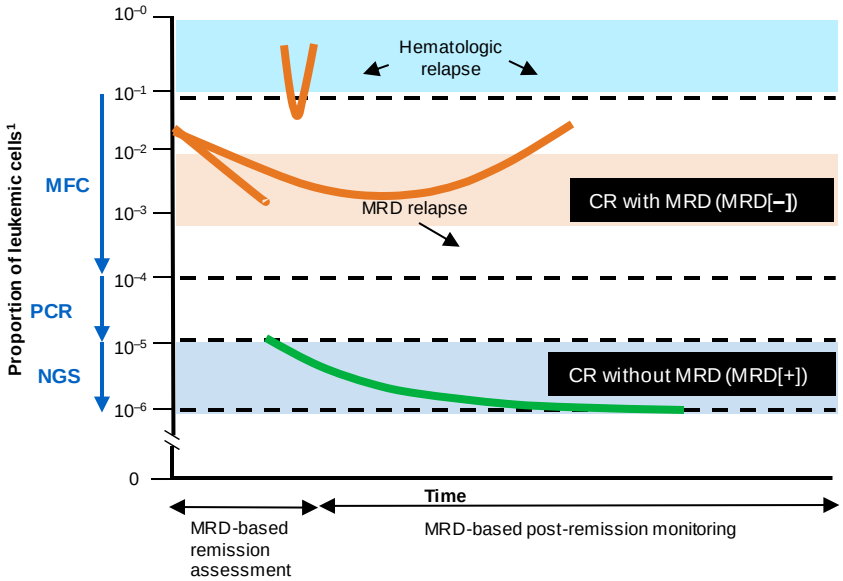
Flow Cytometry	Molecular Biology
Aspirate 5−10 mL BM and use the first pull for MRD assessment	Aspirate 5−10 mL BM and use the first pull for MRD assessment
Use 500,000 to 1,000,000 white blood cells	Patients with mutant *NPM1, RUNX1-RUNX1T1, CBFB-MYH11,* or *PML-RARA* should have molecular assessment 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, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel.*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.

Measurable Residual Disease

- Eradication of even the tiniest remnants of disease after therapy is likely to be a requirement for cure in AML
- Strongly prognostic for clinical outcomes and may have therapeutic implications in the management of AML
- Little consensus regarding its utility to guide treatment decisions

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



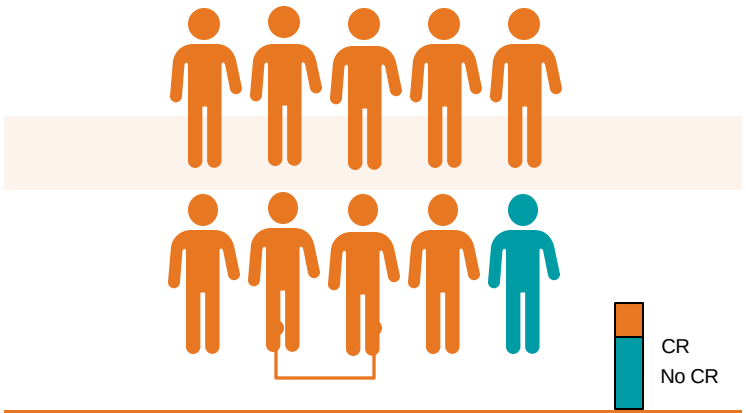
- MRD is defined as the presence of detectable leukemic cells (generally >10^{-4} or 0.01%) within the BM during remission[5,6]
- Studies collectively show the high prognostic value of MRD (both during and after initial induction therapy) in assessing relapse risk for patients with ALL[2]
- Patients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

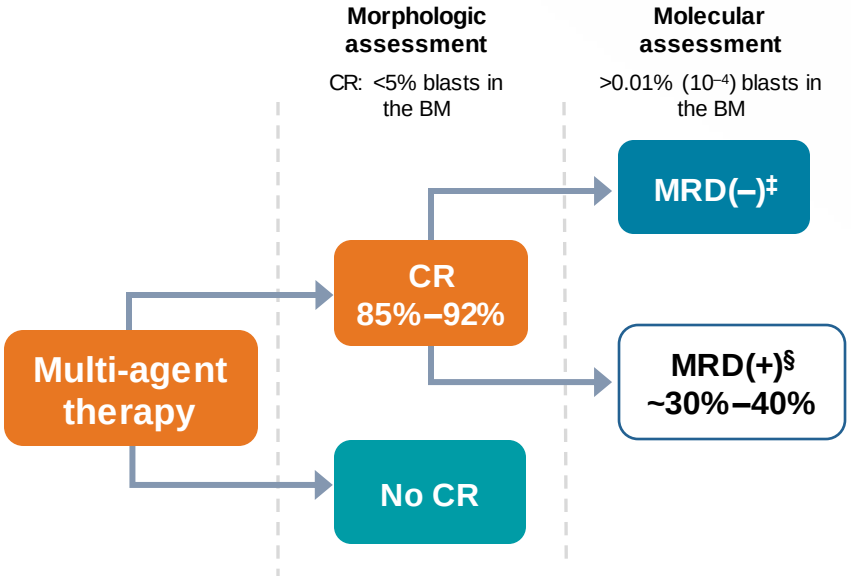
Patients Who Achieve CR May Still Harbor MRD[1-6]

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[1]

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

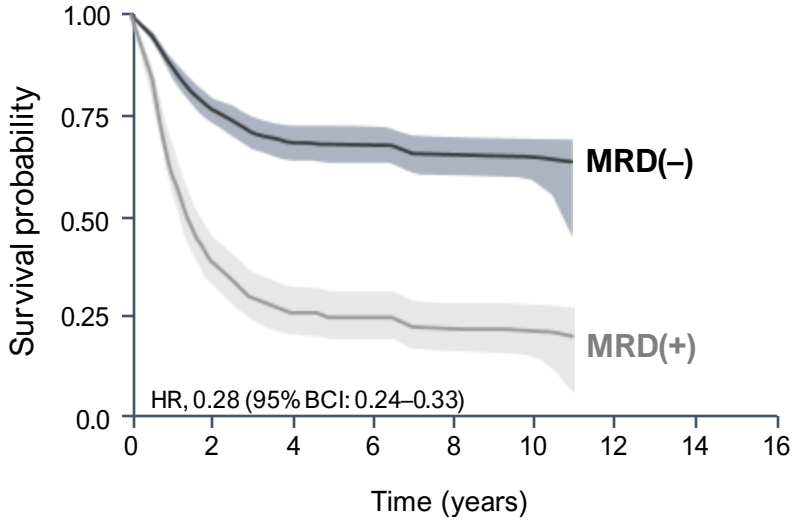
ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; MRD, measurable/minimal residual disease; Ph, Philadelphia chromosome.

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

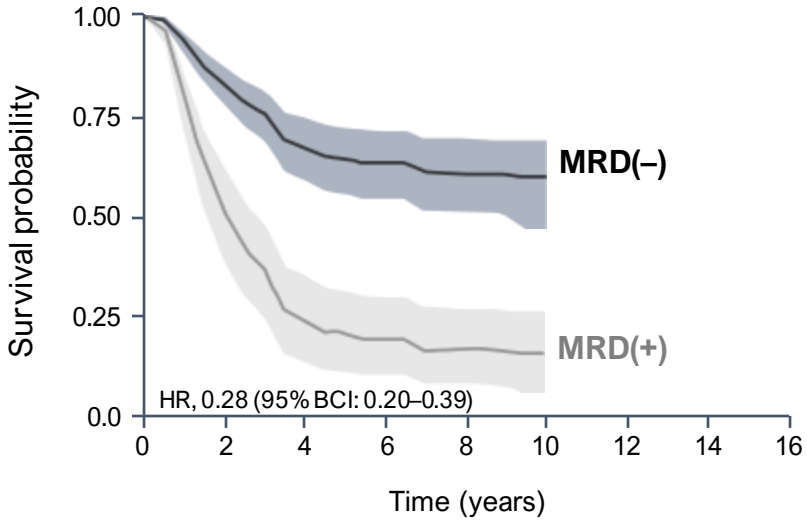
MRD Status Has Been Shown to Be a Predictor of EFS and OS in Adult Patients With ALL

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

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



OS for Adult ALL: 5 Studies With 806 Patients



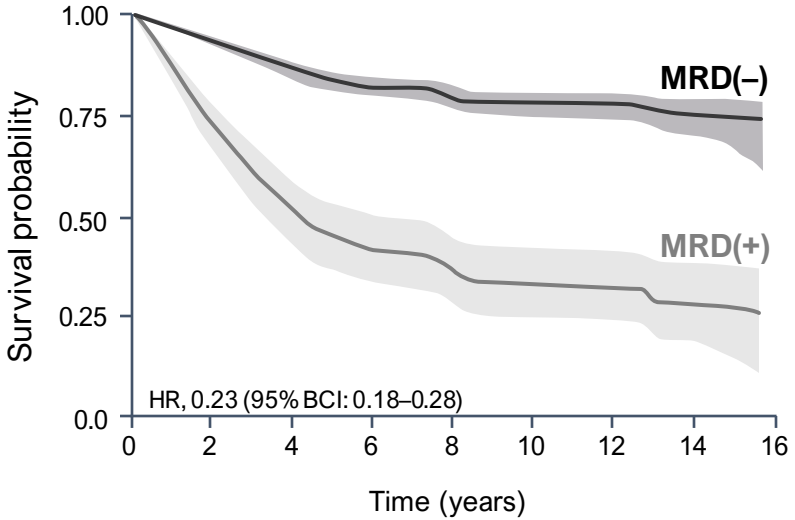
These data include various treatments and are not intended to make any sort of survival claim, nor is the benefit specific to any treatment.

This information is presented for the purpose of demonstrating the utility of MRD testing as a prognostic indicator in B-ALL. Treatment decisions are the sole discretion of the healthcare provider.
ALL, acute lymphoblastic leukemia; BCI, Bayesian credible intervals; EFS, event-free survival; HR, hazard ratio; MRD, measurable/minimal residual disease; OS, overall survival.
Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

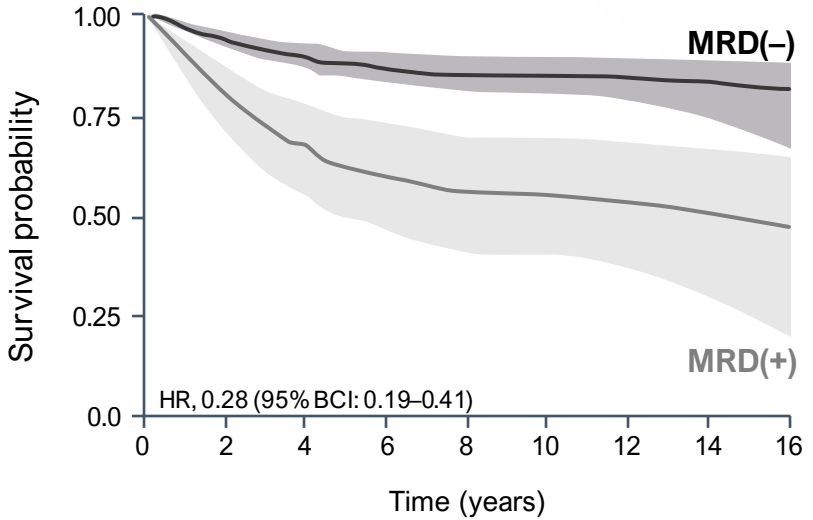
MRD Status Has Been Shown to Be a Predictor of EFS and OS in Pediatric Patients With ALL

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

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



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



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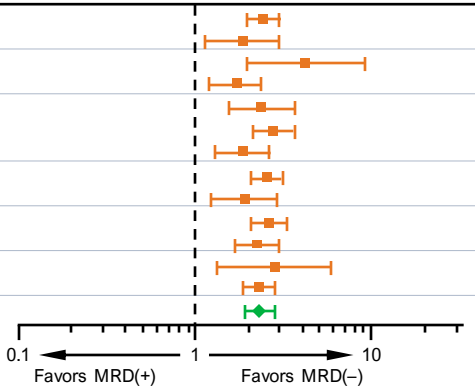
ALL, acute lymphoblastic leukemia; BCI, Bayesian credible intervals; EFS, event-free survival; HR, hazard ratio; MRD, measurable/minimal residual disease; OS, overall survival.
Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

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 time points 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]

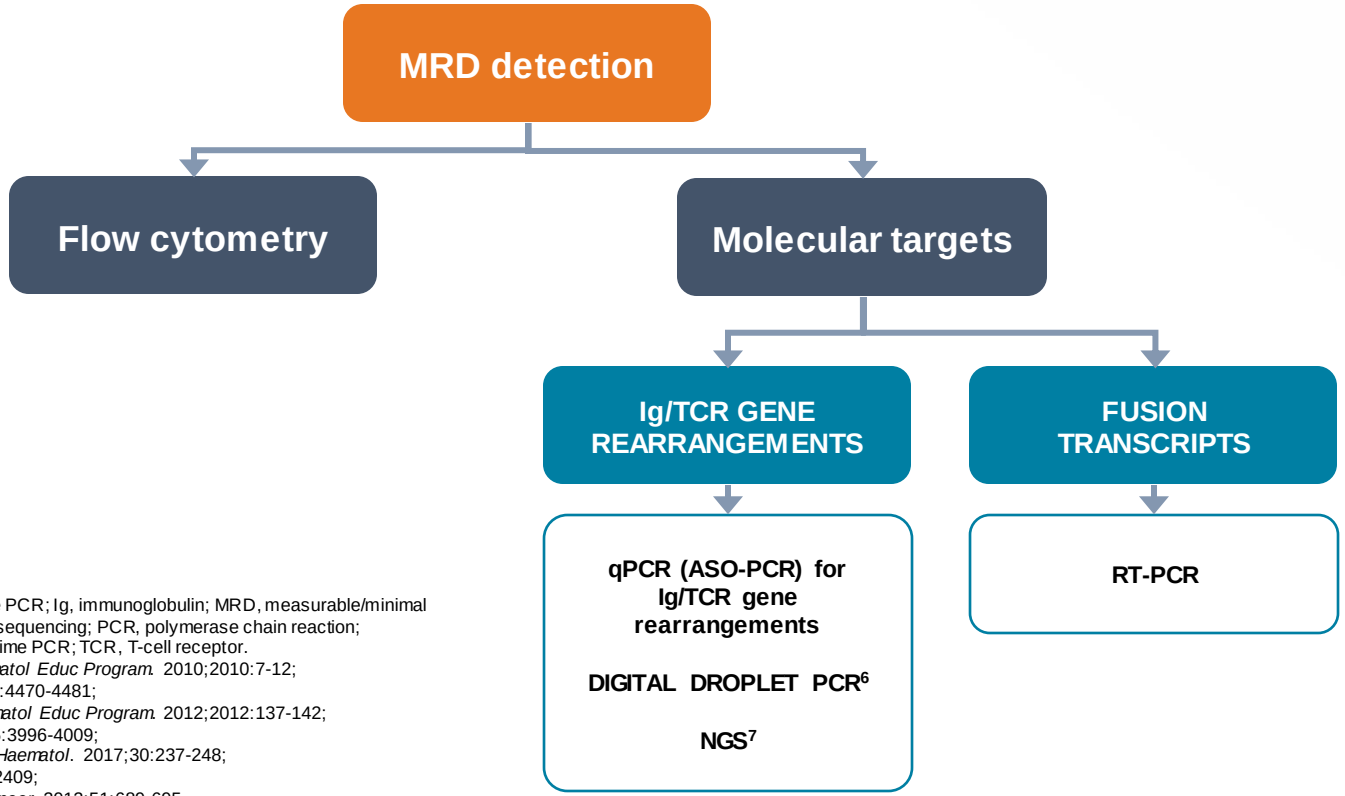
NCCN Guidelines state that the optimal sample for MRD testing is the first pull of the bone marrow aspirate[1]

- 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.

MRD Testing Methodologies[1-5]



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

1. Campana D. *Hematology Am Soc Hematol Educ Program*. 2010;2010:7-12;
2. Brüggemann M, et al. *Blood*. 2012;120:4470-4481;
3. Schrappe M. *Hematology Am Soc Hematol Educ Program*. 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. Taylor SC, et al. *Nat Sci Rep*. 2017;7:2409;
7. Thol F, et al. *Genes Chromosomes Cancer*. 2012;51:689-695.

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	• 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)

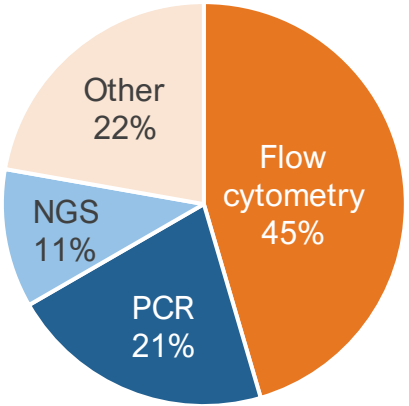
ASO-PCR, allele-specific oligonucleotide PCR; FDA, US Food and Drug Administration; Ig, immunoglobulin; MRD, measurable/minimal residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-qPCR, real-time quantitative PCR; TCR, T-cell receptor.

1. Campana D. *Hematology Am Soc Hematol Educ Program*. 2010;2010:7-12; 2. Brüggemann M, et al. *Blood*. 2012;120:4470-4481; 3. Schrappe M. *Hematology Am Soc Hematol Educ Program*. 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.

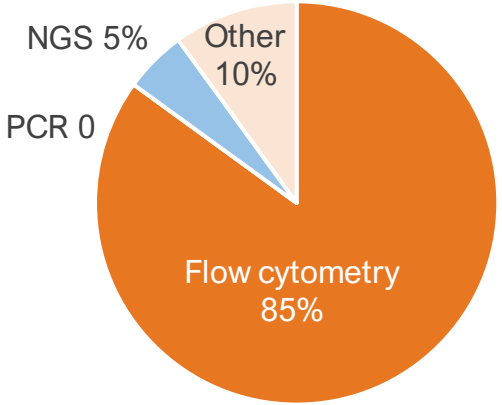
Flow Cytometry Is the Most Commonly Used Method of MRD Detection in the US

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

Adult B-ALL (n = 150)



Pediatric B-ALL (n = 30)



While flow cytometry is frequently used in the US,
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.

Advantages and Parameters of Flow Cytometry[1-5]

Advantages[1]

- Applicable for >90% of ALL cases
- Sensitivity of 10^{-3} to 10^{-4}
- Rapid results (few hours) to evaluate responses after induction
- Fresh samples; requires immediate analysis
  - Challenges for MRD referral and central evaluation
- Standardized by EuroFlow Consortium

Parameters

- Total number of cells analyzed[1-3]
  - Dependent on total numbers of cells analyzed
  - More than 4 million cells should be analyzed to consistently achieve a sensitivity of at least 10^{-3} by 8-color flow cytometry
- 6 vs 8 colors[1,2]
  - 10^{-2} vs 10^{-3}
  - Validation studies and patient reports to include LOD
- Sample quality (first pull vs others), viability (necrotic)[1,3,4]
- Days from therapy (regenerating hematogones)[5]
- Sample type: BM vs PB[1,6]

ALL, acute lymphoblastic leukemia; BM, bone marrow; LOD, limit of detection; MRD, measurable/minimal residual disease; PB, peripheral blood.

1. Della Starza I, et al. *Front Oncol*. 2019;9:726; 2. Theunissen P, et al. *Blood*. 2017;129:347-357; 3. Sedek L, et al. *Cancers*. 2022;14:473; 4. 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; 5. DiGiuseppe JA, Wood BL. *Cytometry B Clin Cytom*. 2019;96:256-265; 6. Short NJ, et al. *AmJ Hematol*. 2019;94:257-265.

Challenges With Flow Cytometry

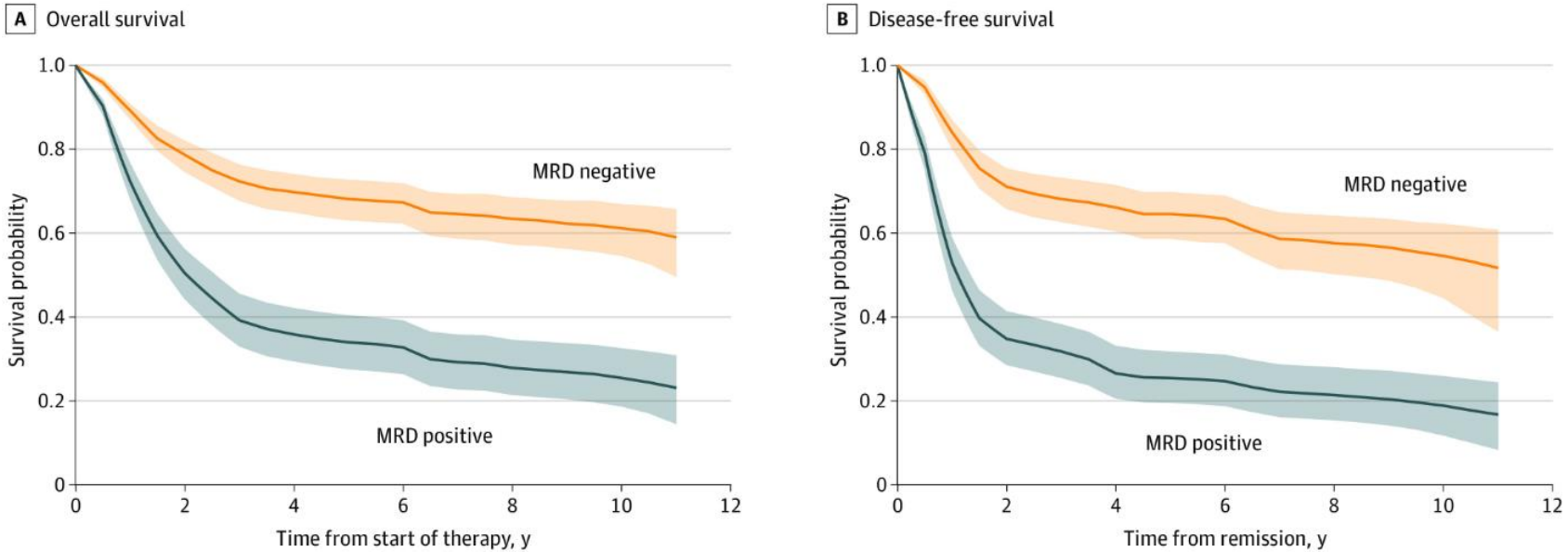
- Validated in complex flow labs at tertiary care academic centers[1]
- Flow cytometry protocols and antibody panels are variable across institutions[2]
- Technical expertise needs extensive standardization[3]
- Expert review for interpretation
  - Erroneous interpretations with low sample quality (hypocellularity post-induction)[2]
  - False negativity resulting from immunophenotypic shifts of confounding regenerating blasts[2]
  - Possibility of CD19-negative relapse – following anti-CD19 therapies[4]

CD, cluster of differentiation.

1. Theunissen P, et al. *Blood*. 2017;129:347-357; 2. Chen X, Wood BL. *Best Pract Res Clin Hematol*. 2017;30:237-248;
3. van Dongen JJM, et al. *Blood*. 2015;125:3996-4009; 4. Jabbour E, et al. *AmJ Hematol.* 2018;93:371-374.

MRD in AML

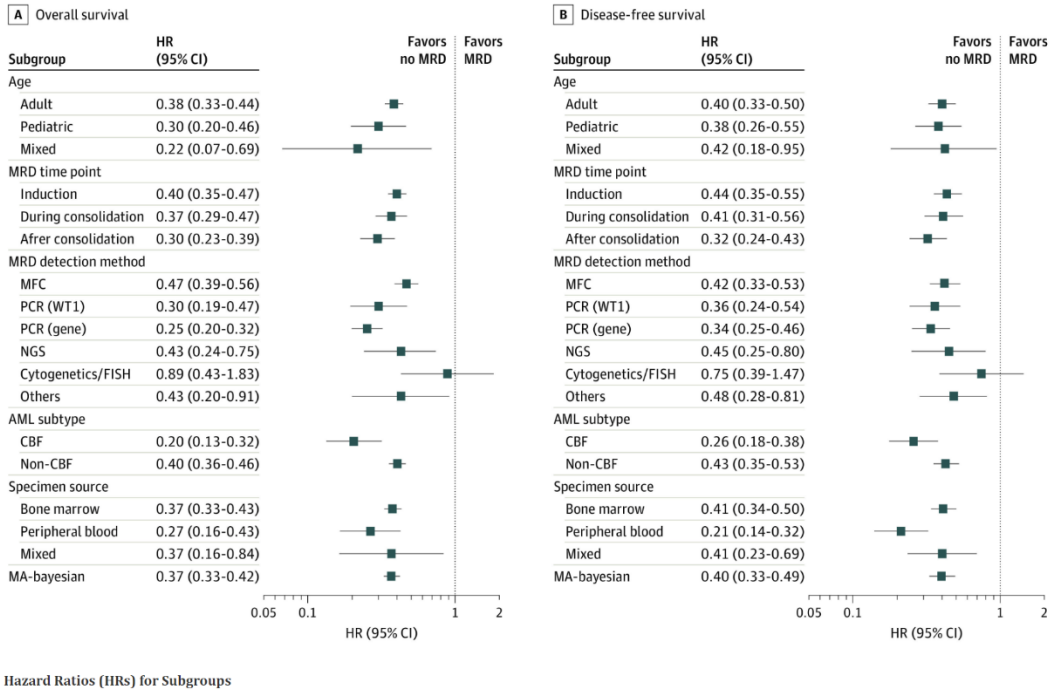
- In the context of MRD assessment, targeted NGS is commonly used for serial assessment of mutations found at diagnosis
- Caution, as several AML-associated mutations (eg, *DNMT3A, TET2, ASXL1*) are associated with CHIP (DTA)
- A meta-analysis of 81 trials with over 11,000 patients found strong associations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



Estimated Survival Curves, Stratified by Measurable Residual Disease (MRD) Status

Short NJ, et al. *JAMA Oncol*. 2020;6:1890-1899.

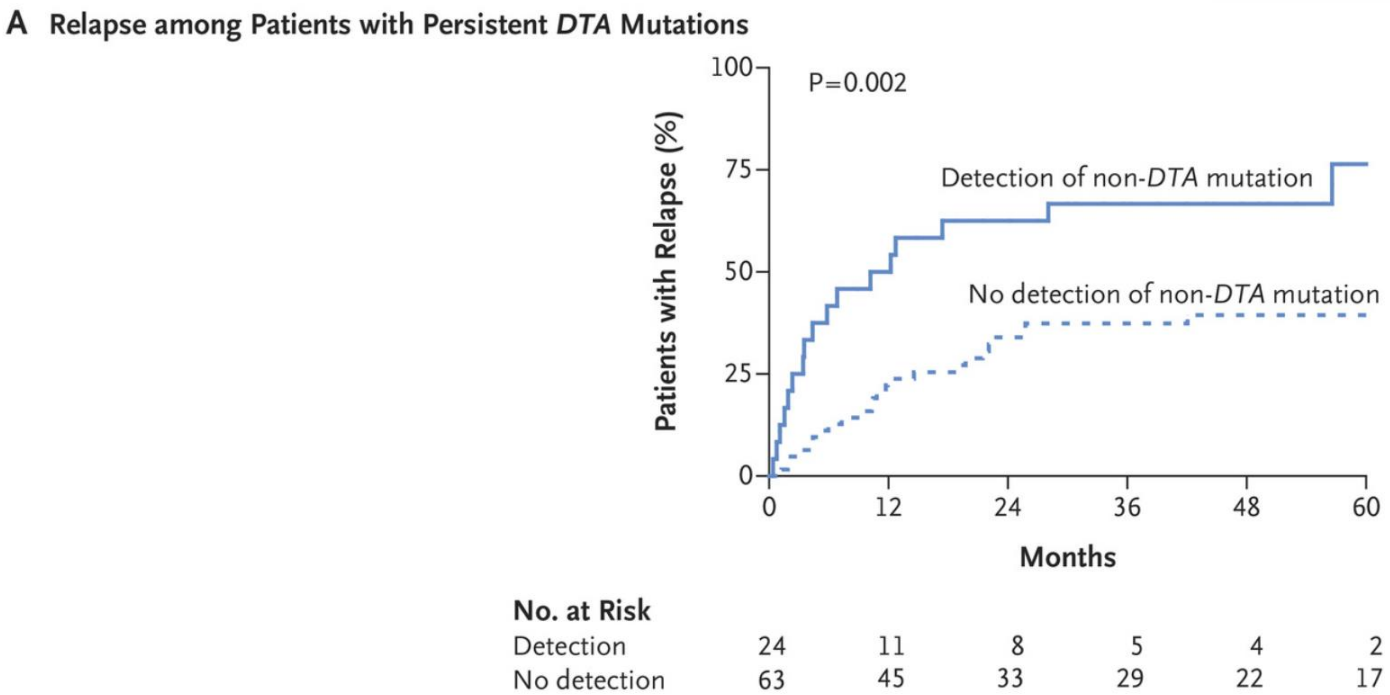
MRD in AML



Hazard Ratios (HRs) for Subgroups

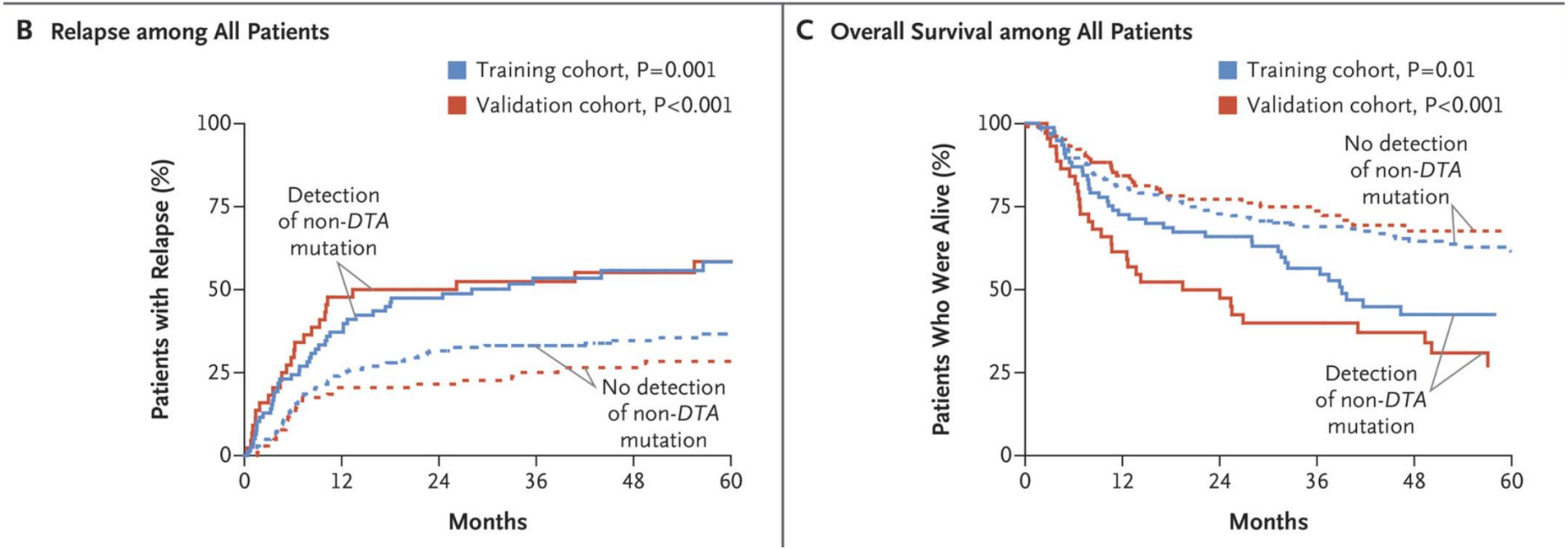
Short NJ, et al. *JAMA Oncol*. 2020;6:1890-1899.

MRD in AML



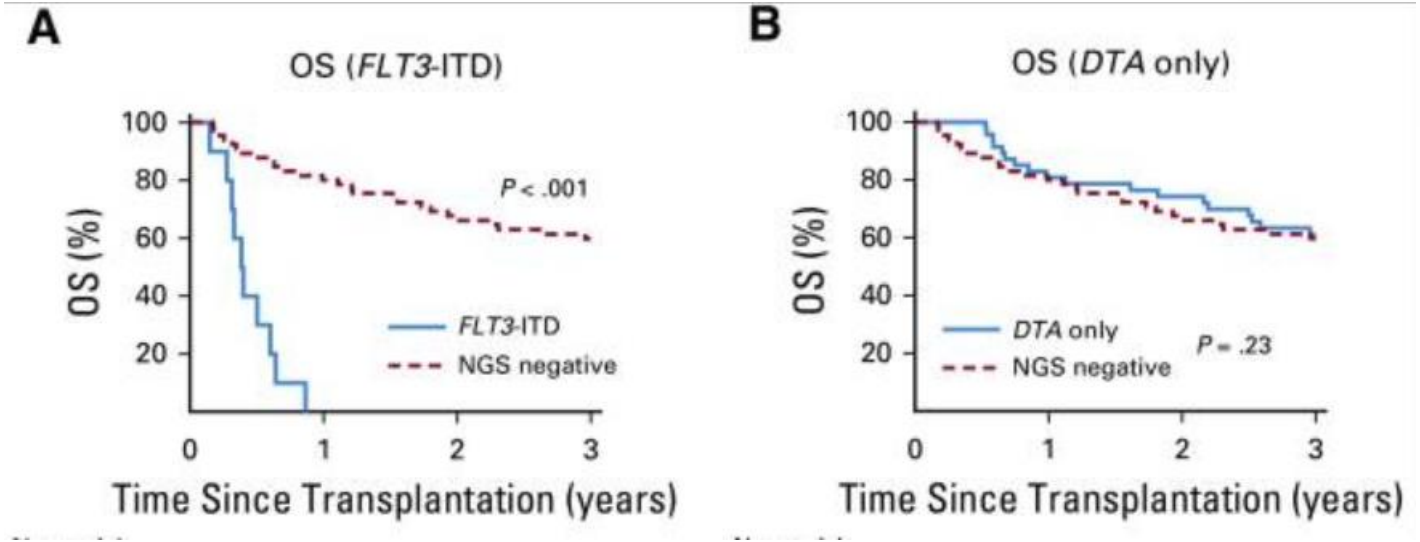
Jongen-Lavrencic M, et al. *N Engl J Med*. 2018;378:1189-1199.

MRD in AML



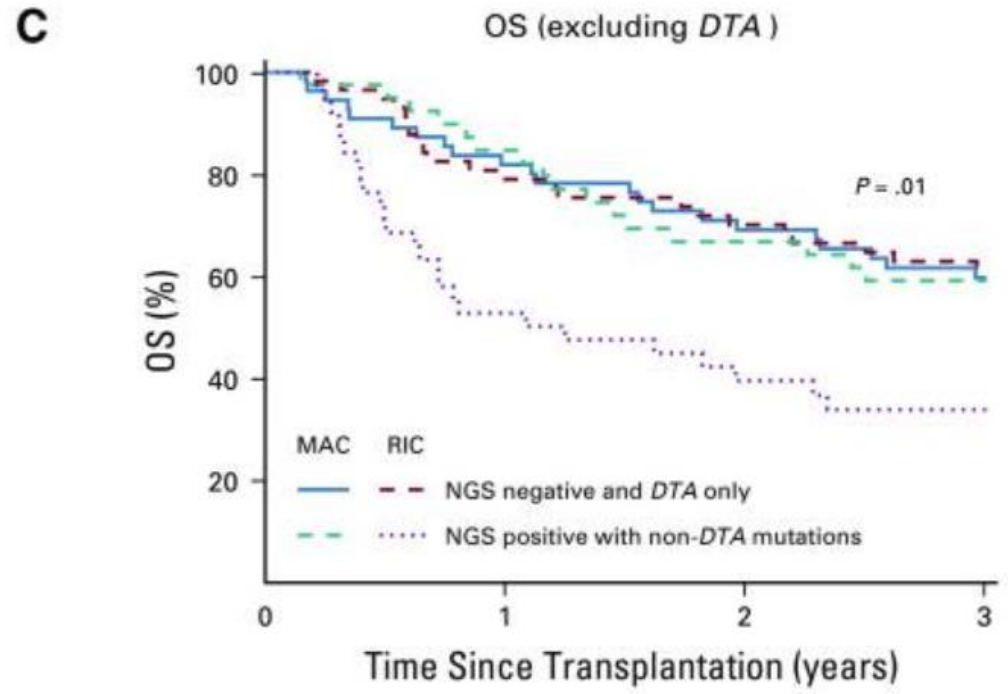
Jongen-Lavrencic M, et al. *N Engl J Med*. 2018;378:1189-1199.

MRD in AML



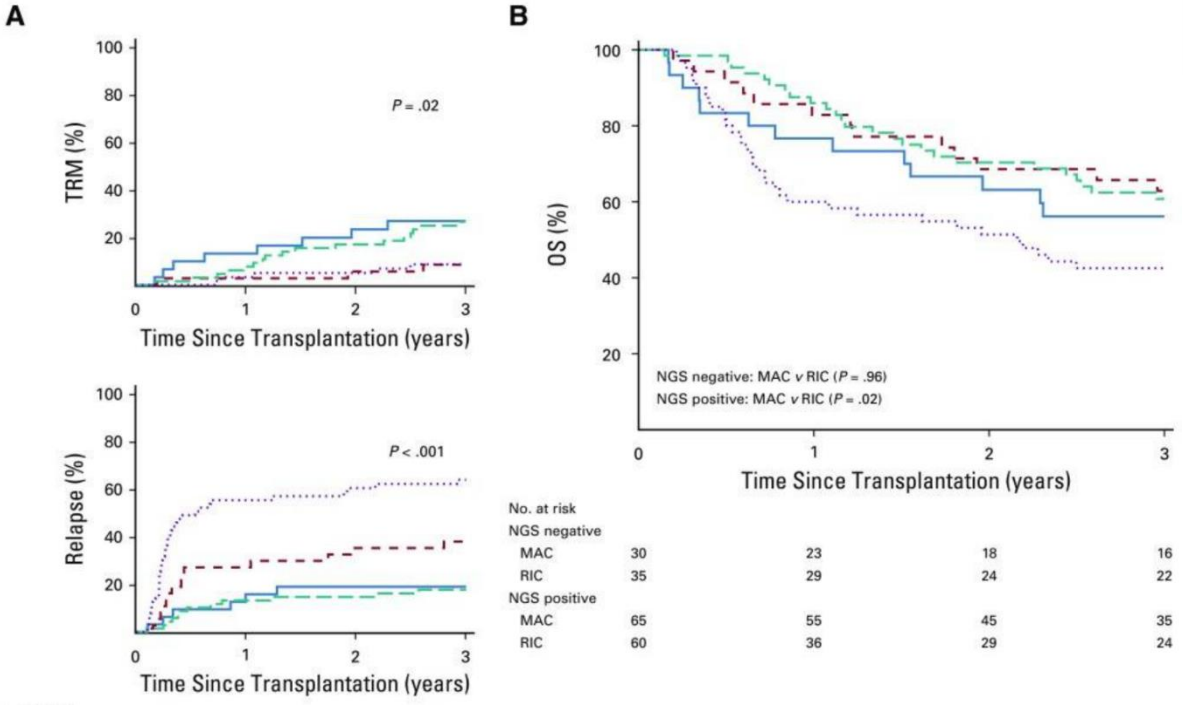
Hourigan CS, et al. *J Clin Oncol.* 2020;38:1273-1283.

MRD in AML



Hourigan CS, et al. *J Clin Oncol.* 2020;38:1273-1283.

MRD in AML

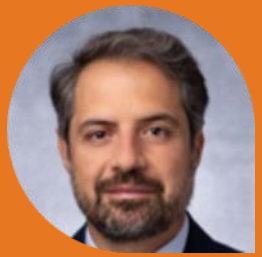


Hourigan CS, et al. *J Clin Oncol.* 2020;38:1273-1283.

Global Leukemia Academy

Latest achievements and developments in ALL and AML

Elias Jabbour



APTITUDE HEALTH®

Latest achievements and developments in ALL and AML

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

2023

Classification of Leukemias Today

Easy Leukemias (5/10-yr survival 70+%)	Intermediate Leukemias (5-yr survival 40%–70%)	A Bit Difficult Leukemias (5-yr survival <40%)
HCL, APL, CBF AML	Older ALL	Older AML
CML	Younger AML	Rx related/2nd AML
CLL		Complex CG,TP53, MECOM,t(11q23;xx)
Ph-positive ALL; Younger ALL		

Leukemia Research: Progress in 2023

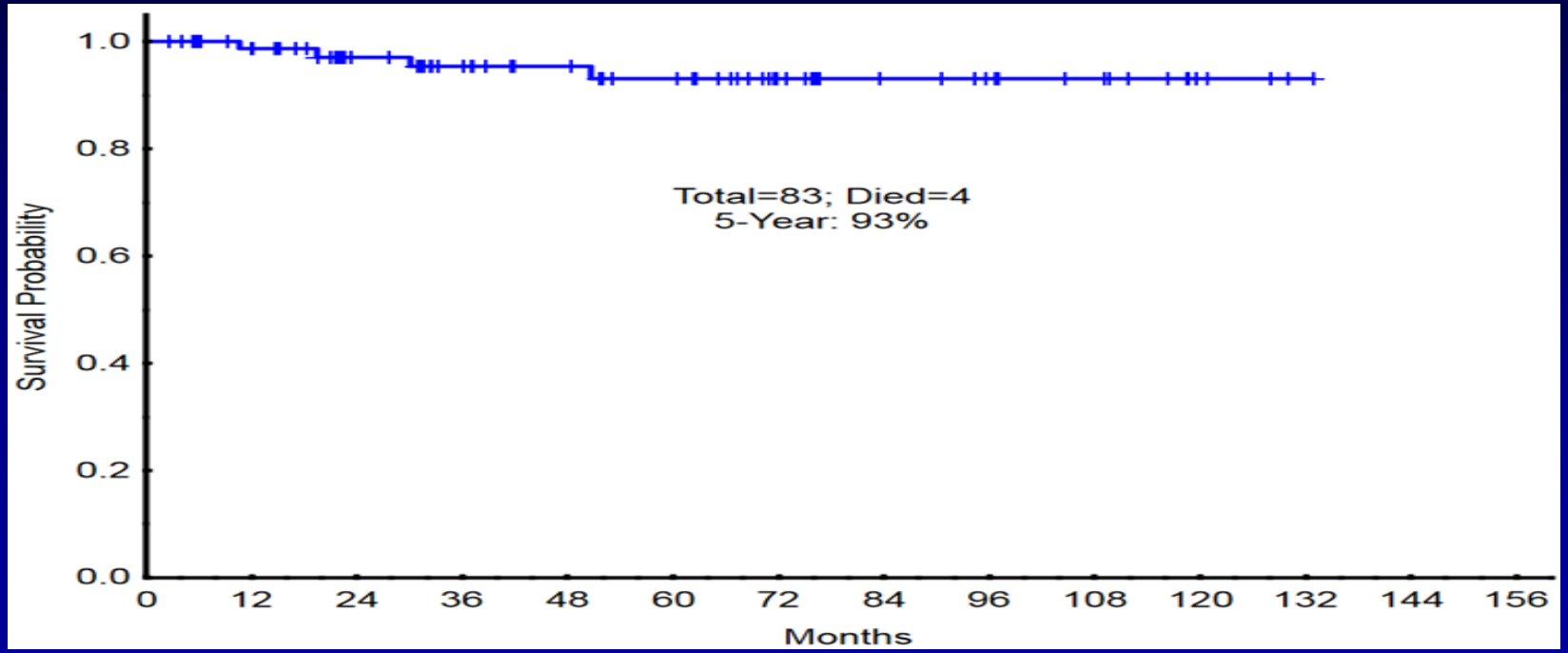
Disease	Therapies	% cure/10-yr survival
Hairy cell leukemia	CDA + rituximab	90
APL	ATRA + arsenic	80–90
CBF AML	FLAG-GO/IDA	80–90
AML – younger	FLAG-IDA-VEN and CLIA-VEN + FLT3i/IDHi; MoAbs	60+
AML – older	Triple-nucleoside + venetoclax low intensity Rx, FLT3i/IDHi, MoAbs,	20 → 50+?
ALL	ChemoRx + CD19/CD22/CD20 Abs	50 → 80
Ph+ ALL	Ponatinib-blinatumomab	70–80+??
CML	Bcr-Abl1 TKIs	90
CLL	Ibrutinib + venetoclax ± CD20 MoAbs	80–90+?

The “Easy” Leukemias

- HCL
- APL
- CBFAML
- CML
- CLL
- Ph-positive ALL and younger ALL

Hairy Cell Leukemia: Survival with CDA + Rituximab

- CDA 5.6 mg/m^2 daily ×5, followed by rituximab 375 mg/m^2 weekly ×8
- CR rate 100%; 10-year DFS 80%



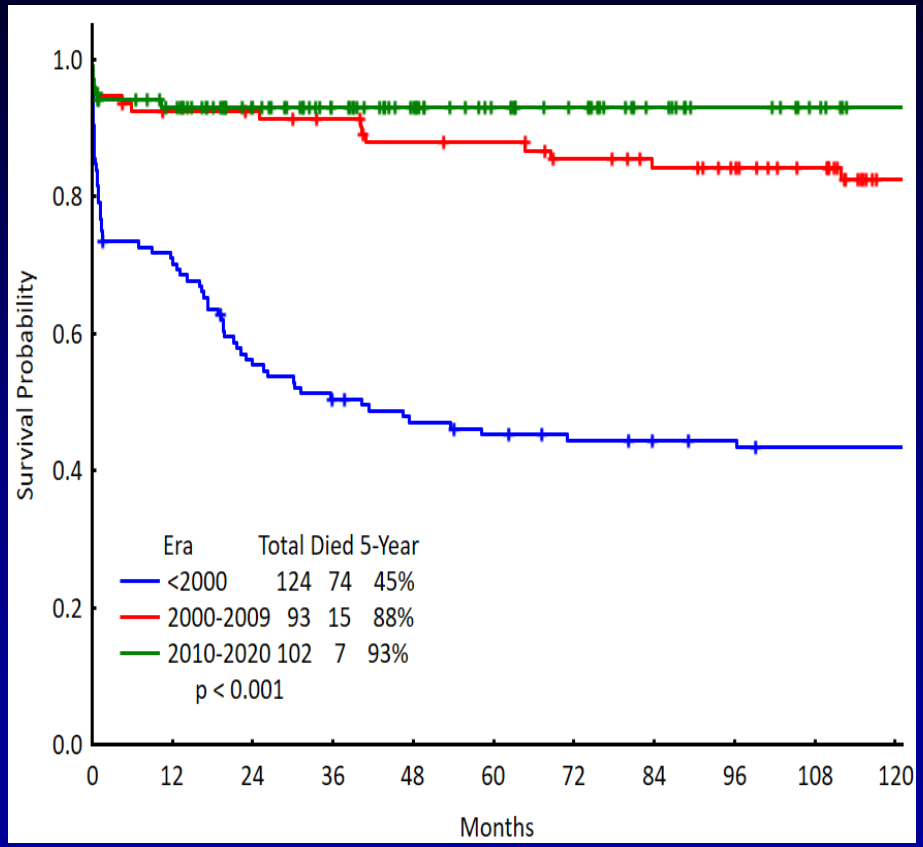
Chihara. BJH. March 2016.

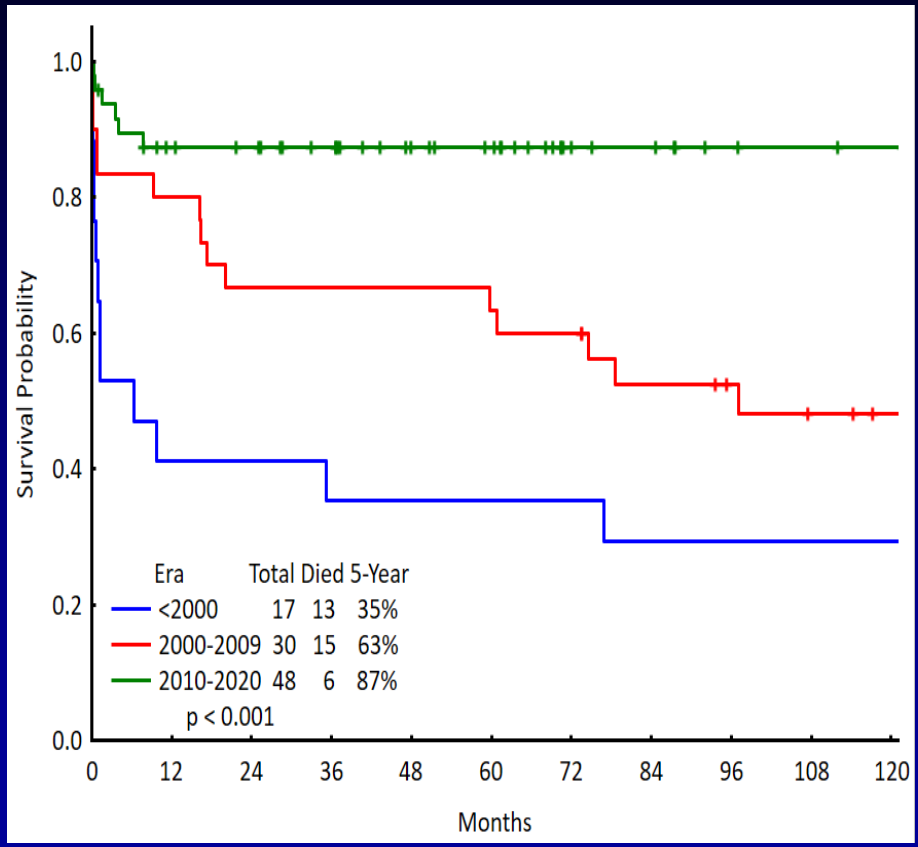
ATRA + As_2O_3 Without Chemotherapy in APL: MD Anderson Experience

- **Induction**
  - ATRA 45 mg/m^2/D until CR
  - As_2O_3 0.15 mg/kg/D until CR
  - Gemtuzumab (GO) 9 mg/m^2 × 1 if WBC >10 × 10^9/L
- **Maintenance**
  - ATRA 45 mg/m^2/D × 2 wk Q mo × 6
  - As_2O_3 0.15/kg/D × 4 wk Q2 mo × 3
  - GO in PCR+

Ravandi F, et al. *J Clin Oncol*. 2009;27:504-510.

APL Young and Old: MDACC





Courtesy of Dr Kantarjian.

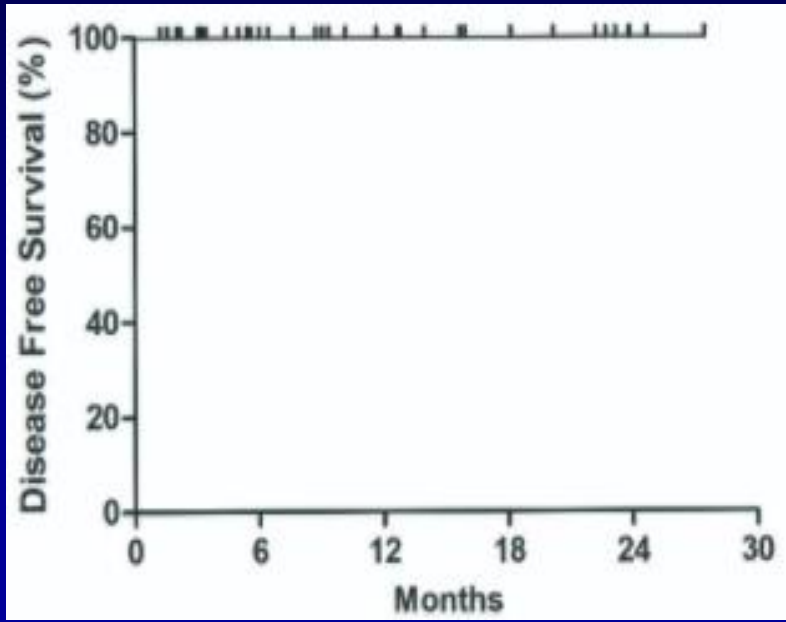
MDACC: FLAG-GO in CBF-AML

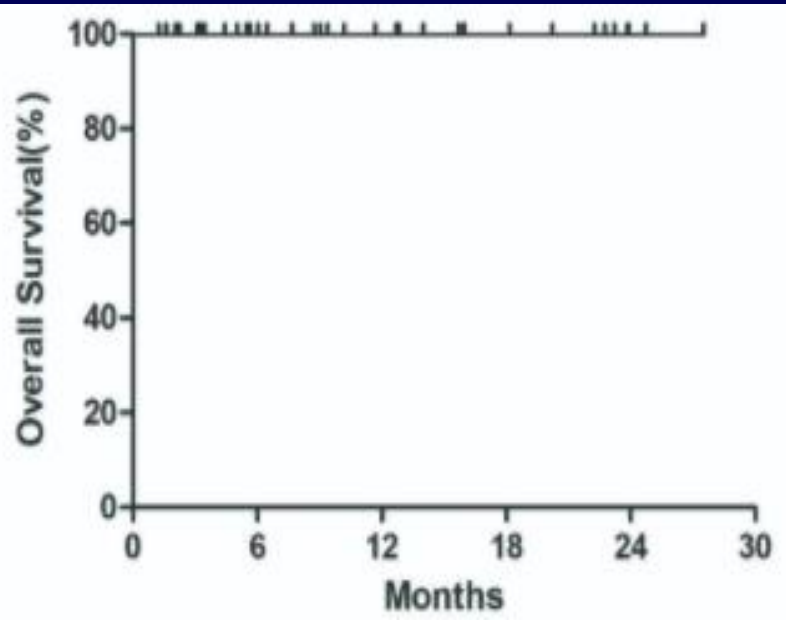
- Induction: fludarabine (FL) 30 mg/m^2 days 1–5; cytarabine (A) 2 g/m^2 IV days 1–5; gemtuzumab ozogamicin (GO) 3 mg/m^2 day 1; G-CSF (G) 5 μg/kg day –1 until neutrophils recovery (can use pegfilgrastim 6 mg × 1 day 4)
- Consolidation: FA × 3 days for 5 courses; GO in 2–3 courses
- Replaced GO with low-dose idarubicin 6 mg/m^2 days 3 and 4 after patient 50 – results worse

Personal communication from Dr Kantarjian.

ATRA + Realgar Indigo (oral arsenic) in APL

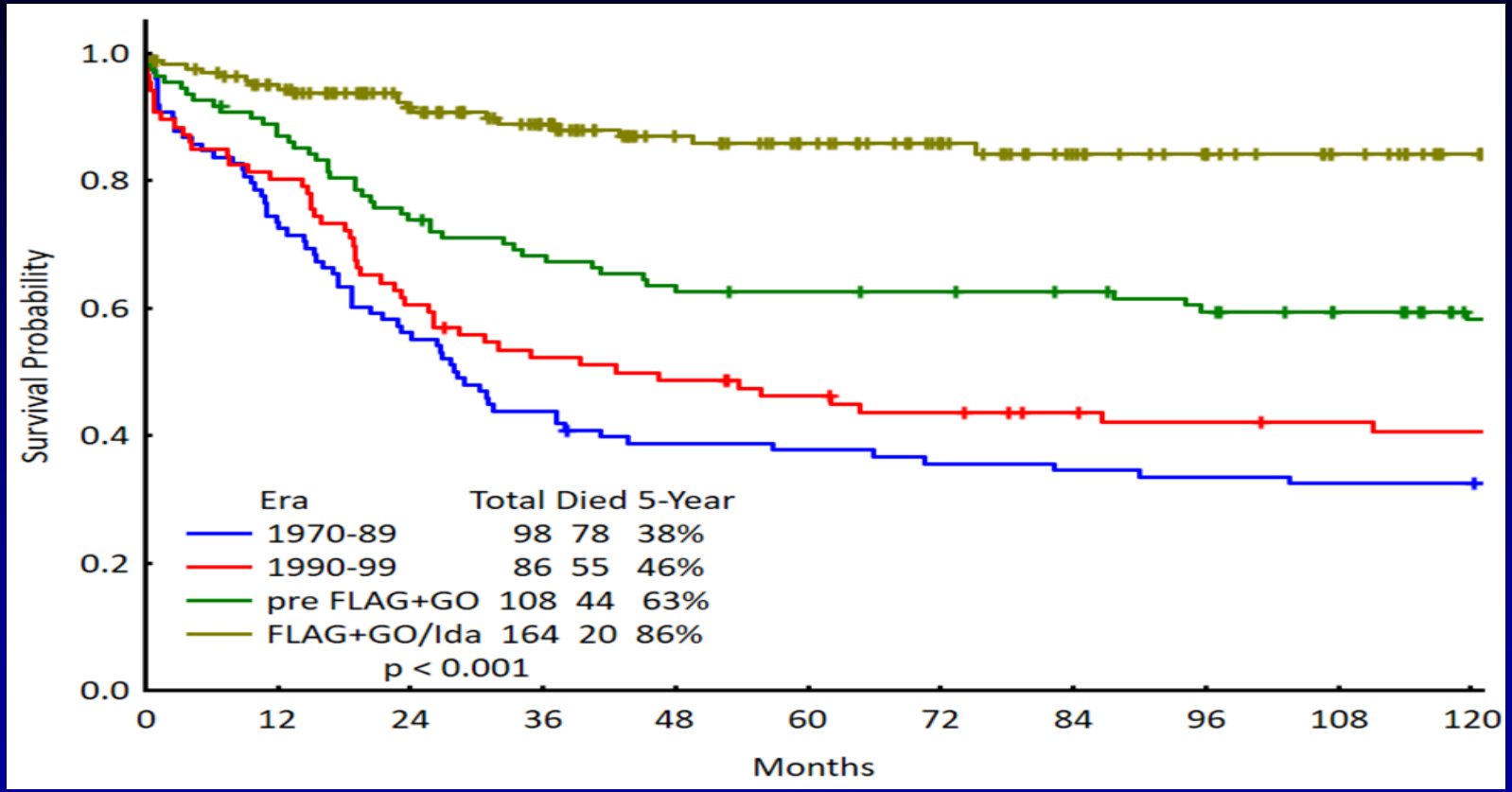
- 38 pts Rx post induction with oral ATRA + realgar 60 mg/kg daily 4 wks on, 4 wks off, ×7 courses. Median age 47 yrs (18–77)
- CMR 100%; no relapses





Zhu et al. *Blood*. 2021;138:abstract 873.

FLAG-GO/IDA in CBF-AML: Survival

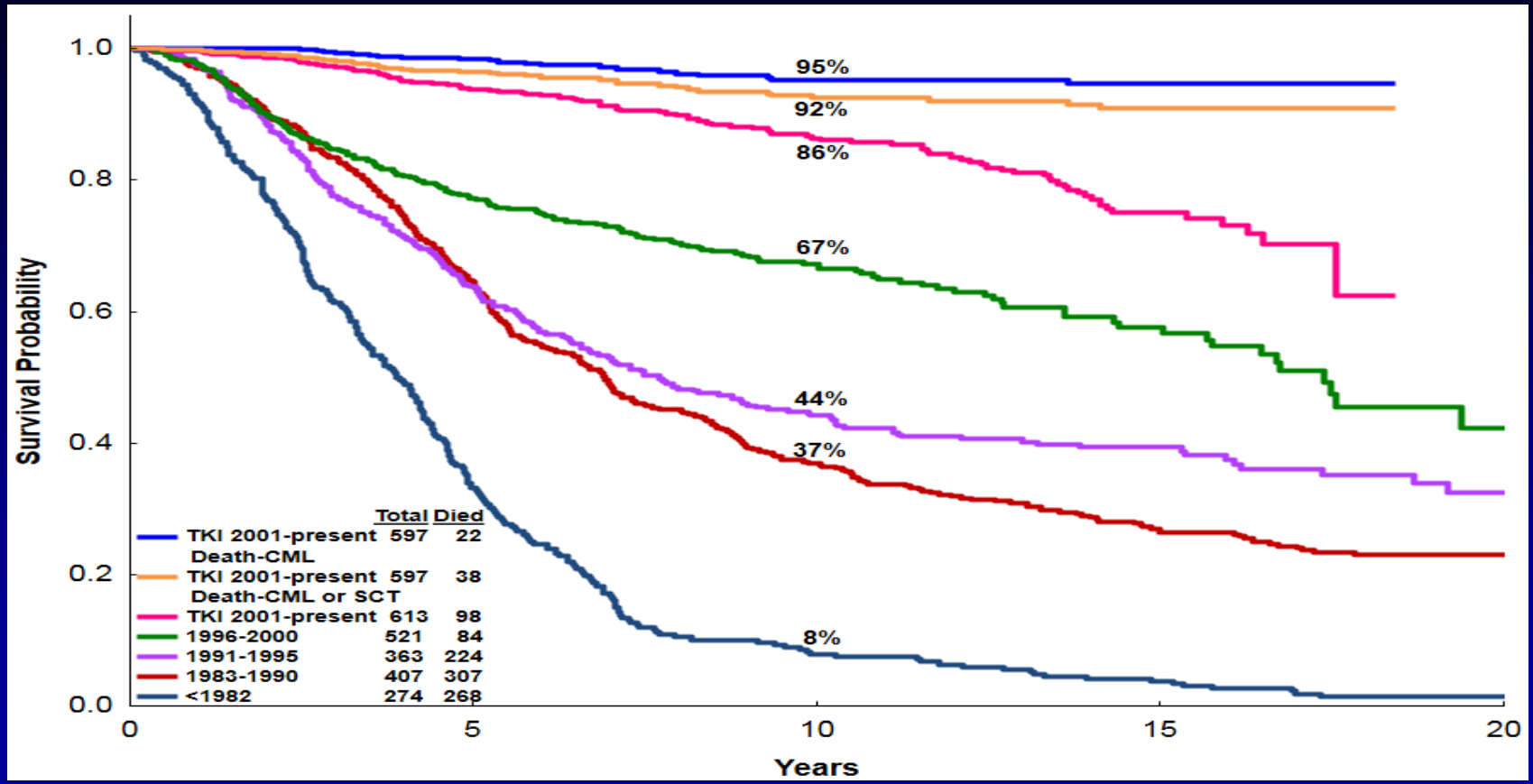


Courtesy of Dr Kantarjian.

Therapy of CML in 2023

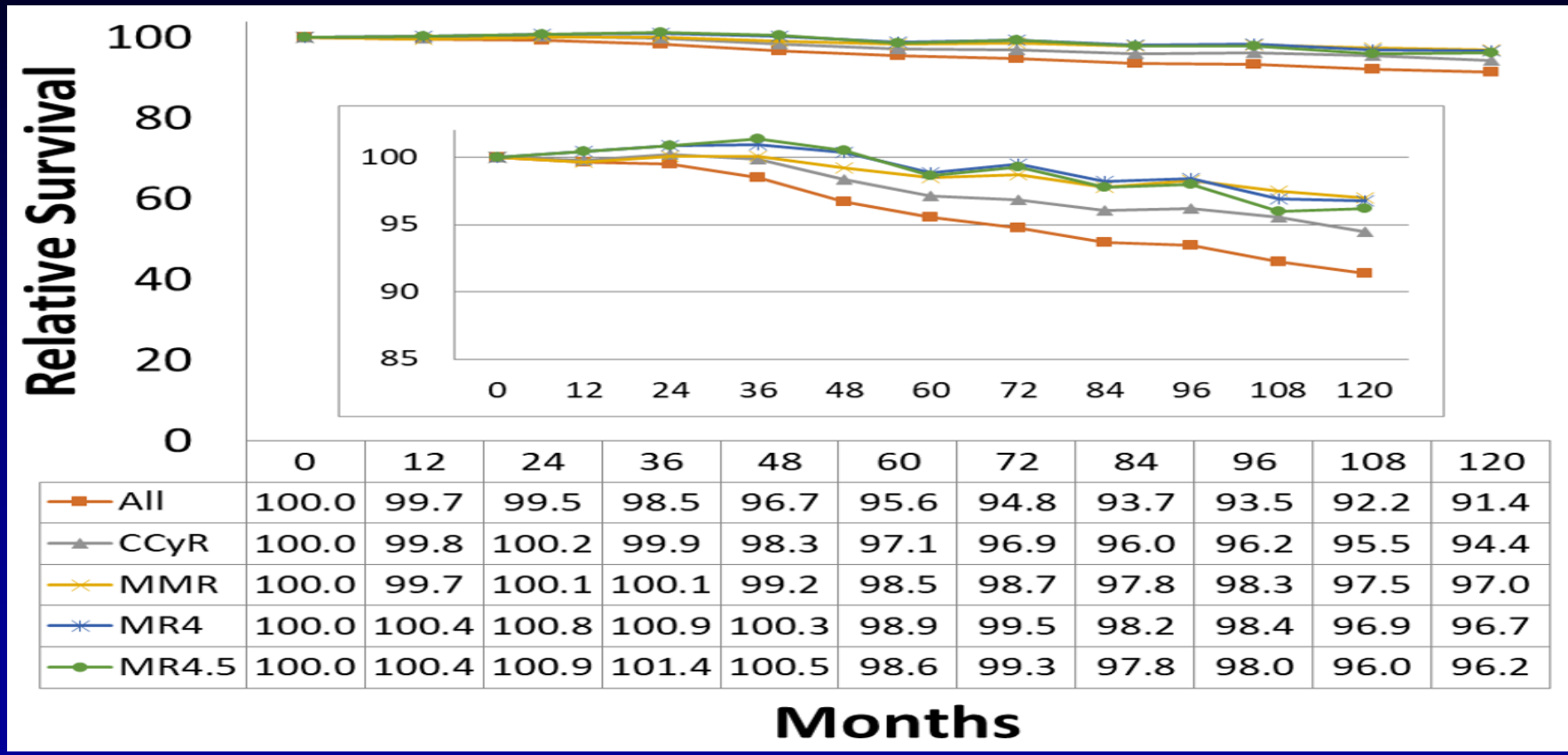
- Frontline
  - Imatinib 400 mg daily
  - Dasatinib 100 mg daily (50 mg at MD Anderson)
  - Nilotinib 300 mg BID
  - Bosutinib 400 mg daily
- Second/third line
  - Nilotinib, dasatinib, bosutinib, ponatinib, asciminib, omacetaxine
  - Allogeneic SCT
- Other
  - Decitabine, peg IFN, omacetaxine (only 2–5 days/mo)
  - Hydrea, cytarabine, combos with TKIs

CML: Survival at MDACC 1975–2019



Harrison's Principles of Internal Medicine. 2014 and unpublished update 2019.

Long-Term FU in CML: Relative Survival by Response



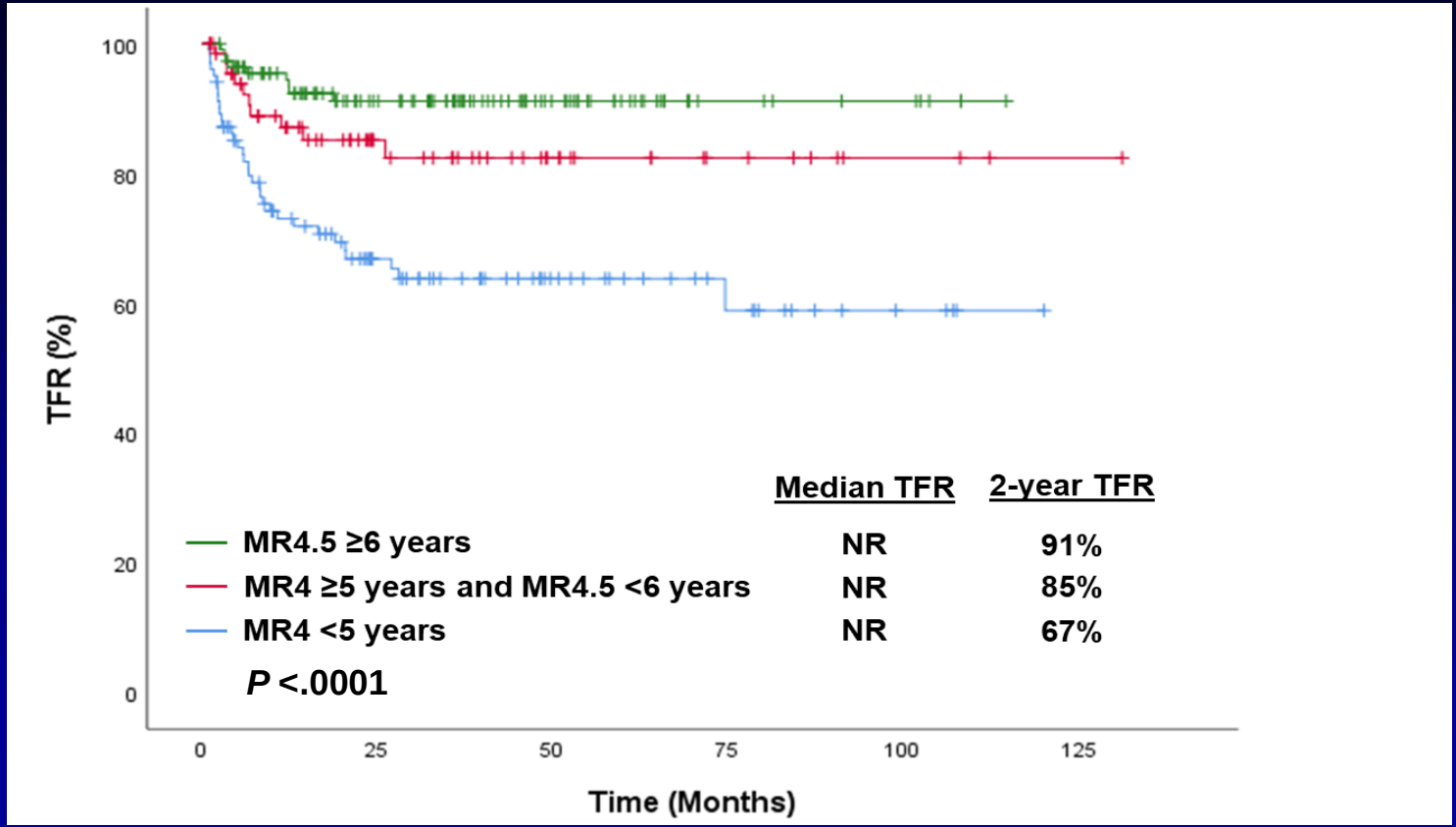
	0	12	24	36	48	60	72	84	96	108	120
All	100.0	99.7	99.5	98.5	96.7	95.6	94.8	93.7	93.5	92.2	91.4
CCyR	100.0	99.8	100.2	99.9	98.3	97.1	96.9	96.0	96.2	95.5	94.4
MMR	100.0	99.7	100.1	100.1	99.2	98.5	98.7	97.8	98.3	97.5	97.0
MR4	100.0	100.4	100.8	100.9	100.3	98.9	99.5	98.2	98.4	96.9	96.7
MR4.5	100.0	100.4	100.9	101.4	100.5	98.6	99.3	97.8	98.0	96.0	96.2

Haddad. *Blood*. 2022;140:abstract 1696.

Rx Endpoints in CML

- Survival
- Rx DC and “Rx-free remission”
- Long-term safety
- Cost; cost-effectiveness = “Rx value”

Treatment-Free Remission in CML Patients: Rates by MR4 and MR4.5 Durations



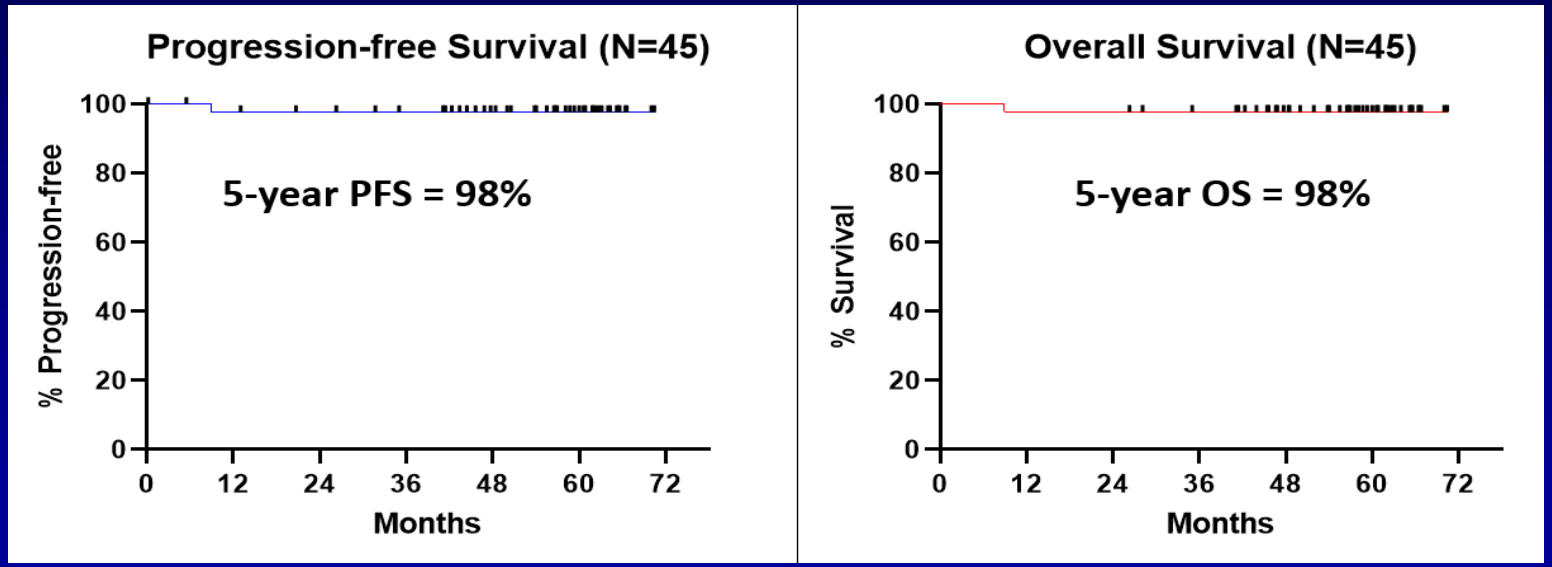
Haddad. *Blood*. 2021;138:abstract 1480.

Frontline CML Therapy in 2023+

- **Completed frontlines: dasatinib 50 mg daily ± venetoclax 200 mg daily**
- **Current frontline: dasatinib 50 mg daily + oral decitabine 35 mg daily × 3–5 q mo. Aim to achieve higher rates of durable DMRs and Rx discontinuation = TFR (molecular cure)**

iFCG in *IGHV*-M, non-del(17p)/*TP53*-mutated CLL

- 45 pts, median age 60 (25–71)
- iFCG ×3 cycles, followed by 9 cycles of ibrutinib (with 3 or 9 cycles of obin)
- Best bone marrow U-MRD4 = 44/45 (98%) (ITT analysis)
- No CLL progression or Richter transformation



Jain N, et al. *Leukemia.* 202135(12):3421-3429; Jain N, et al. EHA 2022 (submitted).

*Sole event in both PFS and OS curve is patient's death from CHF

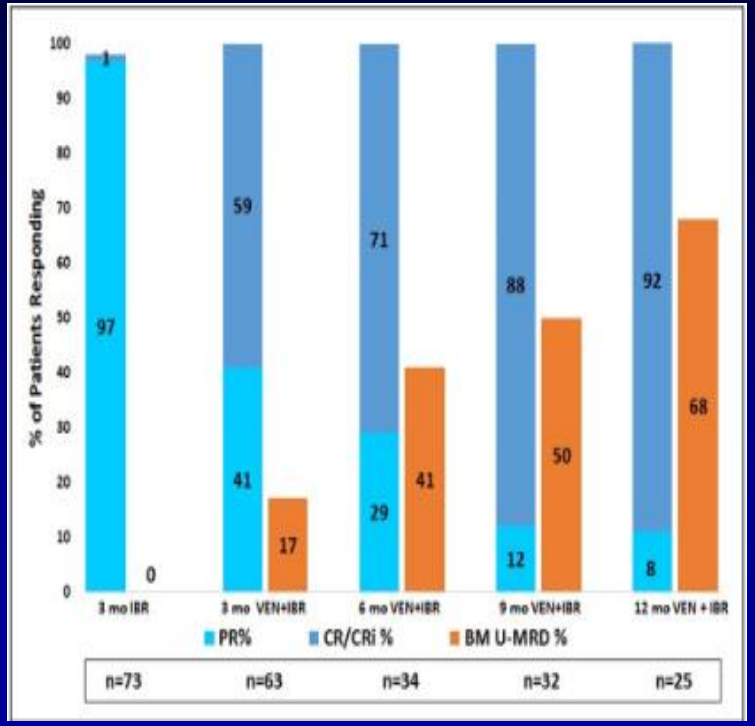
Cure of CLL – Couplets vs Triplets

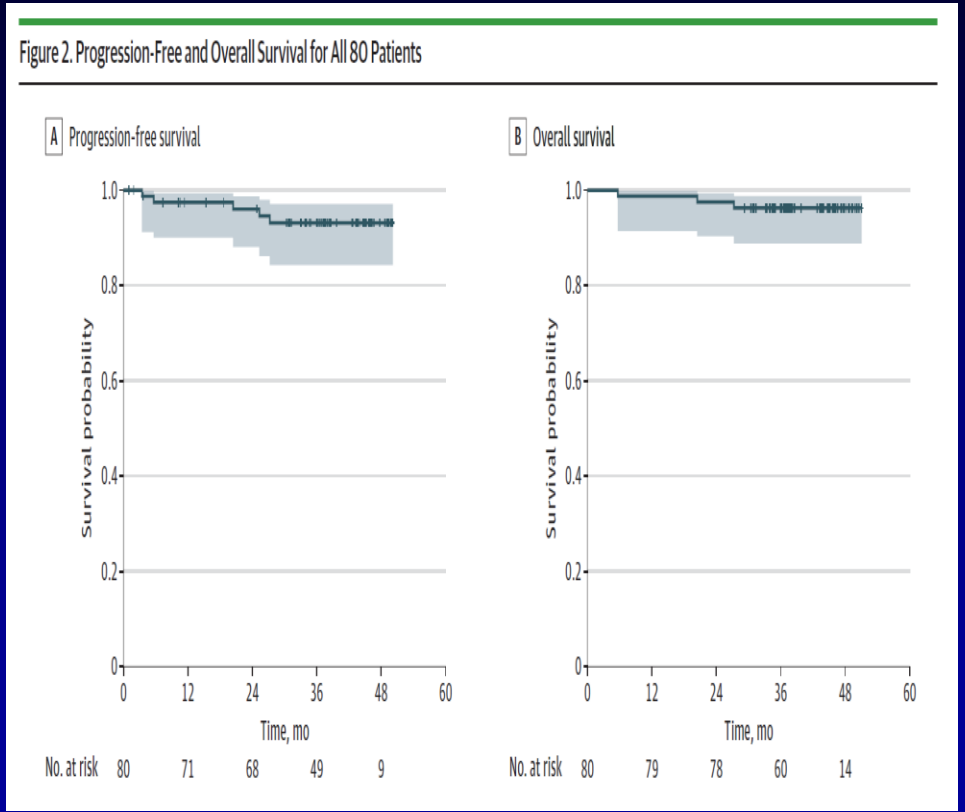
- Ibrutinib-venetoclax finite Rx duration = cure
- Questions: duration (2 vs more years); couplets vs triplets

BTK inhibitors	BCL2 inhibitors	CD20 Ab
Ibrutinib	Venetoclax	Rituximab
Acalabrutinib; zanubrutinib	---	Obinutuzumab
Pirtobrutinib (Loxo305)	---	Bispecific T-cell engagers(BiTEs)

Ibrutinib + Venetoclax in TN High-risk CLL

- 80 pts Rx; median age 65 yrs (26–83)
- 12-mo CR-CRi 92%; MRD-neg 68%





Jain N, et al. *JAMA Oncol*. 2021.

CLL Therapy in 2023+

- Ibrutinib + venetoclax = outstanding results
- Better BTK inhibitors
  - 1) Covalent BKIs: acalabrutinib, zanubrutinib
  - 2) Non-covalent BTKis: pirtobrutinib (LOXO305)
- Role of CD20 Abs
- Future CLL Rxs : Pirtobrutinib + venetoclax; need for CD20 Abs?

The New “Easy” Leukemias

- Ph-positive ALL
- Younger ALL

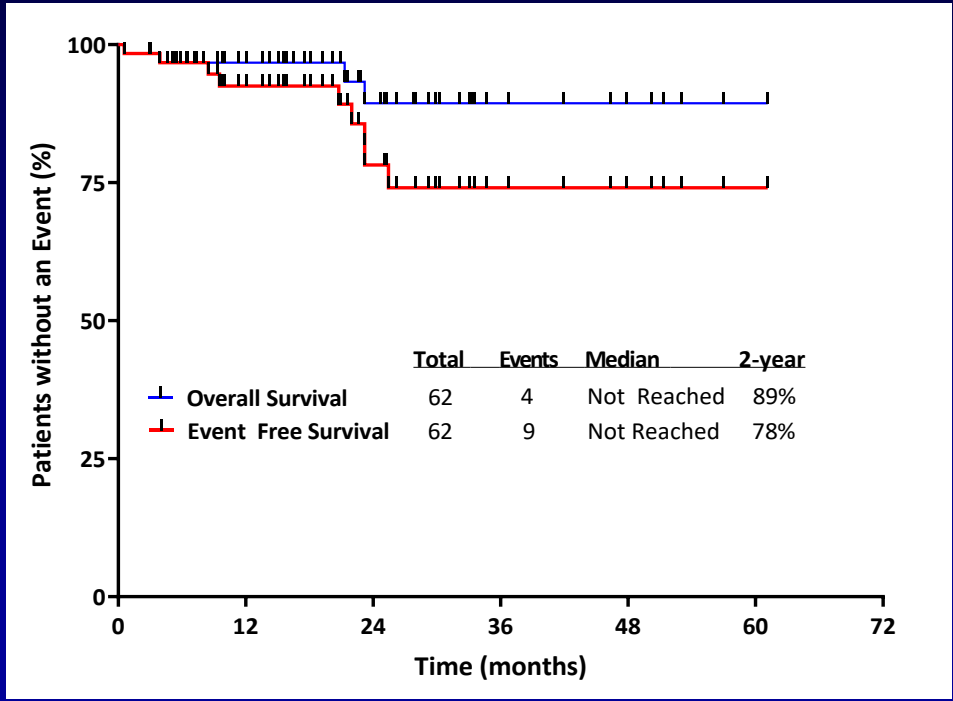
Reasons for Recent Success in Adult ALL

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

Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

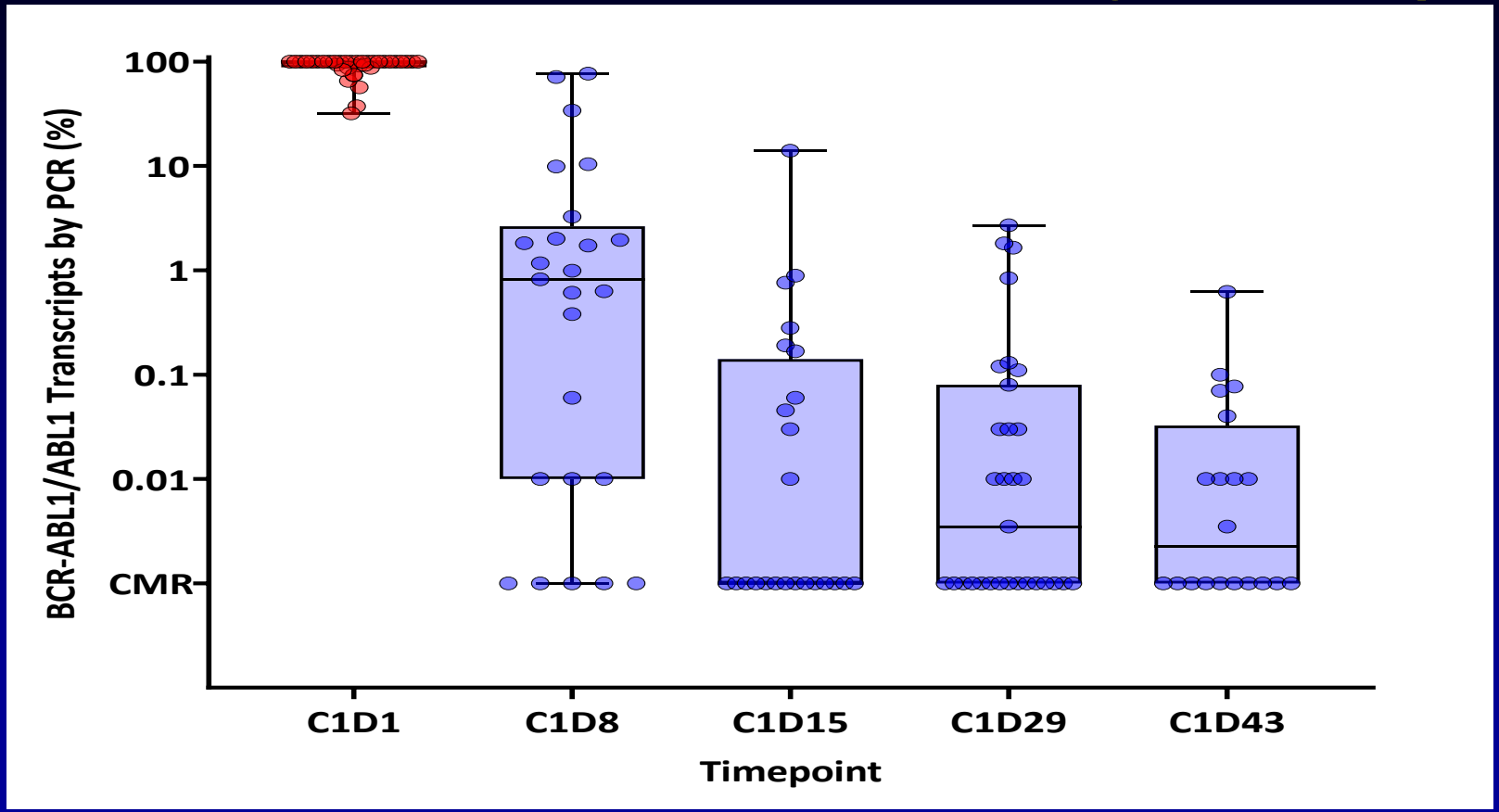
- 62 pts Rx with simultaneous ponatinib 30–15 mg/D and blinatumomab ×5 courses. 12–15 ITs
- Only 1 pt had SCT(2%)
- Median F/U 19 months. 2-yr EFS 78%, OS 89%
- 6 relapses (all p190): 3 CNS, 1 CRLF2+ (Ph–), 2 systemic

Parameter	%
CR-CRi	98
% CMR	84
% NGS-MRD negative	91
% 2-yr OS	89



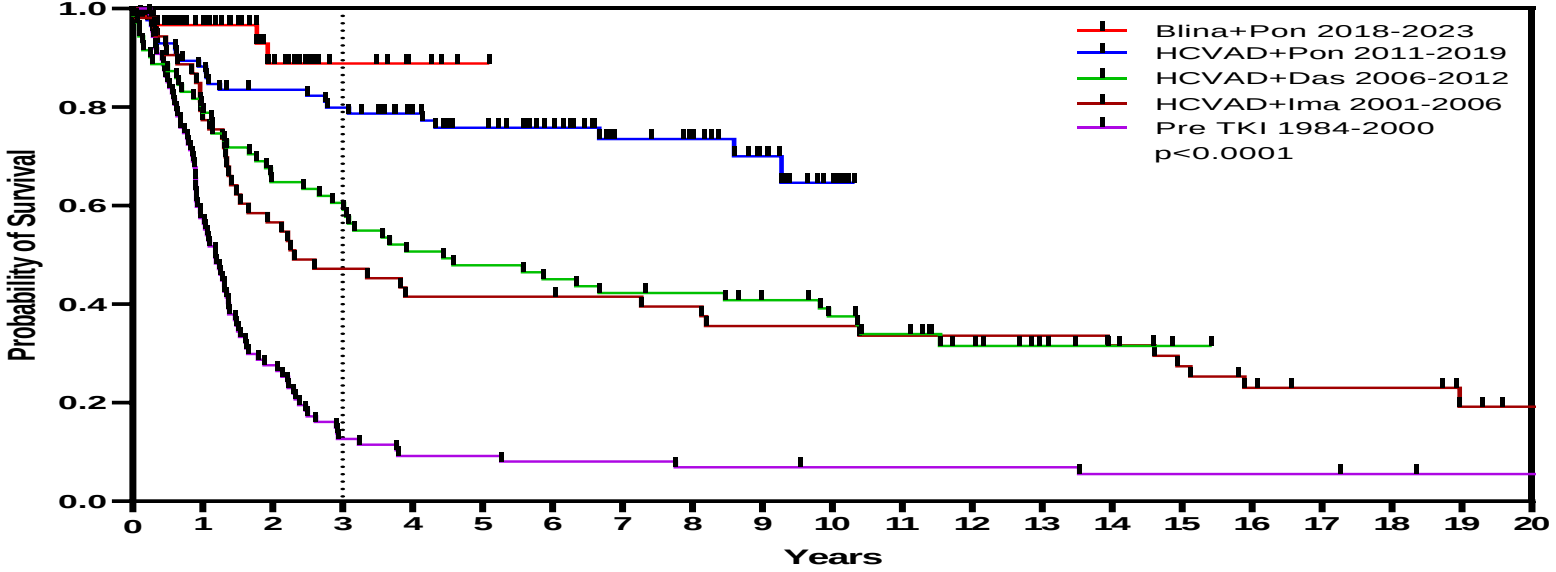
Short. *HemaSphere.* 2023;7:abstract S118 (updated August 2023).

Ponatinib + Blinatumomab in Ph+ ALL: Early MRD Responses



Short. *HemaSphere.* 2023;7:abstract S118 (updated August 2023).

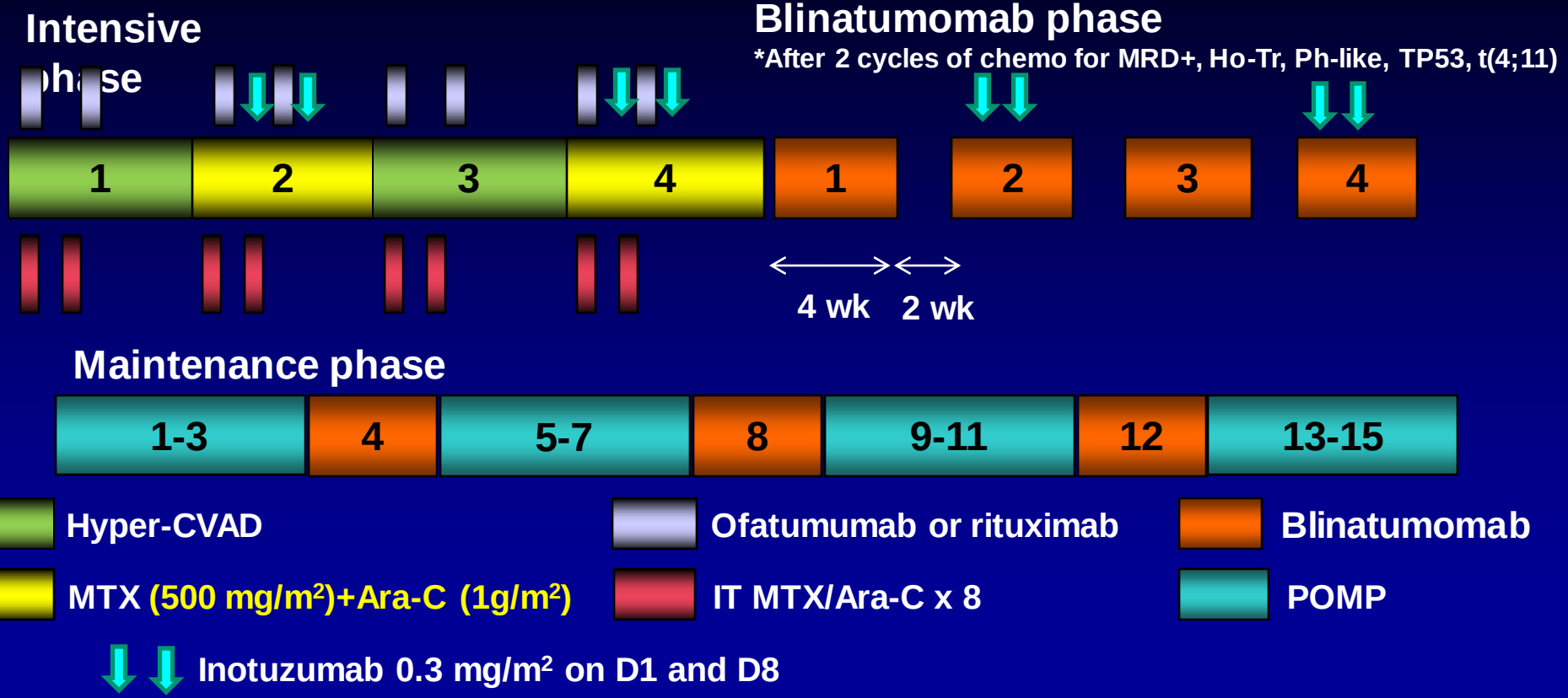
Ph+ ALL: Survival by Decade (MDACC 1984–2023)



	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

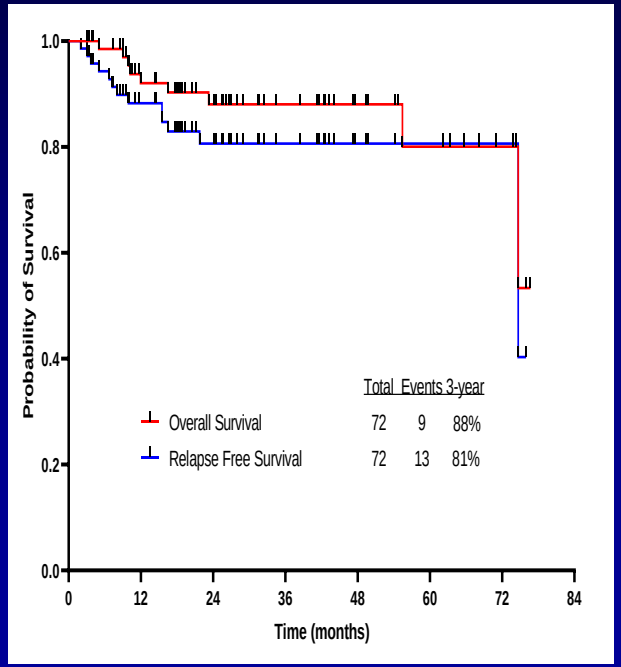
Hyper-CVAD + Blina + InO in B-ALL: Regimen

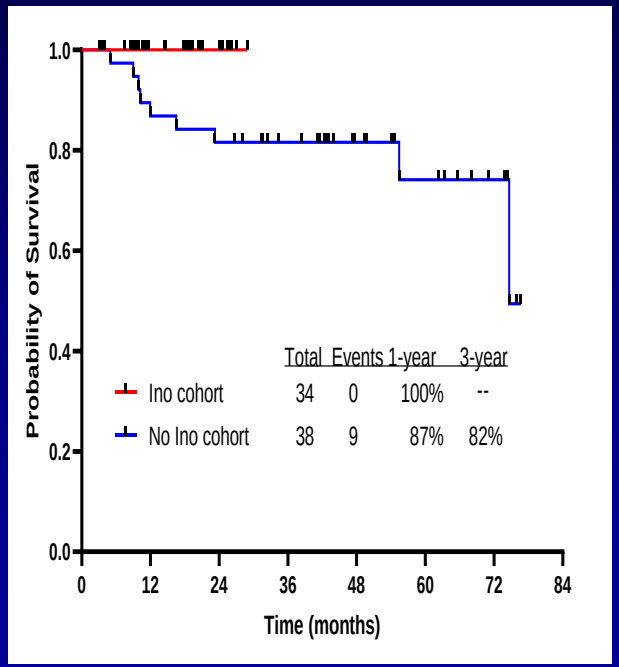


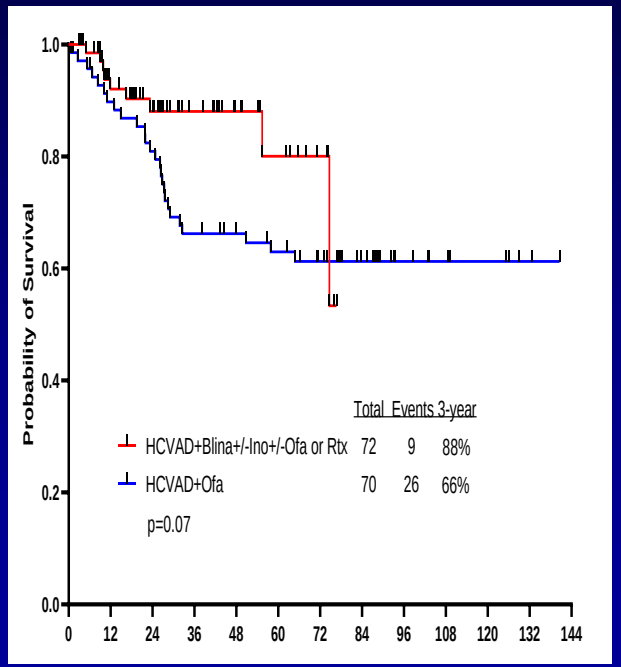
Short. *HemaSphere.* 2023;7:abstract P358.

Hyper CVAD-Inotuzumab → Blinatumomab in Newly Dx Adult ALL

- 72 pts; median age 34 yrs (18–59)
- Rx with O-HCVAD ×4; Blina ×4 → POMP 1 yr with blina Q3 mos; Ino 0.3 mg/m² D1 & 8; C2, 4, 6, 8 (2.4 mg/m²)
- CR rate 100%; MRD negative 95% (69% at CR); NGS-MRD negative 74%; 60-day mortality 0%; 21 (32%) allo-SCT



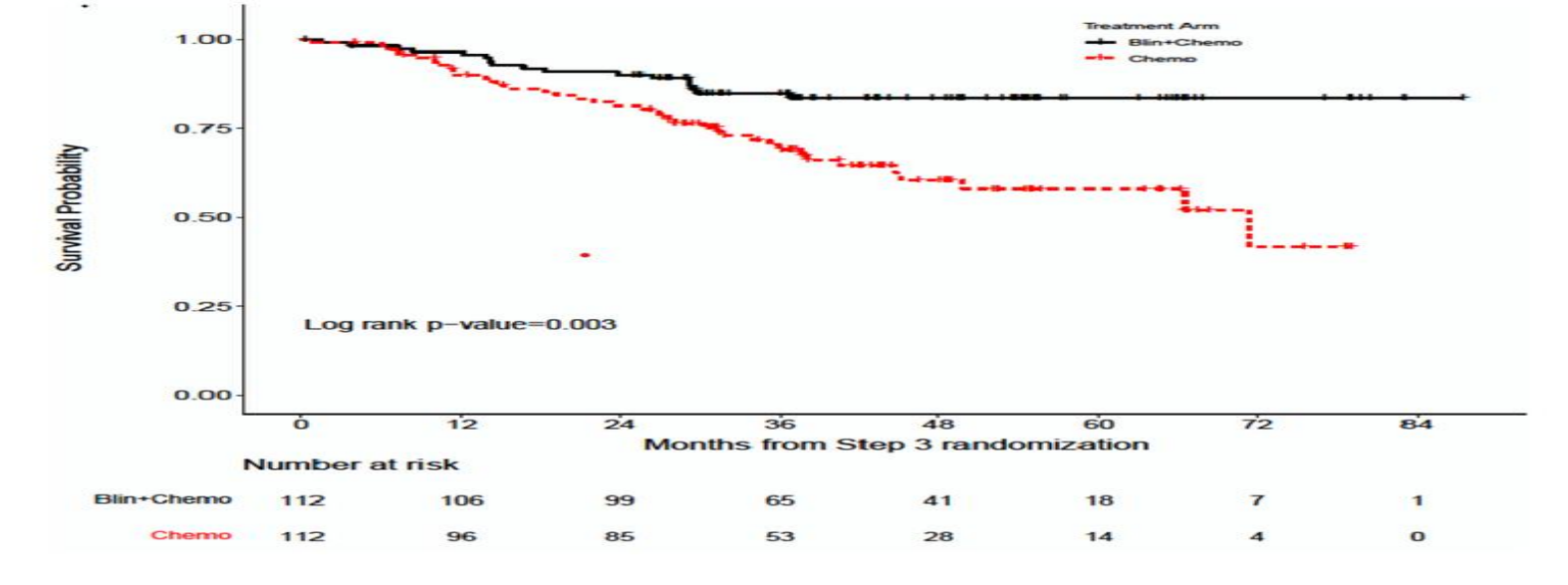




Short. *HemaSphere.* 2023;7:abstract P358.

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

- 488 pts median age 51 yr (30–70)
- 224 MRD-negative CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median FU 43 months; median OS NR vs 71.4 mo (HR = 0.42; *P* = .003)



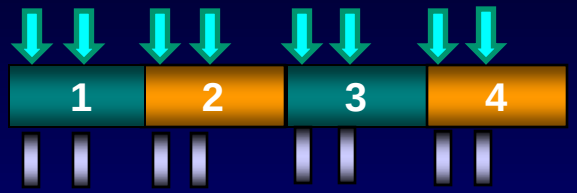
Litzow MR, et al. *Blood*. 2022;140(suppl 2): abstract LBA-1.

The “Intermediate” Leukemias

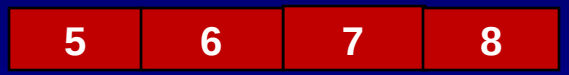
- Older ALL
- Younger AML

Mini-HCVD + Ino ± Blina in Older ALL: Modified Design (pts 50+)

Intensive phase



Consolidation phase



Maintenance phase

Mini-HCVD

Mini-MTX + cytarabine

Blinatumomab

IT MTX + Ara-C

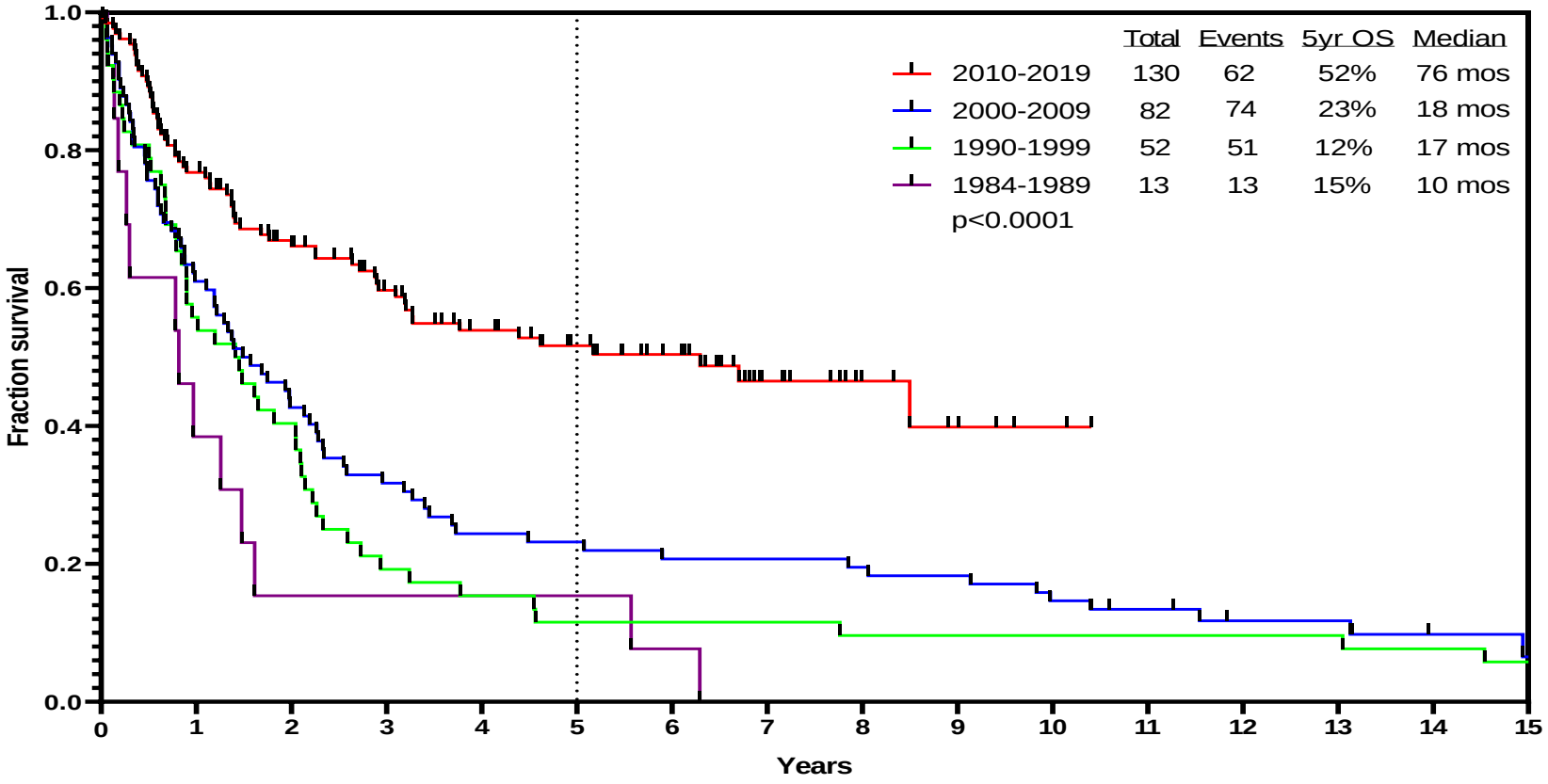
POMP

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

Total Ino dose = 2.7 mg/m^2

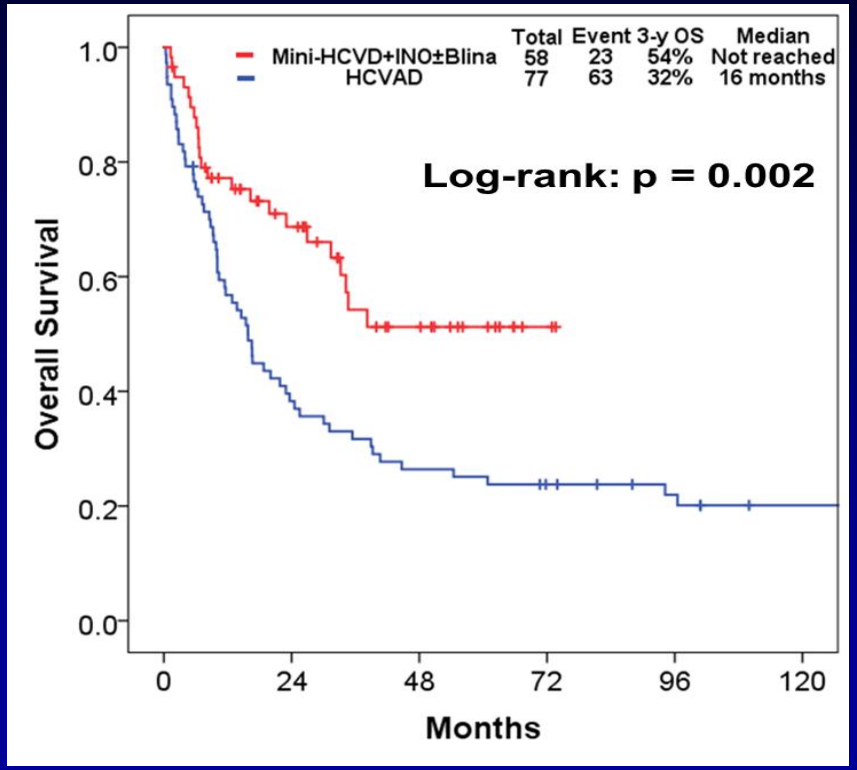
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Short et al. *Blood*. 2018;132:abstract 36.

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

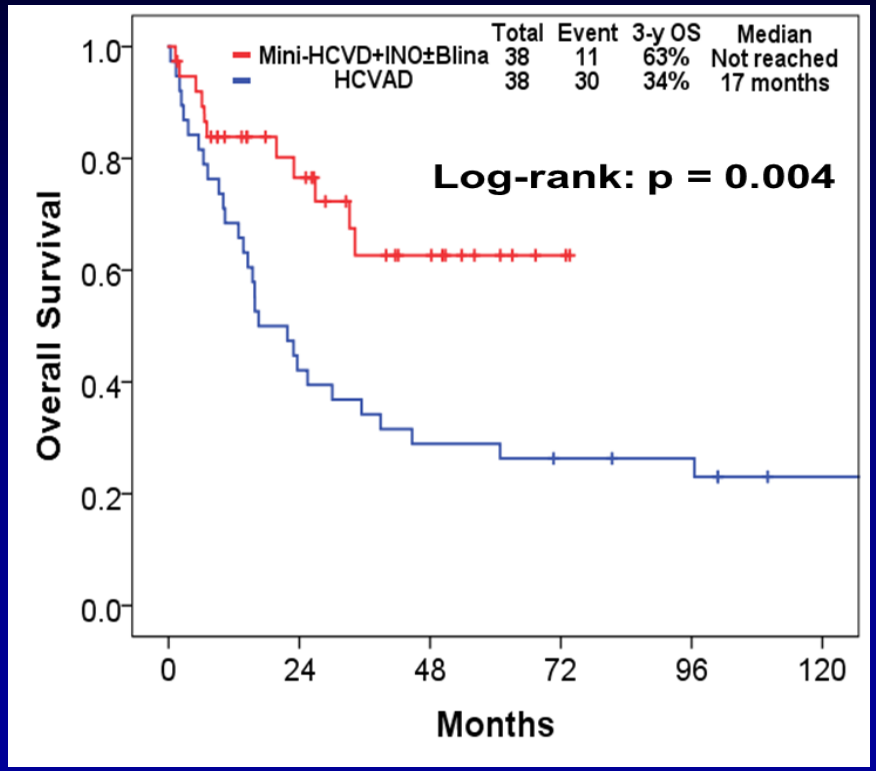


Mini-HCVD + INO ± Blina vs HCVAD in Older ALL: Overall Survival

Pre-matched



Matched



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

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

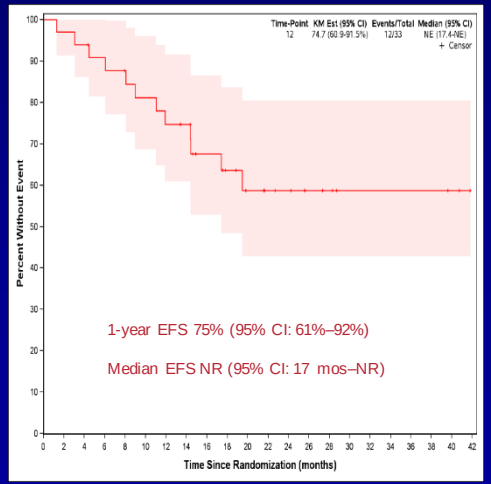
- 33 pts; median age 71 yrs (60–84). Median CD22 92%. **F/U 22 months**
- Induction: INO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 & 15 (1.8 mg/m^2)
- Maintenance: If CR-CRi INO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) ×2 then BLINA ×2
- If no CR-CRi—BLINA 28 mcg/D ×21 then ×28 ×3
- IT ×8
- **CR 85% post INO ×3; cumulative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

N=33	Induction InO I A/B/C	Blinatumomab Course II
Composite CR*	28 (85%)	32 (97%)
CR	15 (45%)	19 (58%)
CRh	11 (33%)	12 (36%)
CRi	2 (6%)	1 (3%)
Refractory	3 (9%)*	-
Survival		
1-yr EFS	75% (95% CI 61-92%)	
1-yr OS	84% (95% CI 72-92%)	

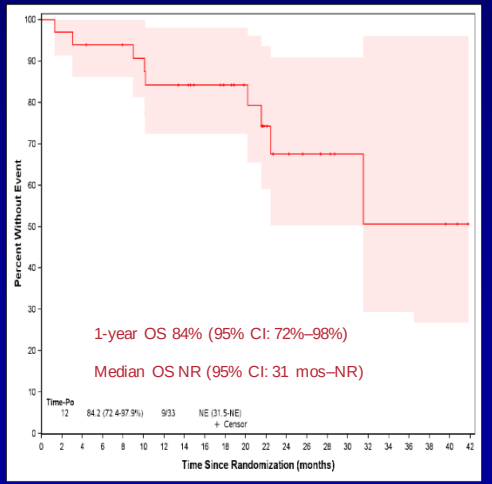
*CR+CRh+CRi

* 1 completed IA only, 2 proceeded to course II

EFS



OS

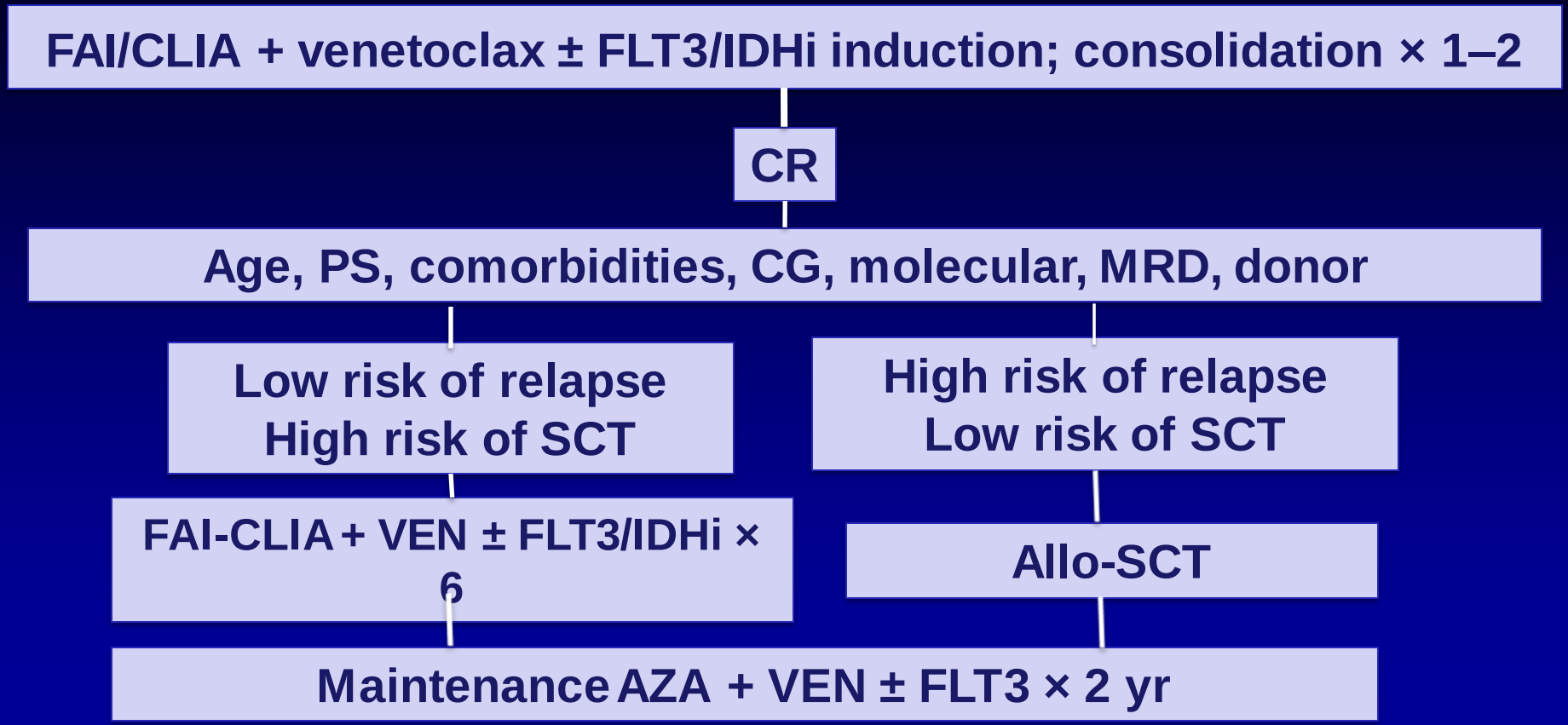


Wieduwilt et al. *HemaSphere.* 2023;7:abstract S117.

AML in 2017–2023 – 12 Agents FDA Approved

- **Midostaurin** (RYDAPT) – de novo younger AML (≤60 yrs), FLT3 mutation – April 2017
- **Gilteritinib** (FLT3 inhibitor) – FLT3 + R/R AML
- **Enasidenib** (AG-221; IDHIFA) – R/R AML and *IDH2* mutation – August 2017
- **Ivosidenib** (AG-120) – R/R AML and *IDH1* mutation – August 2018
- **CPX 351** (Vyxeos) – newly Dx Rx-related AML and post MDS AML – August 2017
- **Gemtuzumab ozogamycin** revival – frontline AML Rx – August 2017
- **Venetoclax** – newly Dx older/unfit for intensive chemo, with AZA/DAC, ara-C
- **Glasdegib** – newly Dx older/unfit, with ara-C
- **Oral decitabine** – **HMA Rx for MDS and CMML** – August 2020
- **Oral azacitidine** – AML maintenance – Sept 2020
- **Olutasidenib** – (IDH1 inhibitor; Rezlidhia) – R/R AML and *IDH1* mutation – Dec 2022
- **Quizartinib** – (VANFLYTA) – de novo AML, *FLT3* mutation – Jul 2023

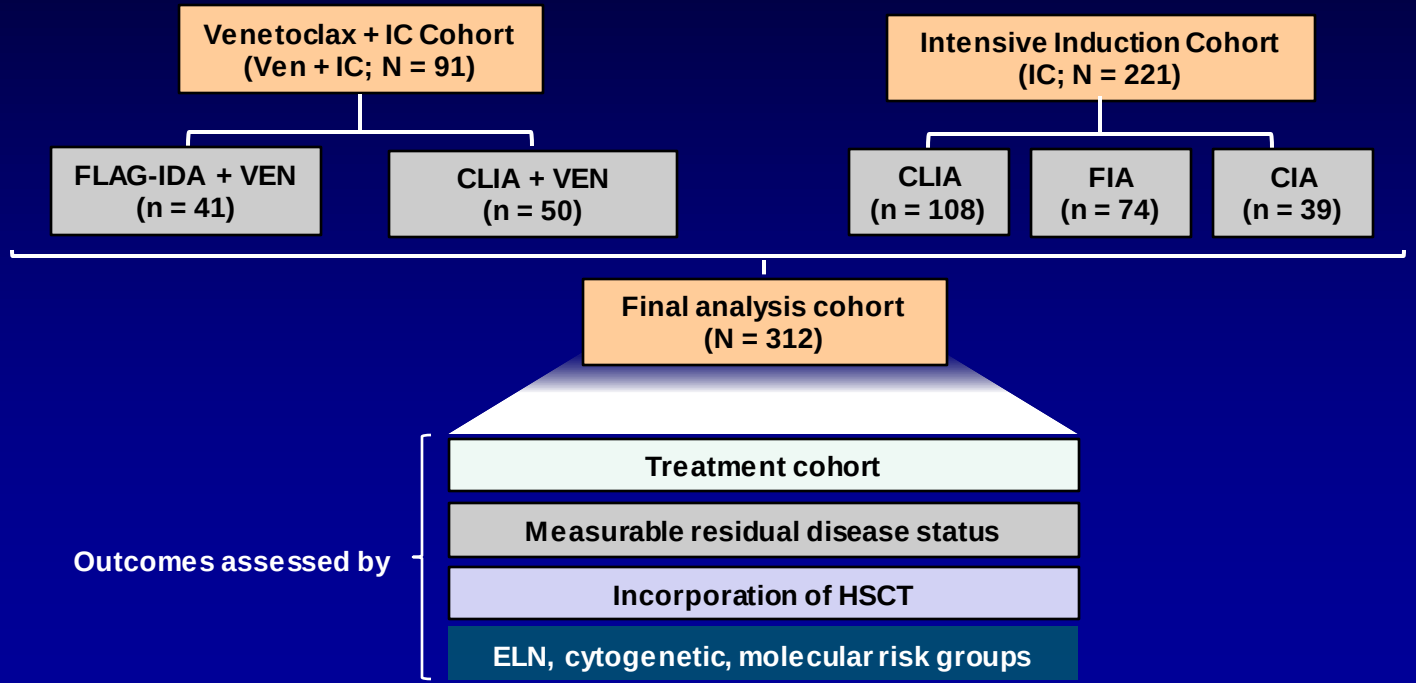
Therapy of Younger AML at MD Anderson in 2023+



Personal communication from Dr Kantarjian.

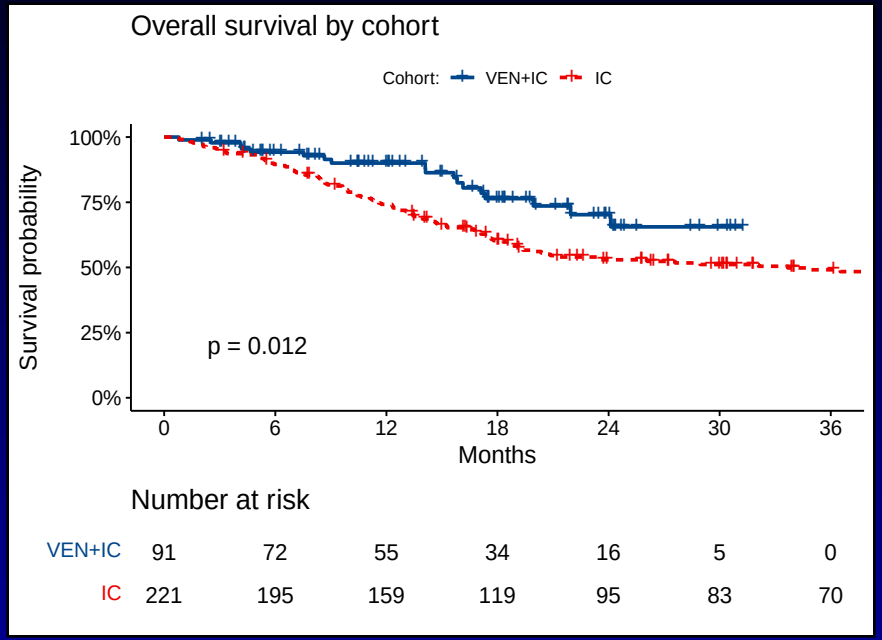
VEN + IC in AML – Study Design

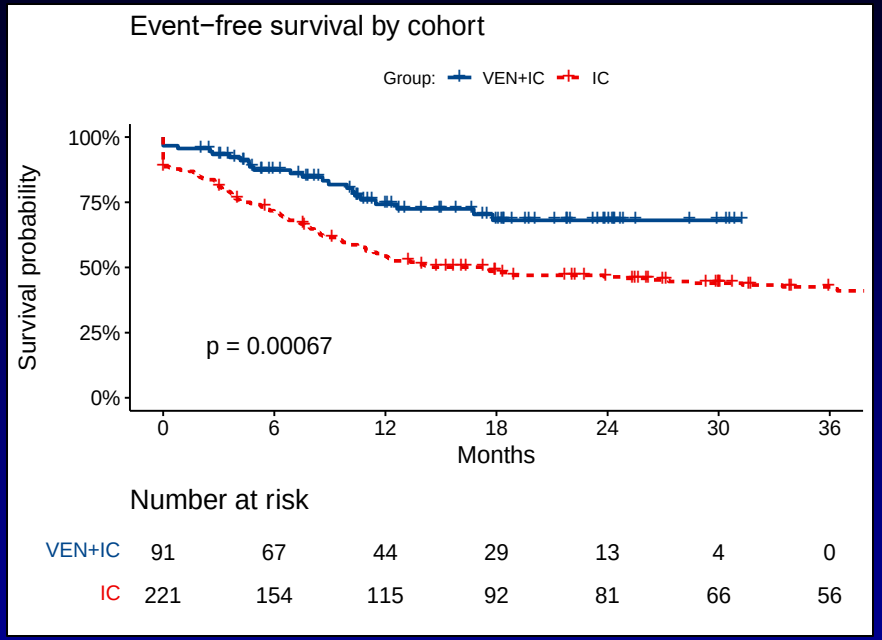
Patients with ND-AML (de novo, sAML, tAML, stAML) treated with intensive chemotherapy (IC) at MDACC on prospective clinical trial protocols



Lachowiez CA, et al. *Lancet Haematol.* 2022;9:e350-e360.

AML – Outcome With Intensive ChemoRx ± Venetoclax





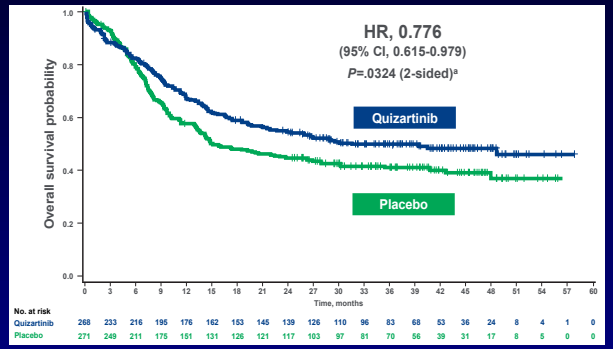
Demographic Median (95% CI) or %(SE)	Ven + IC	IC
Median OS, months	**NR (–)**	**34 (20–NR)**
12-Month OS	90 (3)	74 (3)
24-Month OS	70 (6)	52 (4)

Demographic Median (95% CI) or %(SE)	Ven + IC	IC
Median EFS, months	**NR (-)**	**17 (11-34)**
12-Month EFS	74 (5)	54 (3)
24-Month EFS	68 (6)	46 (3)

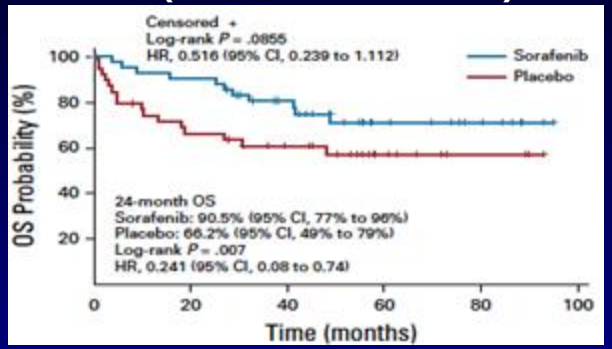
Lachowiez CA, et al. *Lancet Haematol.* 2022;9:e350-e360.

FLT3 Inhibitors Improve OS in AML

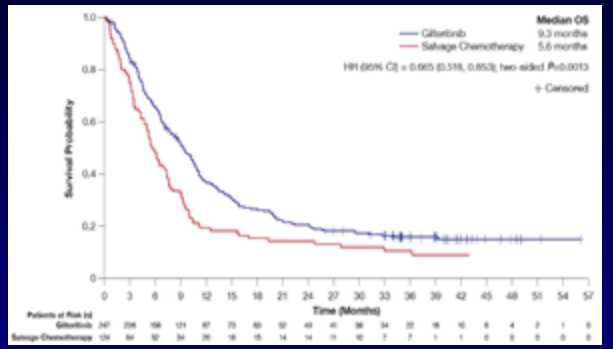
New Dx AML
intensive chemoRx + TKI/placebo

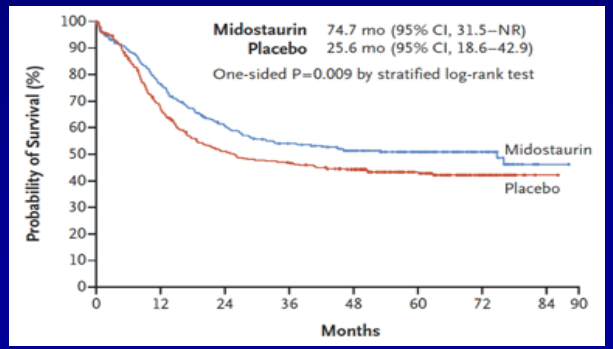


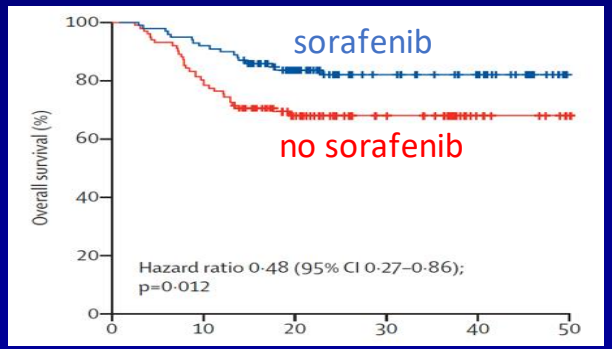
TKI post allo SCT
(sorafenib 2 studies)

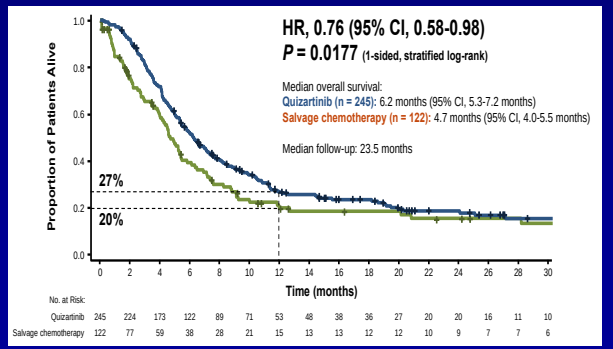


R/R AML
TKI vs chemoRx







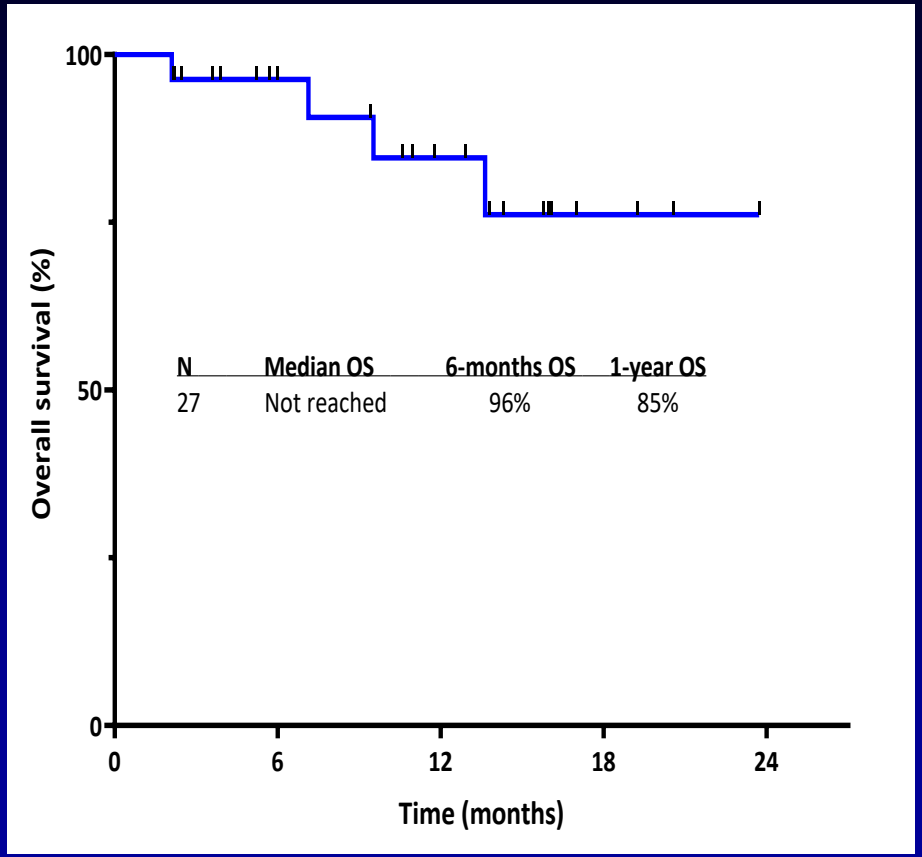


Erba HP, et al. EHA 2022. Abstract S100; Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464; Burchert A, et al. *J Clin Oncol.* 2020;38(26):2993-3002; Xuan Y, et al. *Lancet Oncol.* 2020;21(9):1201-1212; Perl AE, et al. Blood. 2022;139(23):3366-3375; Cortes JE, et al. *Lancet Oncol.* 2019;20(7):984-997.

Triplet Azacitidine-Venetoclax-Gilteritinib in *FLT3*-Mutated AML

- 47 pts: 27 newly Dx; 20 R/R
- AZA ×7; VEN ×14; GILT 80–120 mg/D ×14 – In CR: AZA ×5-VEN ×7-GILT daily
- Figure: OS in newly Dx

Parameter	Frontline (n = 27)	R/R (n = 20)
No (%) CR	25 (92)	4 (20)
No (%) ORR	27 (100)	14 (70)
% MRD-neg	82	43% of responders
% 1-yr OS	85	30

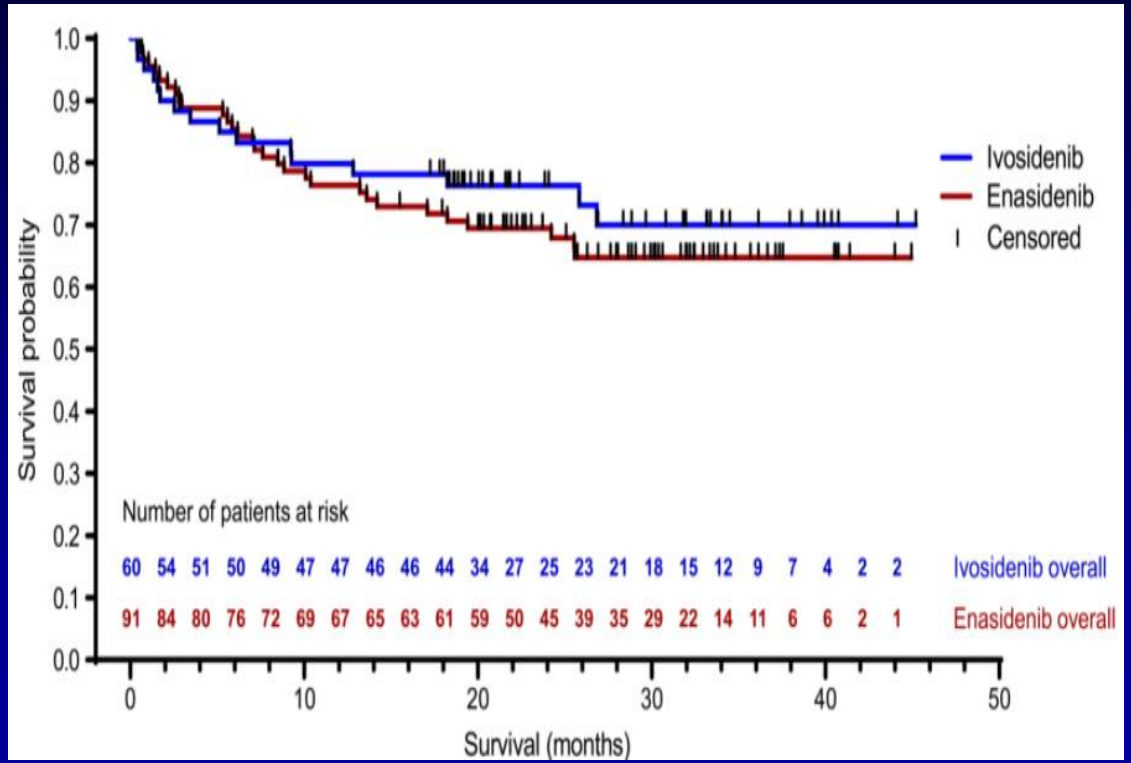


Short. Blood. 2022;140:abstract 831.

IDH Inhibitors With 3+7 in *IDH*-Mutated AML

- 151 pts; median age 62 yrs (24–73) Rx with 3+7 and ivosidenib (n = 60) or enasidenib (n = 93)

% Parameter	IVO	ENA
CR	70	57
CR+CRi+CRp	78	74
% 3-yr OS	67	61



Stein. *Blood.* 2021;138; Stein. *Blood.* 2021;138:abstract 1276.

The “Difficult” Leukemias

- Elderly AML
- MDS

Azacitidine ± Venetoclax (VIALE-A) Study Design

Eligibility

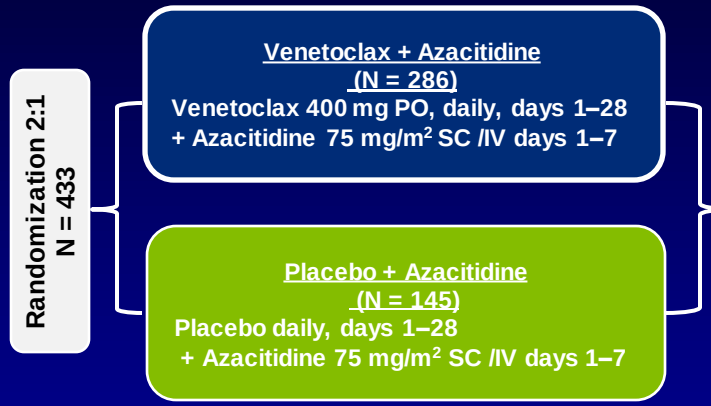
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities
    - CHF requiring treatment or ejection fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment



Endpoints

Primary

- Overall survival

Secondary

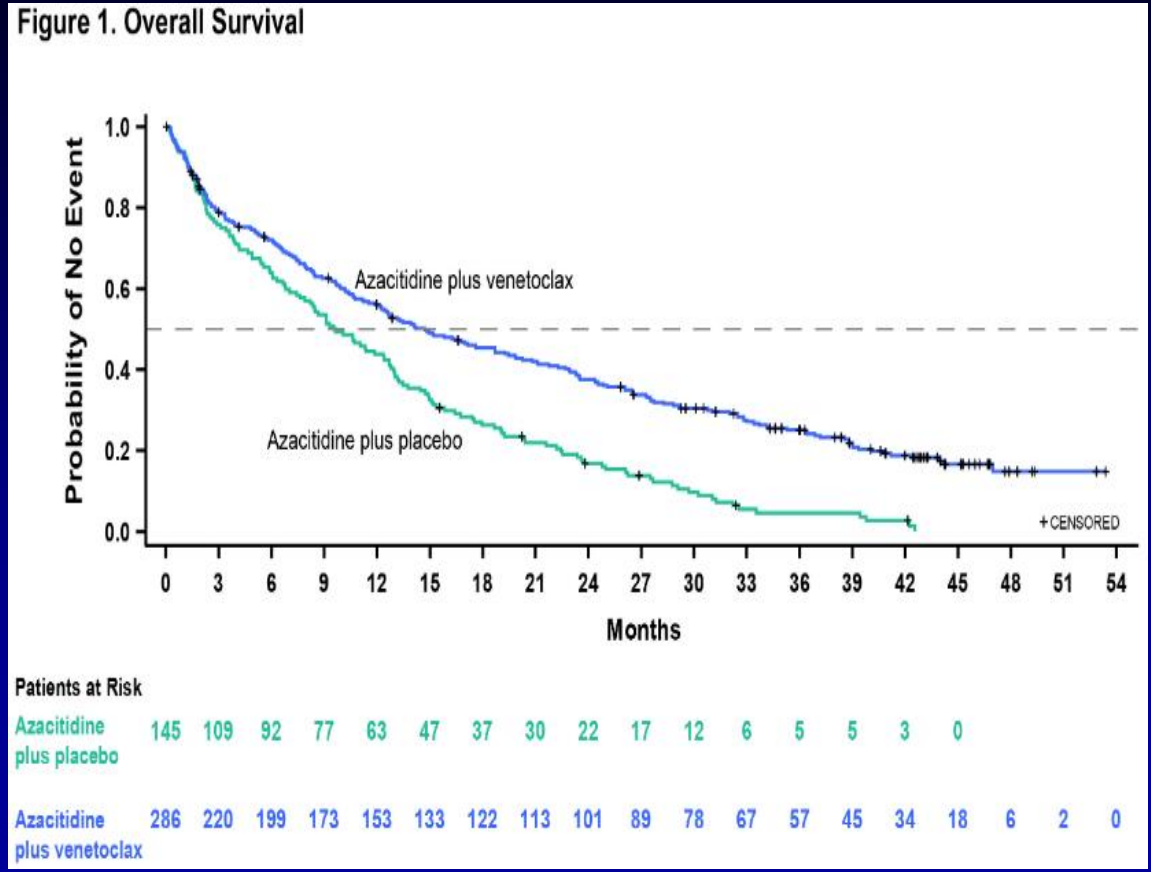
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors	Age (<75 vs ≥75 years); cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3–28: 400 mg **Cycle 2** → Day 1–28: 400 mg

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

VIALE-A Azacitidine ± Venetoclax – Long-Term Follow-Up

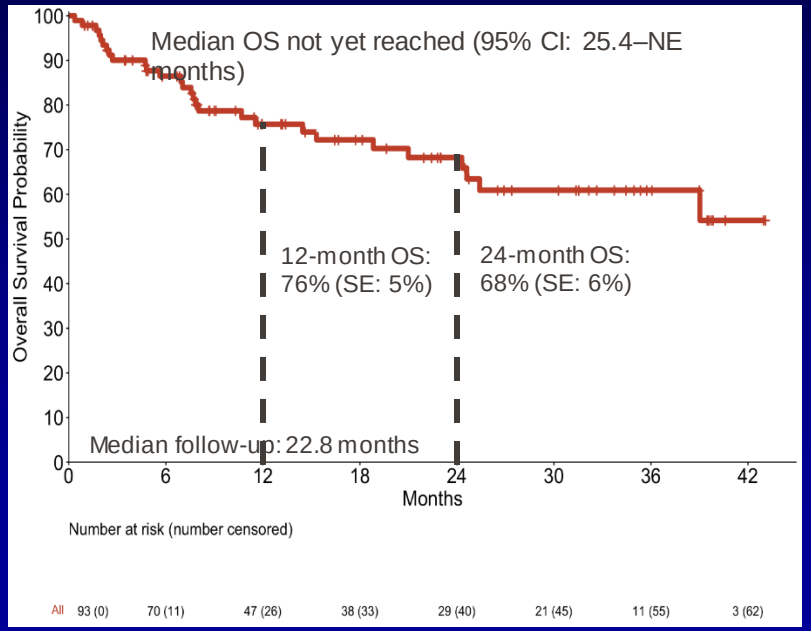
- 431 pts older, unfit with newly Dx AML randomized 2:1 to AZA-VEN (n = 286) or AZA (n = 145)
- 3-yr OS ≈7% with AZA; ≈25% with AZA-VEN
- Interpretation – HMA + VEN suboptimal

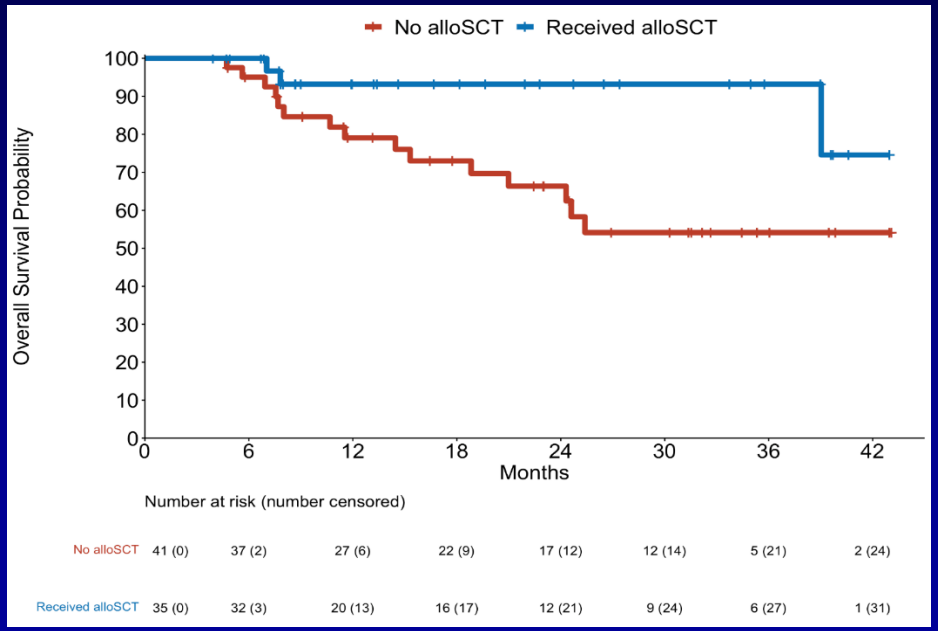


Pratz KW, et al. ASH 2022. Abstract 219.

Triple-Nucleoside Regimen (CDA-LDaraC-AZA) + Venetoclax in Newly Dx older ALL

- 93 pts; median age 68 yrs (57–84)
- CDA-LDaraC-VEN ×2 alternating with AZA VEN ×2. Total 2 years
- CR 72/92 = 78%. CR + CRi 85/92 = 92%. MRD-negative 66/81 = 81%. Early (4-wk) death 2/93 (2%)
- 2-yr OS 68%. 2-yr DFS 63%. Allo SCT = 35/85 (41%)





Kadia. *J Clin Oncol.* 2022;21 and update im Reville. *Blood.* 2022;140:abstract 4074.

SNDX-5613 in R/R AML (Mostly MLL)

- 54 pts Rx: 44 AML, 9 ALL, 1 MPAL. 35 (65%) MLL; 10 (19%) NPM1
- SNDX-5613 113–339 mg orally BID; phase II 163–276 mg BID
- ORR 20/45 = 44% – CR/CRh 10 (22%), CRi/MLFS 5
- MRD-negative 14/20 responders = 70%
- ORR in MLL 17/35 = 49%; ORR NPM1 3/10 (30%)
- Adverse events: QTc prolongation in 7 = 13%; TLS in 1

Issa. *Nature*. 2023;615:920-924.

Exciting Research in MDS

- HMAs + venetoclax
- Oral decitabine and azacytidine
- Addition of FLT3 and IDH inhibitors when indicated by molecular studies
- Growth factors; luspatercept; imetelstat
- AML-type Rx in *NPM1*+ MDS CG diploid
- NK cellular Rx
- Progress in allo SCT

Exciting Research in MPN

- JAK_2 inhibitors in MF
  - Ruxolitinib
  - Fedratinib (prior ruxo; GI tox)
  - Pacritinib (low plts)
  - Momelotinib (low plts, anemia; not approved)
- Others in MF
  - Pelabresib (BET protein BMD inhibitor; +++)
  - Bomedemstat (LSD_1 inhibitor; also for ET)
  - Imetelstat
- Others
  - Mastocytosis— Avapritinib
  - FGFR1— Pemigatinib
  - PV— Rusfertide (PTG 300); ROPEG IFN; ruxolitinib

Leukemia Questions?

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Global Leukemia Academy

Best practices for first-line treatment in ALL

Josep-Maria Ribera

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GLOBAL LEUKEMIA ACADEMY LATIN AMERICA
October 19–20, 2023

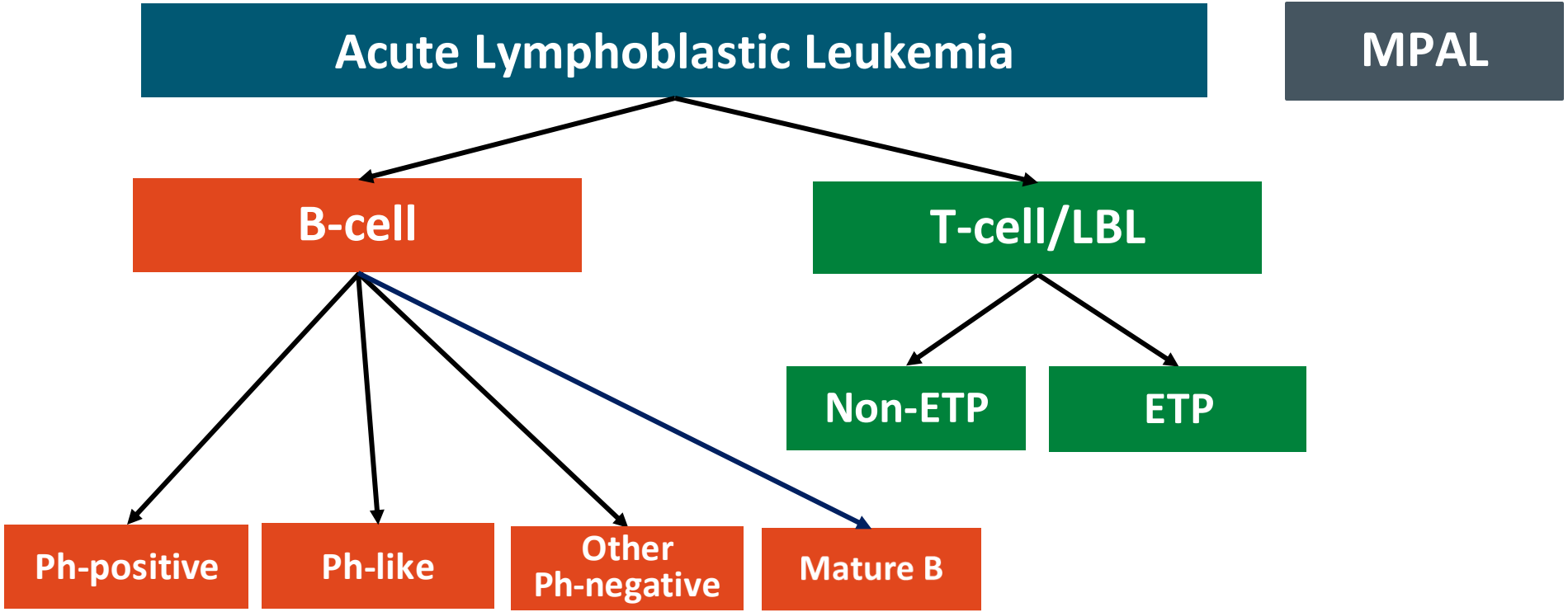
Optimizing and Personalizing Frontline Therapy and Maintenance in Young and Fit ALL

J.M. Ribera
Clinical Hematology Department
ICO-Hospital Germans Trias i Pujol
Josep Carreras Research Institute
PETHEMA Group

Disclosures

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

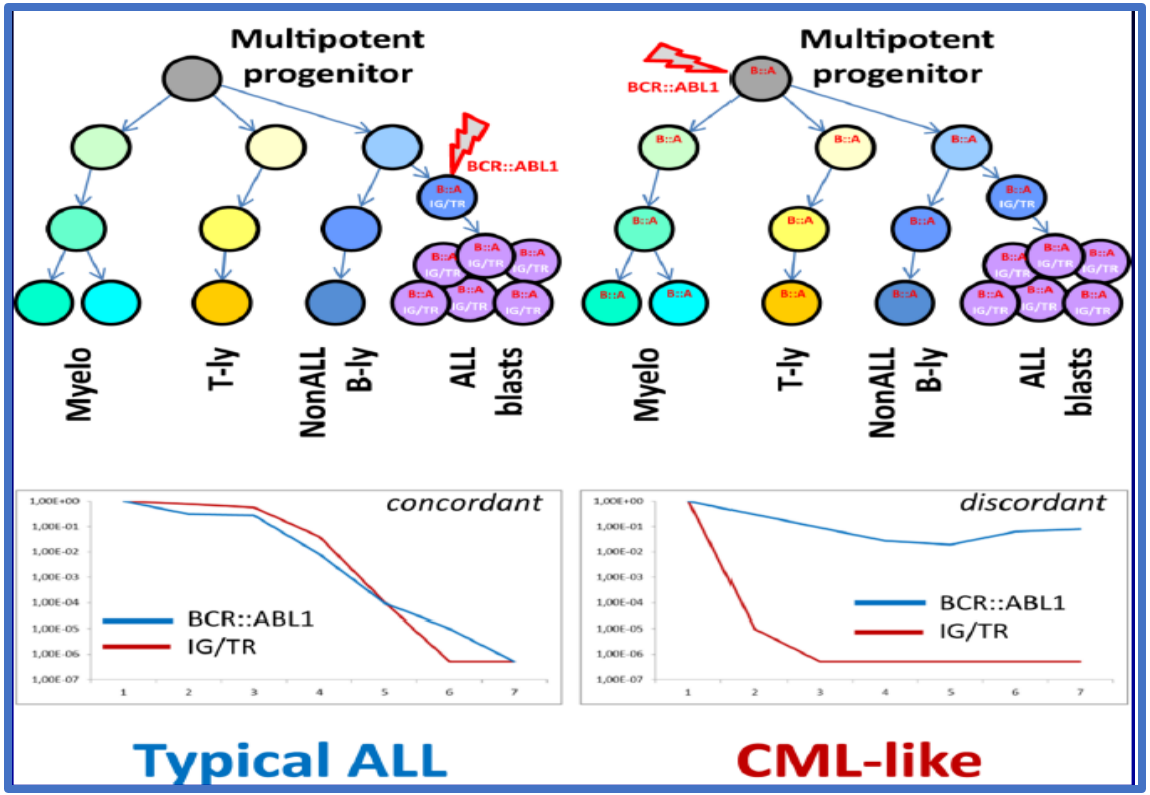
ALL: Practical Approach for Therapy



Ph-Positive ALL: Issues to Be Considered

- Ph-positive ALL subtype (typical vs CML-like)
- Genetic background of ALL (especially *IKZF1*^{plus} signature)
- Robust methodology for MRD assessment (*BCR-ABL1* ratio vs NGS)
- Availability of ponatinib for first-line Tx
- Availability of immunotherapy (blinatumomab) for first-line Tx
- Fitness for allogeneic HSCT

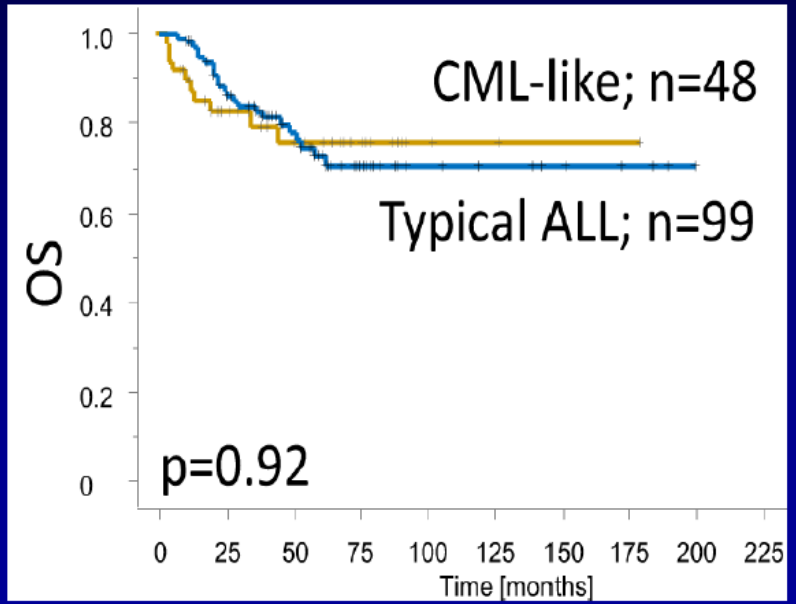
Typical vs “CML-Like” Ph-Positive ALL



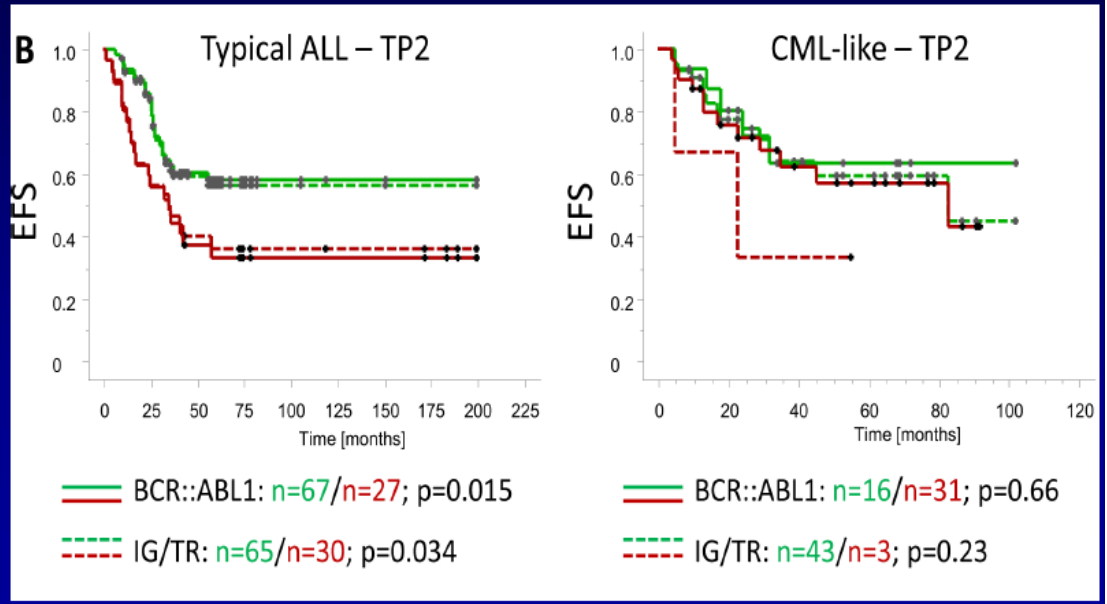
Zuna J, et al. *Leukemia.* 2022;36:2793-2801.

Outcomes of Typical vs CML-Like Ph-Positive ALL

Typical and CML-like Ph+ ALL have similar long-term survival



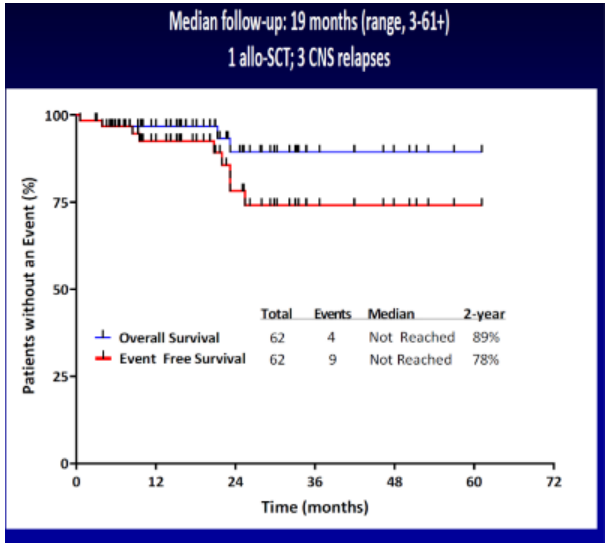
PCR for *BCR::ABL1* is prognostic in typical Ph+ ALL but not in CML-like Ph+ ALL



Zuna J, et al. *Leukemia.* 2022;36:2793-2801.

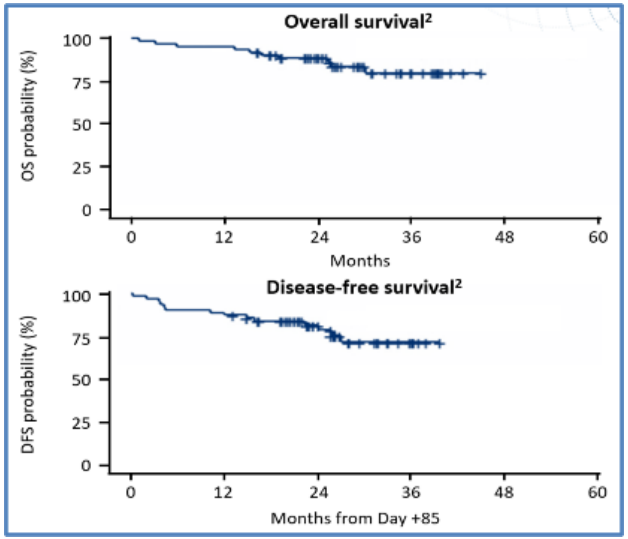
Recent Advances in Newly Diagnosed Ph-Positive B-ALL

Ponatinib + Blinatumomab (n = 62)



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

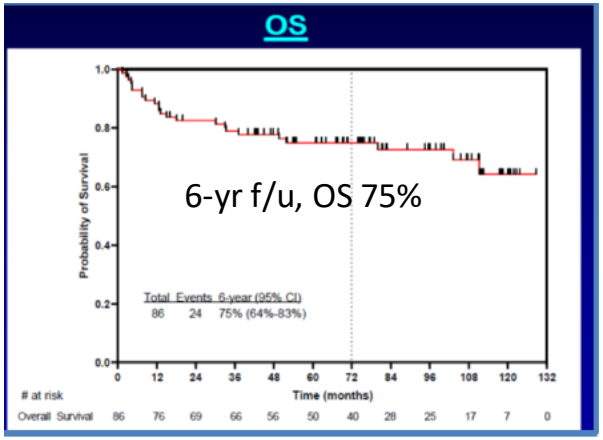
Dasatinib + Blinatumomab (n = 63)



4-yr OS 78%; DFS 75%
29/58 (50%) allo-SCT

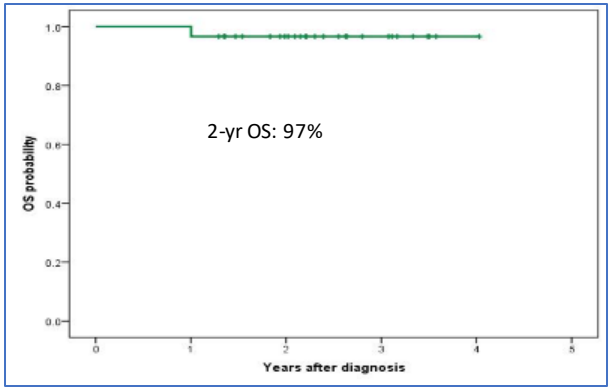
Foà R, et al. *N Engl J Med*. 2020;383:1613-1623.

Ponatinib + Hyper-CVAD (n = 86)



Kantarjian H, et al. *Am J Hematol.* 2023;98:493-501.

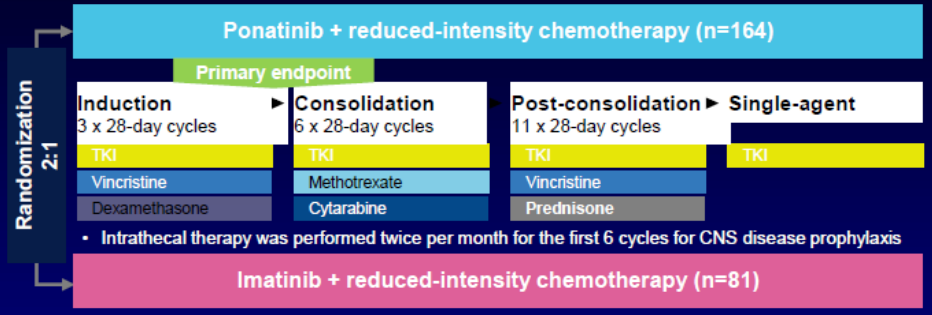
Ponatinib, QT, and Allo-HSCT (n = 30)



Ribera JM, et al. *Blood Adv.* 2022;6:5395-5402.

Ponatinib vs Imatinib with Rx in Ph-positive ALL. PhALLCON

Study design

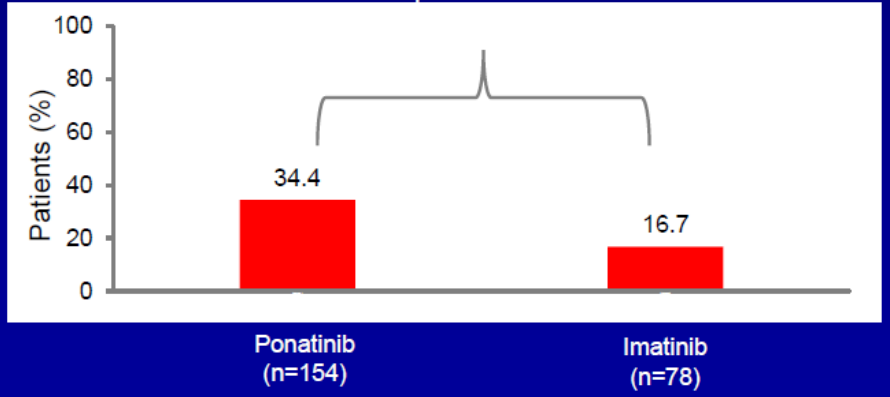


Primary endpoint:

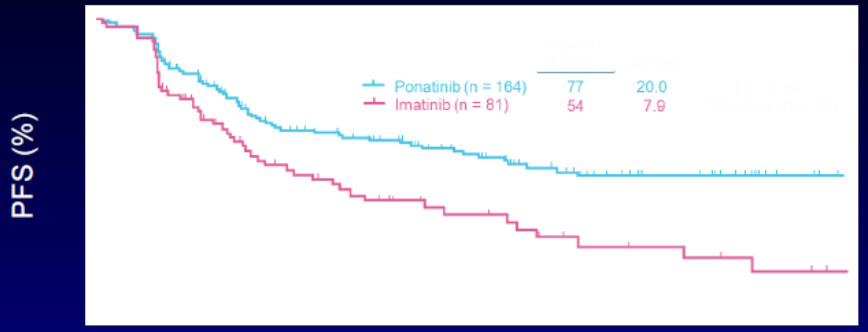
MRD– (MR4) CR at end of induction

RR: 2.06 (95% CI=1.19–3.56)

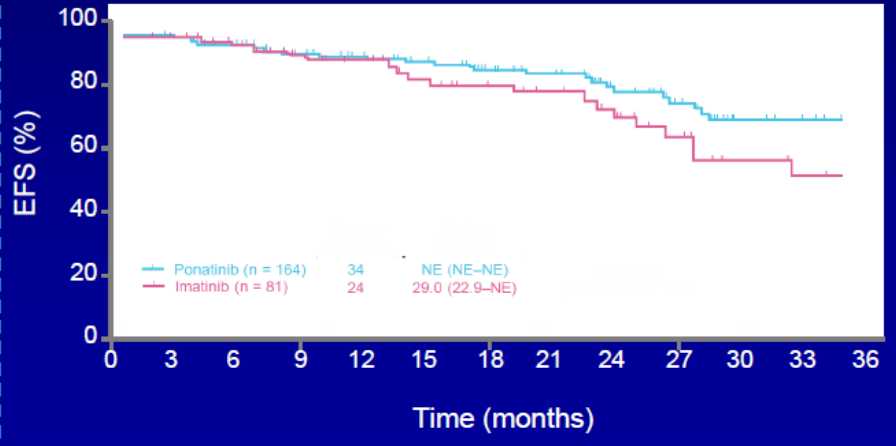
p=0.0021



PFS

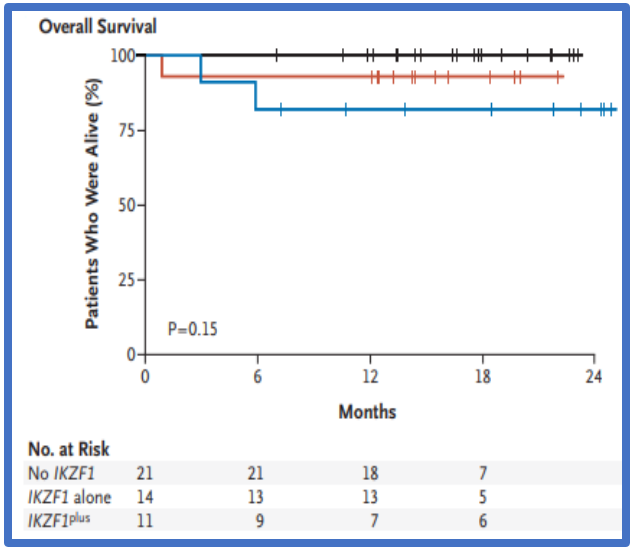


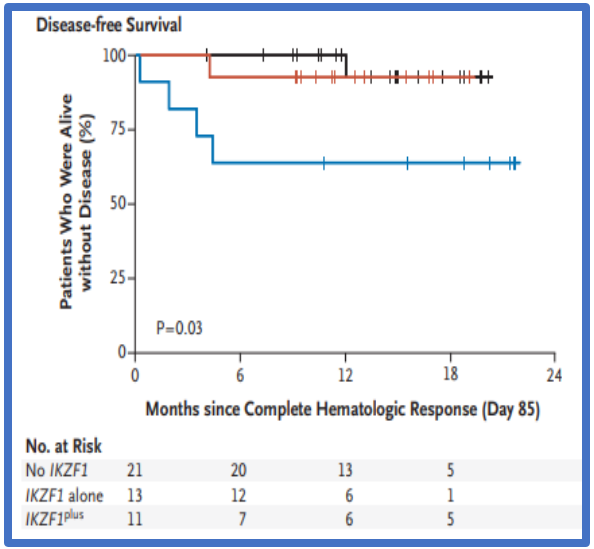
EFS

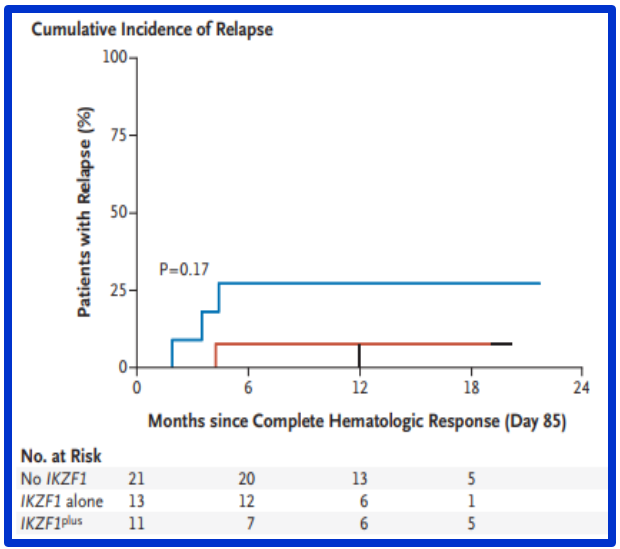


Jabbour. ASCO plenary 2023: abst# 398868

Prognostic Relevance of Genomic Lesions in Ph-Positive ALL Treated With Blinatumomab + Dasatinib

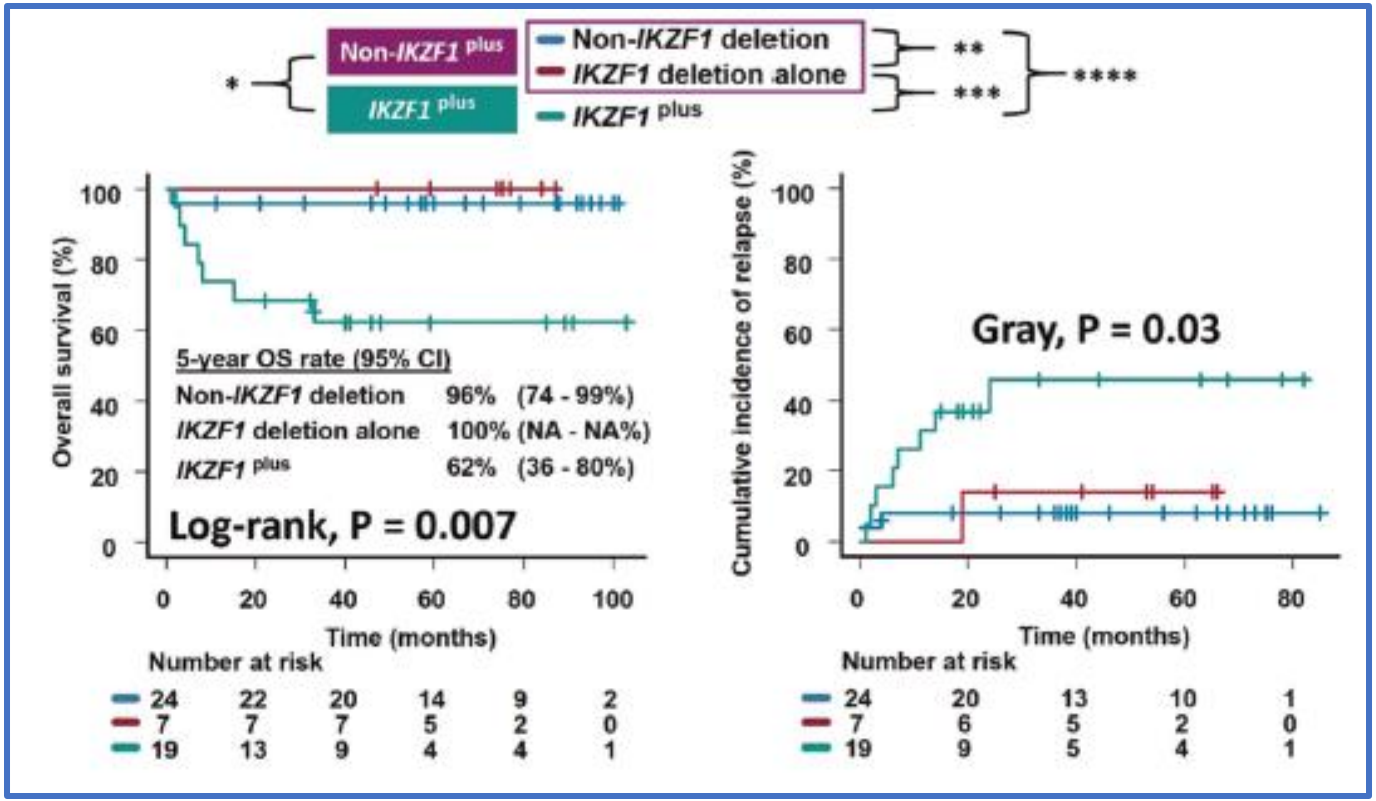




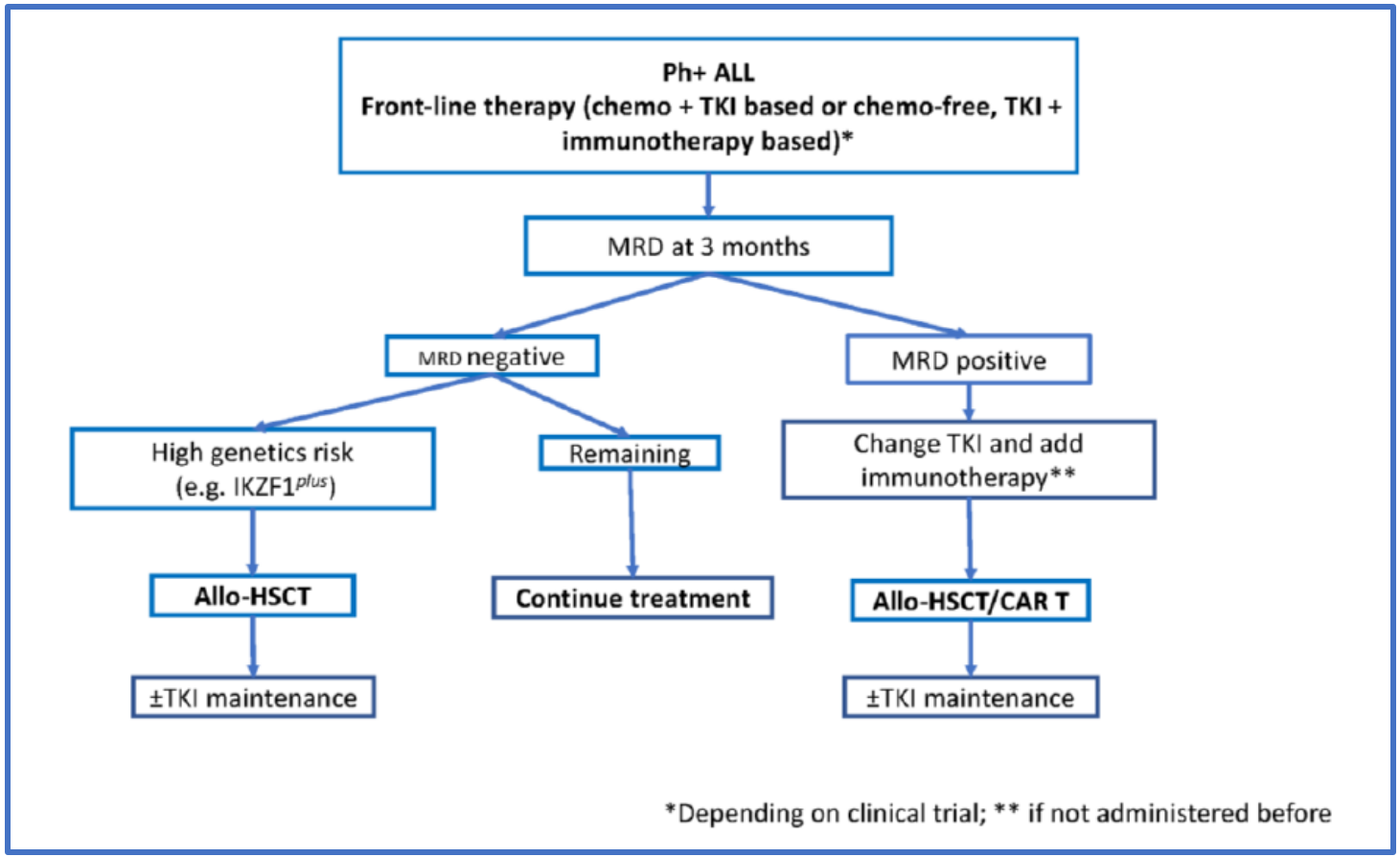


Foà R, et al. *N Engl J Med.* 2022;383:1613-1623.

Prognostic Relevance of IKZF1^{plus} in Ph-Positive ALL Treated With Ponatinib



Sasaki Y, et al. *Leukemia.* 2022;36:1253-1260.



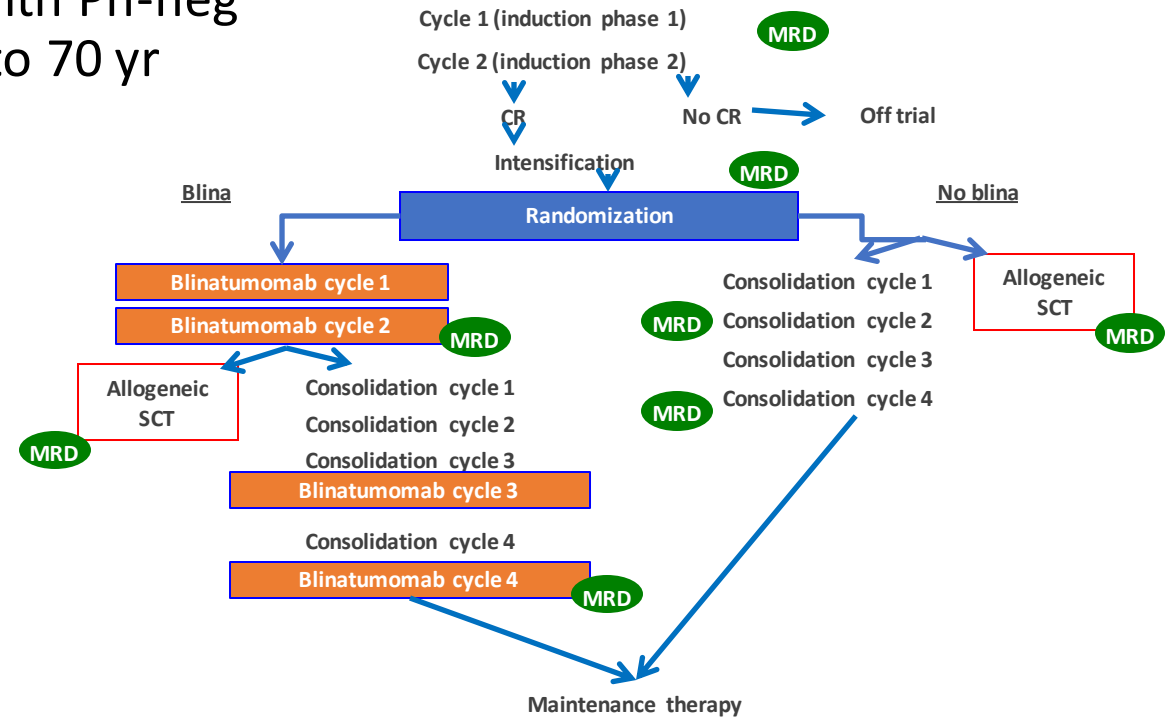
Ribera JM, Chiaretti S. *Cancers (Basel).* 2022;14:4454.

Ph-Negative, BCP-ALL: Issues to Be Considered

- Genetic background (Ph-like, *KMT2A*, low hypodiploidy, complex karyotype, *TP53*)
- Robust methodology for MRD assessment (Flow, PCR for Ig/TCR, NGS)
- Availability of immunotherapy for first-line Tx (with possible reduction of chemotherapy)
- Precise indications for allo-HSCT in CR1 (MRD positivity, poor genetics)
- Emergence of new compounds (eg, menin inhibitors)

First-Line Immunotherapy Phase III Trials: ECOG-ACRIN E1910

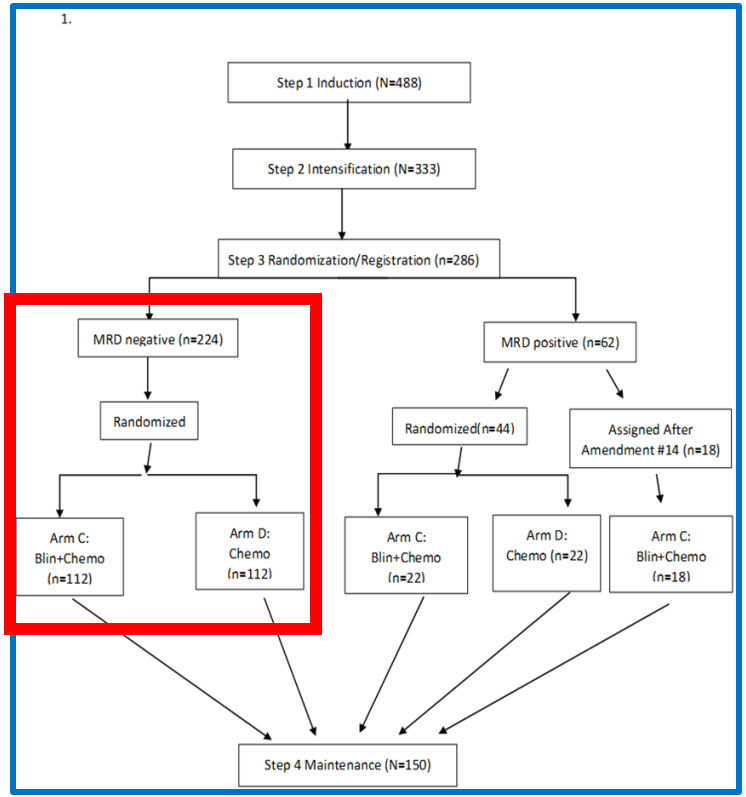
- N = 488 patients with Ph-neg BCP-ALL, aged 30 to 70 yr
- 1:1 randomization

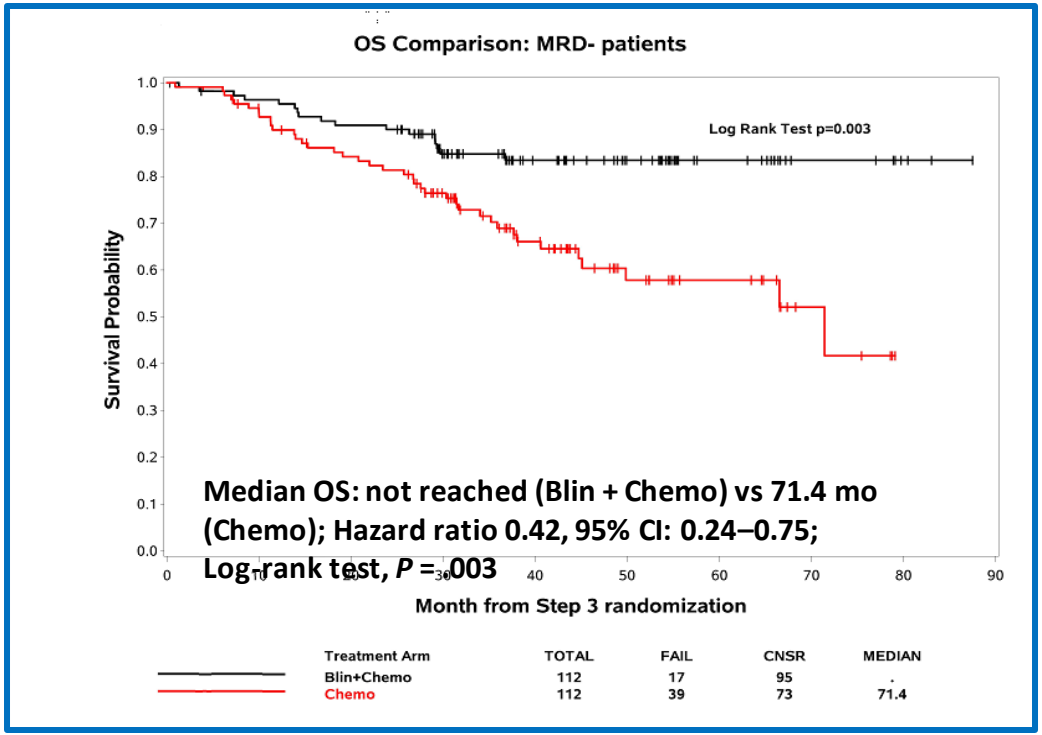


Courtesy of Mark Litzow.
ClinicalTrials.gov: NCT02003222 (closed to enrollment).

BCP, B-cell precursor; SCT, stem cell transplantation.

Overall Survival Comparison: MRD-Negative Patients





Median OS: not reached (Blin + Chemo) vs 71.4 mo (Chemo); Hazard ratio 0.42, 95% CI: 0.24–0.75; Log-rank test, *P* = .003

Deaths on Blin + Chemo arm = 17, Chemo arm = 39

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

Frontline Blinatumomab and Inotuzumab Combinations in Adults With Newly Dx ALL

	Agent	N	Median Age (yr, range)	CR, %	MRD Negativity, %	OS, % (x-yr)
Hyper-CVAD + Blina	Blinatumomab	38	37 (17–59)	100	97	81 (3-yr)
Hyper-CVAD + blina-inotuzumab	Blinatumomab and inotuzumab	25	24 (18–47)	100	91	100 (1-yr)
GIMEMA LAL 1913	Blinatumomab	149	41 (18–65)	90	96	84 (1-yr)
GRAALL-2014-Quest	Blinatumomab	95	35 (18–60)	NA	74	92 (1.5 yr)
Low-intensity blinatumomab	Blinatumomab	30	52 (39–66)	100	73	69 (2-yr)

Short NJ, et al. *Blood.* 2021;138(suppl 1):1223; Bassan R, et al. *HemaSphere.* 2022;6:14-15; Boissel N, et al. *Blood.* 2021;140(suppl 1):1232; Fleming S, et al. *Blood.* 2021;138(suppl 1):1234.

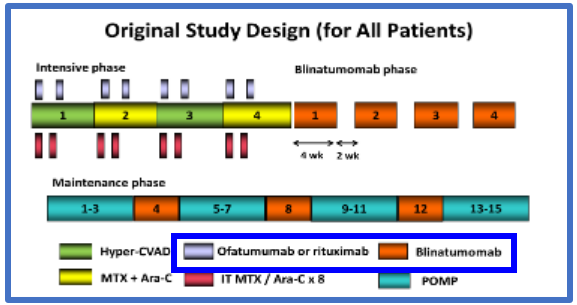
Frontline Blinatumomab and Inotuzumab Combinations in Newly Dx Older ALL

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

Short NJ, et al. *Blood.* 2021;138(suppl 1):3400; Advani AS, et al. *J Clin Oncol.* 2022;40(14):1574-1582; Chevallier P, et al. *Blood*. 2021;140(suppl 1):511; Goekbuget N, et al. *Blood*. 2021;138(suppl 1):3399; Stelljes M, et al. *Blood*. 2021;140(suppl 1):2300.

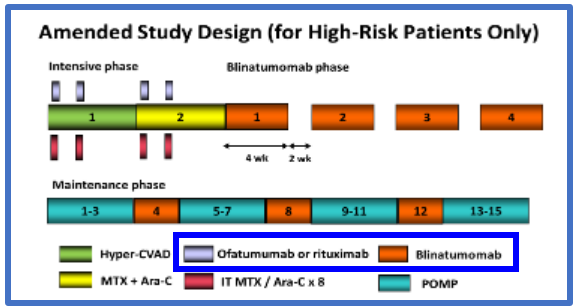
First-Line Immunotherapy With Less Chemotherapy in Adult Ph-Negative B-ALL

50% less intensive chemo*



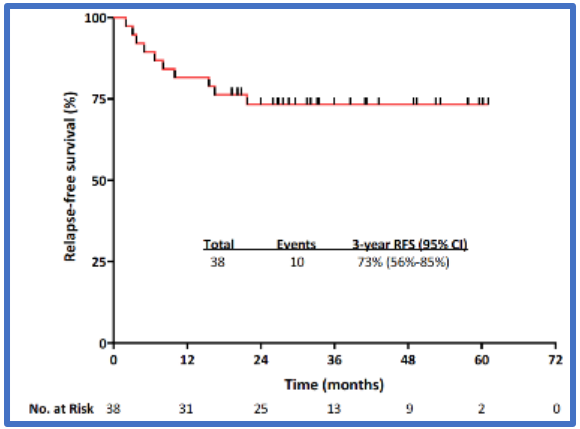
*Vs standard hyper-CVAD regimen.

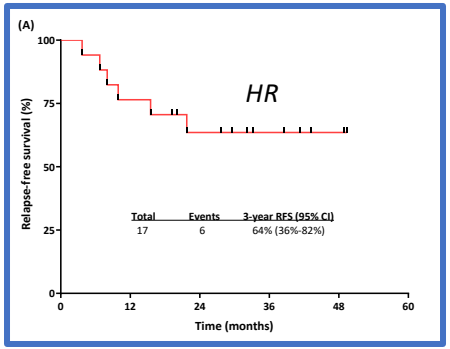
75% less intensive chemo*

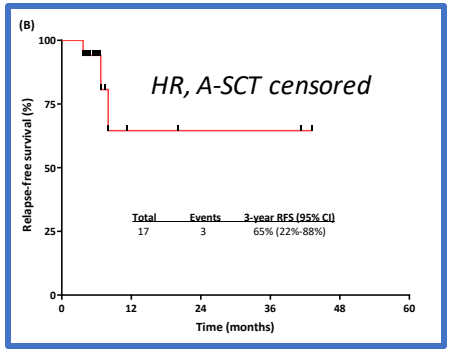


Immunotherapy

- **MD Anderson Cancer Center**
  - **N = 38**: CR 100%, MRD_{neg} 76–97%
  - **3-yr RFS 73%**, 3-year RFS HR 64%







Jabbour ES, et al. *Lancet Haematol.* 2023;10:e24-e34.

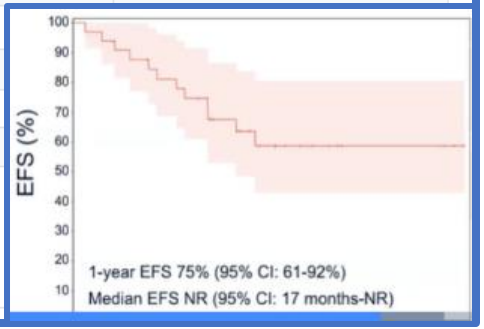
A-SCT, allogeneic stem cell transplantation.

Chemo-Free Treatment With InO and Blinatumomab for Older Adults With Newly-Diagnosed, Ph-Negative, CD22-Positive, B-ALL: ALLIANCE A041703

N=33	Induction InO I A/B/C	Blinatumomab Course II
Composite CR*	28 (**85%**)	32 (**97%**)
CR	15 (45%)	19 (58%)
CRh	11 (33%)	12 (36%)
CRi	2 (6%)	1 (3%)
Refractory	3 (9%)•	
Survival		
1-yr EFS	75% (95% CI 61-92%)	
1-yr OS	84% (95% CI 72-92%)	

*CR+CRh+CRi

, 1 completed IA only, 2 proceeded to course II



- Median age 71 (60–84)
- Median WBC 3.2K (6–38K); median CD22 expression 92% (21%–100%)
- 12 events
  - 9 relapse
  - 2 deaths in CR (1 during blina, 1 after allo-HCT)
  - 1 death w/o remission
  - 2/2 VOD
  - 9 total deaths (6 after relapse)
- Common grade ≥3 AEs occurring in >10% of pts
  - Neutropenia (88%)
  - Thrombocytopenia (73%)
  - Anemia (42%)
  - Leukopenia (39%)
  - Lymphopenia (27%)
  - Febrile neutropenia (21%)
  - Encephalopathy (12%)

Conclusion: InO induction → BLIN consolidation is highly active, tolerable therapy for older adults with ND, Ph-negative, B-lineage ALL with durable remissions in this short-term follow-up.

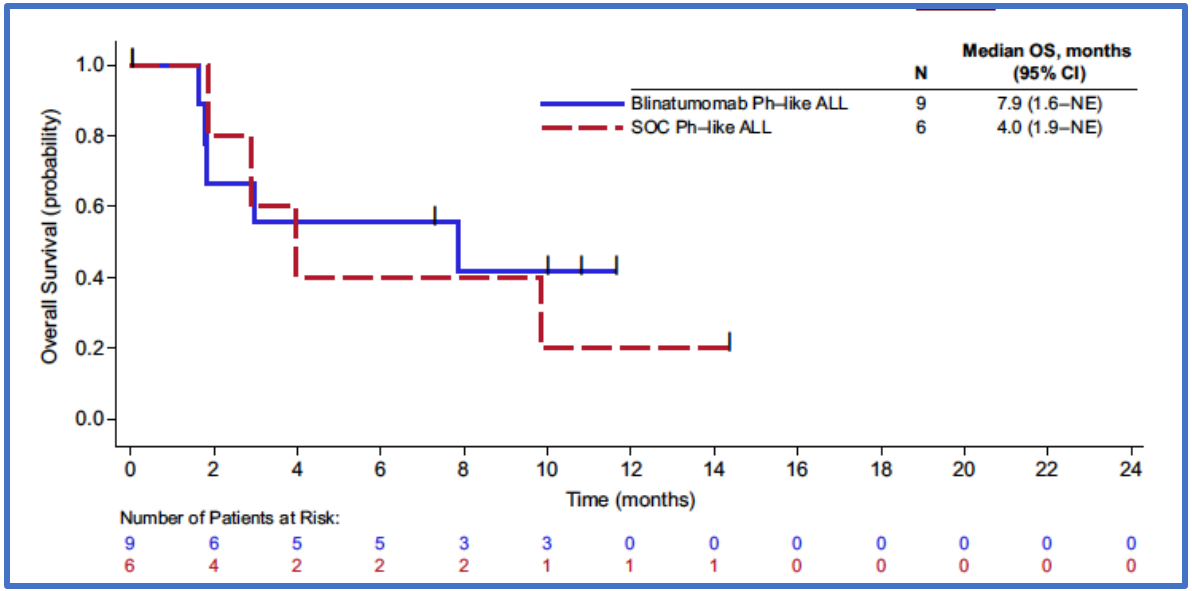
Wieduwilt, M et al. EHA 2023. Abstract S117.

Current Treatment Strategies for Ph-Like ALL

- For "ABL-class" fusions (e.g. involving *ABL1, ABL2, CSF1R, PDGF2*), targeting with Dasatinib has shown efficacy in pediatric population
- For *JAK,CRLF2, EPOR* fusions, ongoing studies of Ruxolitinib in the frontline but no efficacy data yet
- Evidence that immune targeting (CD19, CD22) may be effective: Blinatumomab, Inotuzumab have shown some efficacy
  - Frontline evaluation of these immune targeting strategies with combination chemotherapy

Ph-Like ALL (TOWER)

Ph-Like ALL (All Cohorts)	Blinatumomab	BAT
Complete remission, %	36 (34)	0 (16)
MRD-neg CR	50 (42)	0 (22)



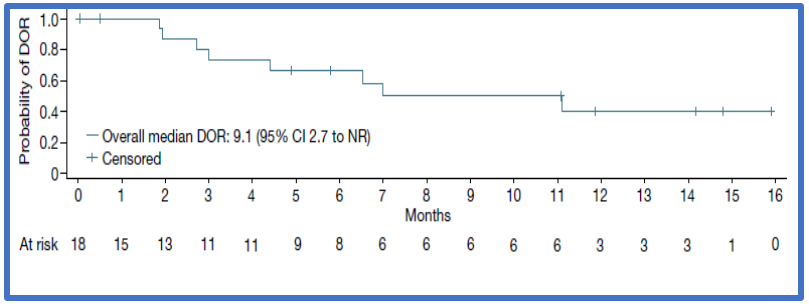
HR for OS (Blin) 0.39 (95% CI, 0.04–3.78)

Jabbour E, et al. *Am J Hematol*. 2021;96:e379-e383.

Immunotherapy and Precision Medicine in *KMT2A*-Rearranged ALL

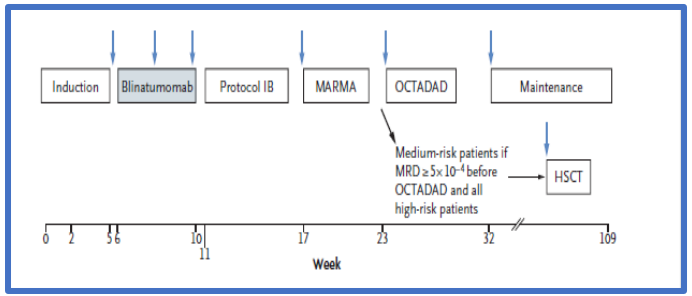
Revumenib in *KMT2A*r or *NPM1*m

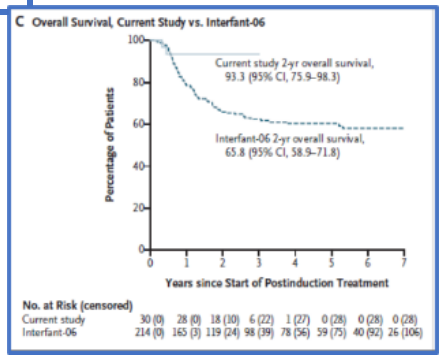
- First-in-human phase I trial (AUGMENT-101, NCT04065399)
- N = 68
- Previous lines Tx: 4 (1–12)
- Prior allo-HSCT: 31 (46%)
- TEAE: QT >500 ms, nausea, febrile neutropenia, and thrombocytopenia
- GR 1–2 differentiation syndrome: 8 (14%)
- ORR: 55% (***KMT2A*r 27/46 [59%]**), CR/CRh: 24%
- Mutations in *MEN1:* 12/31 (38.7%)
- Next trial: AUGMENT-102: revumenib + chemo

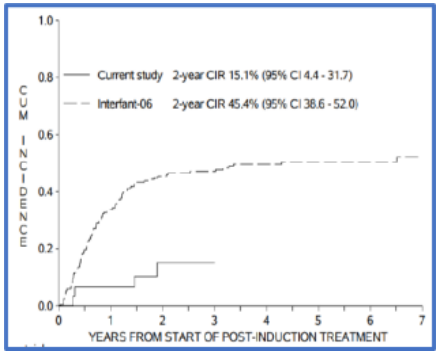


Issa GC, et al. *Nature*. 2023;615:913-919.

Blinatumomab in *KMT2*r Infant ALL







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

T-ALL: Small Improvements for First-Line Tx

- Nelarabine in first line?
  - Positive impact in pediatric ALL
  - 2 studies in adults showing no benefit
    - MD Anderson (retrospective)
    - UKALL randomized trial
- BH3 mimetics in first line combined with chemotherapy

Newly Diagnosed T-ALL: Nelarabine

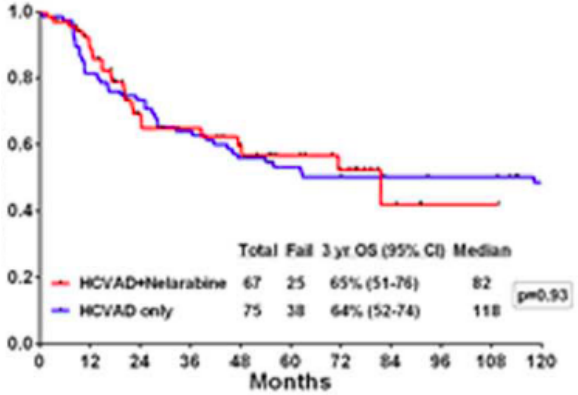
Hyper-CVAD + Nelarabine

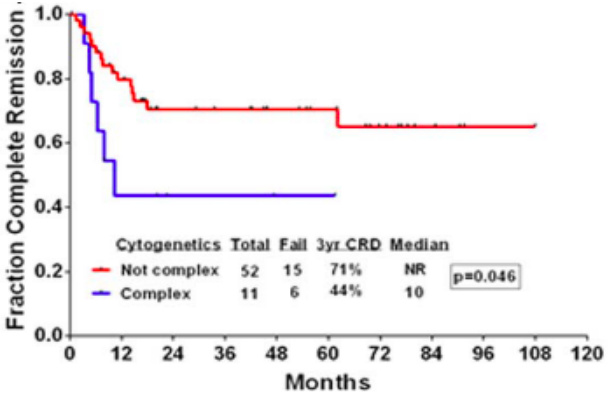
Single-arm phase II study
Hyper-CVAD × 8 c + **2c nelarabine** (end) (N = 30p)
Hyper-CVAD × 8 + **2c nelarabine** (c4 and c5) (N = 37p)
Maintenance POMP + nelarabine

N = 67p (T-ALL, T-LBL) – 15p ETP (22%)
Median F/U 42.5 mo (4–110 mo)

- 3-yr OS 65%
- 3-yr CRD 66%

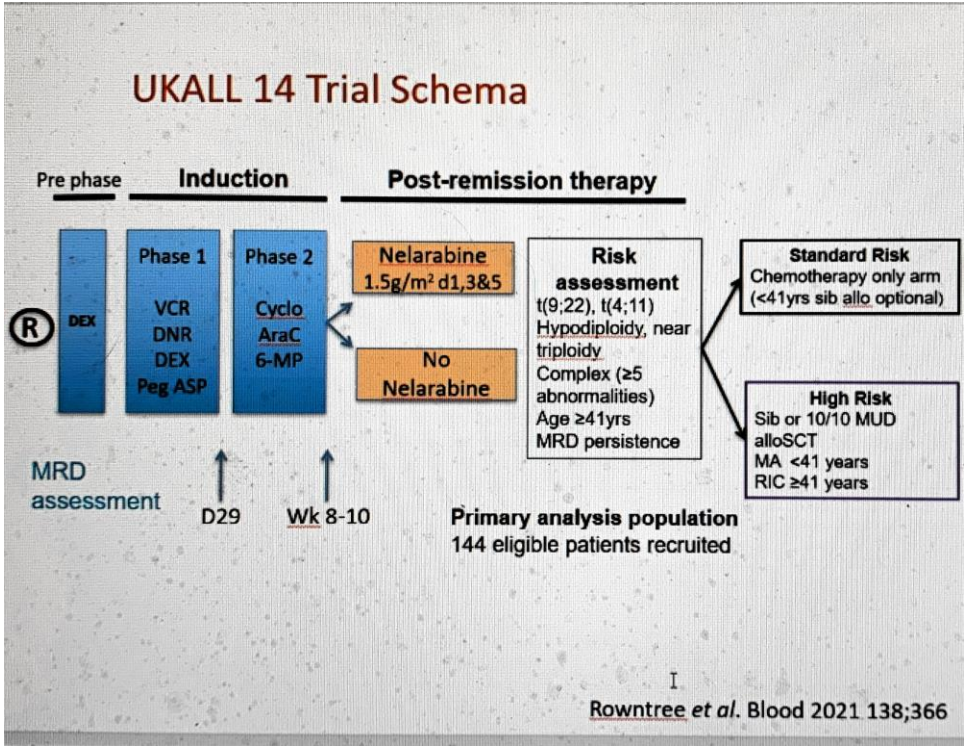
No differences: phenotype, WBC, nelarabine regimens
Complex karyotype: inferior OS and CRD

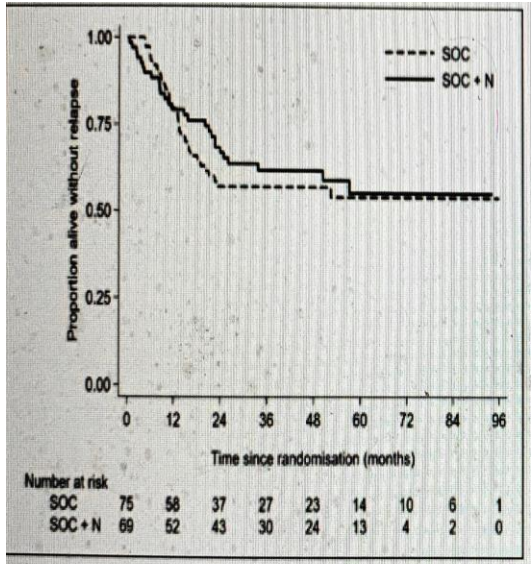




Abaza Y, et al. *Am J Hematol*. 2018;93:91-99.

Nelarabine Up-Front: Randomized Trial (UKALL14)





3 year EFS

- SOC: 57% (44.7-67.5)
- SOC + N: 61.7% (48.7-72.4)

5 year EFS

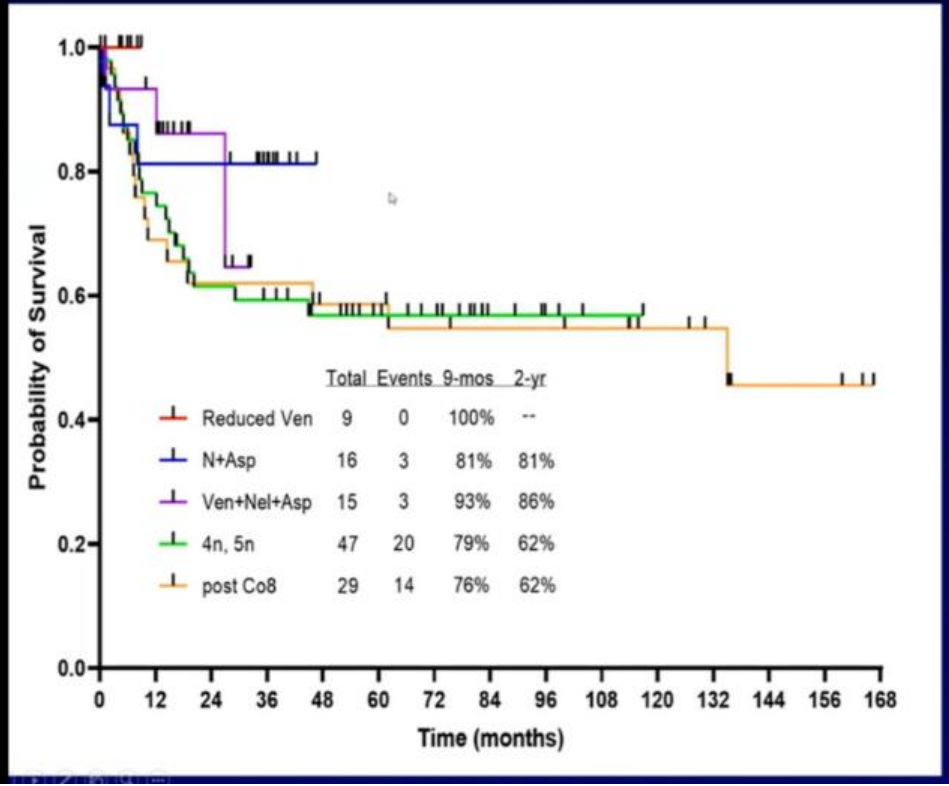
- SOC: 54.1% (41.2-65.4)
- SOC + N: 55.5% (40.8-67.7)

HR: 0.88 (0.52-1.46), p=0.61

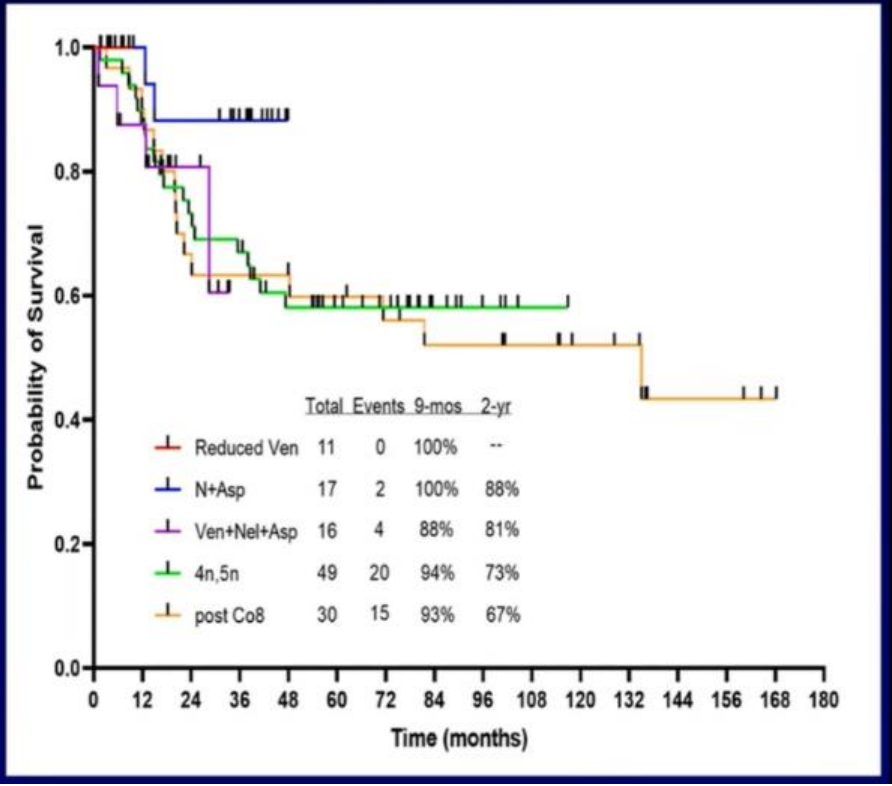
Rowntree *et al.* Blood 2021 138;366

HCVAD-Nelarabine-PEG Asparaginase-Venetoclax in T ALL

PFS



OS



Courtesy of Elias Jabbour.

Conclusion

- First-line therapy can be optimized in young adults with ALL
- Ph-positive ALL
  - Third-generation TKI + immunotherapy
  - Reduced indication for HSCT
- Ph-negative ALL
  - Immunotherapy combined with CHT
  - Reduction of intensity of CHT?
  - Reduction of indications for HSCT?
  - Incorporation of precision medicine (TKI for ABL-class Ph-like, menin inhibitors?)
- Ph-like ALL
  - Incorporation of new drugs front line (BH3 mimetics, nelarabine)


Thank you
jribera@iconcologia.net

Global Leukemia Academy

AYA ALL patients:

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

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

Wellington Silva

Hospital das Clínicas

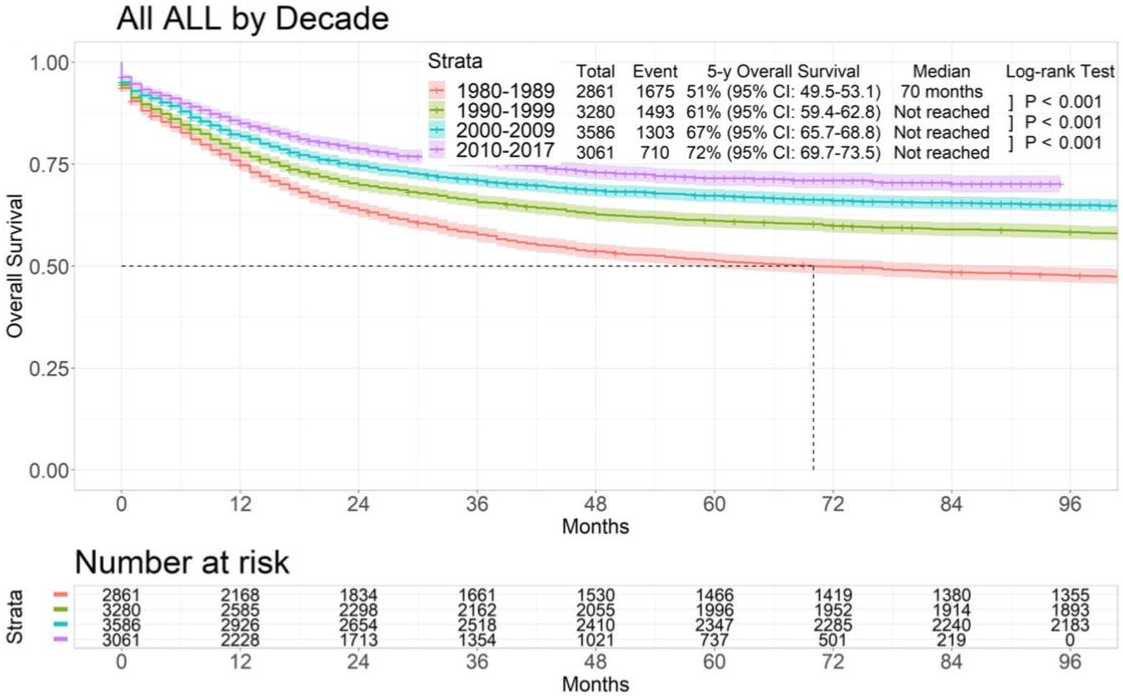
University of São Paulo, Brazil

APTITUDE HEALTH

Disclosures

- Advisory: Pfizer, Amgen, Daiichi, Takeda
- Speaker: Pfizer, Amgen, Servier, Pint-Pharma
- Research funding: Servier, Libbs

Introduction



USA: >70% of AYA patients are treated in adult centers; hyper-CVAD is the most prescribed regimen

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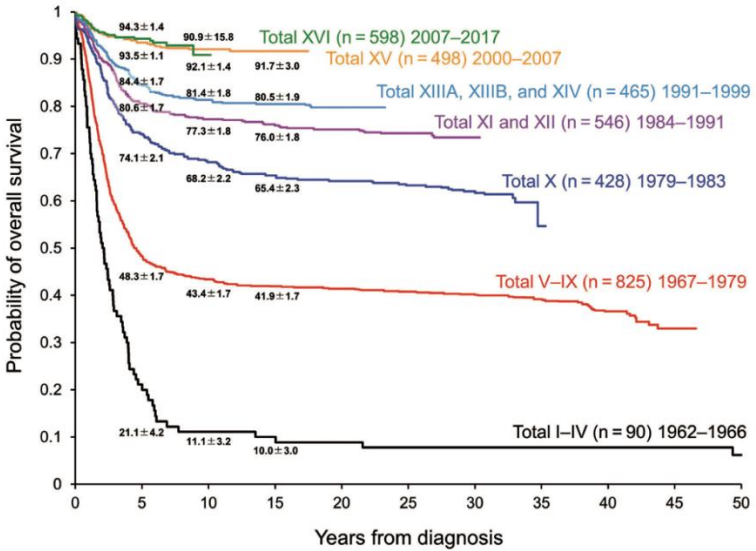
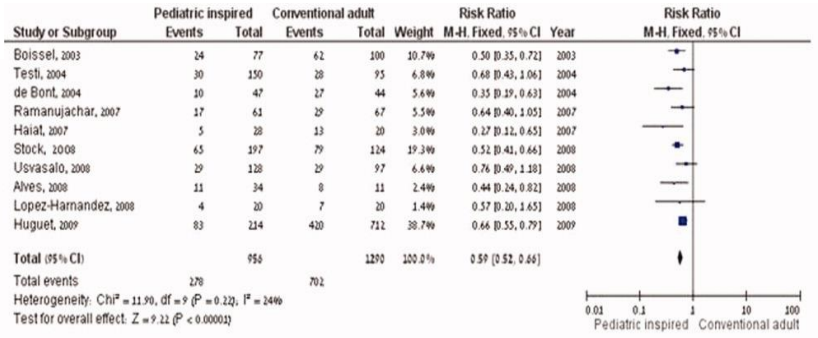
Sasaki K, et al. *Am J Hematol*. 2021;96(6):650-658; Muffly L, et al. *Cancer*. 2017;123 (1):122-130.

Pediatric ALL: A Success History



- Organization through cooperative groups since 1960s
- Genetically homogeneous disease
- More tolerance to chemo
- Psychosocial factors



Pui C, Evans W. *Semin Hematol*. 2013;50(3):185-196; Kansagra A, Litzow M. *Curr Hematol Malig Rep*. 2017;12(3):187-196; Ram R, et al. *Am J Hematol*. 2012;87:472-478.

Study	N	Age, Years	CR	OS, % (timepoint)	ASP Form	ASP Dose (IU/m²) and Cycles
Pediatric regimens						
DFCI *(DeAngelo et al, Blood 2015)*	110	18–50	89%	75 (3 yr)	PEG-ASP	2000–2500 for 8–15 cycles
CALGB 10403 *(Stock et al, Blood 2014)*	296	17–39	NA	78 (2 yr)	PEG-ASP	2500, 7 cycles
Pediatric-inspired regimens						
PETHEMA *(Ribera J et al, J Clin Oncol 2008)*	81	15–30	98%	69 (6 yr)	*E. coli*	10–20000, 3 cycles
GRAALL-2003 *(Hughet et al, J Clin Oncol 2009)*	225	15–45 46–60	94%	64 (3.5 yr) 47 (3.5 yr)	*E. coli*	10000, 9 cycles
USC *(Douer D et al, J Clin Oncol 2014)*	40	18–57	98%	58 (7 yr)	PEG-ASP	2000, 6 cycles
HOVON 70 *(Rijneveld AW et al, Leukemia 2011)*	54	17–39	91%	66 (2 yr)	*E. coli*	6000, 9 cycles
GMALL 07/2003 *(Goekbuget N et al, Blood, 2010)*	1226	15–55	91%	60–67 (3 yr)	PEG-ASP	1000–2000, 7 cycles
UKALL14 *(Patel B et al, Leukemia 2017)*	91	25–65	80%	Not reported	PEG-ASP	1000, 2 cycles

Pediatric-Inspired ALL Protocols

ADULT REGIMENS

- More myelosuppressive agents such as daunorubicin, cytarabine, and cyclophosphamide
- Lack of asparaginase or lower cumulative dose
- Lack of reinduction or delayed intensification
- Allo-HSCT in first remission for the majority of patients

PEDIATRIC REGIMENS

- Dose intensity of less myelosuppressive agents – corticosteroids, vincristine, and asparaginase
- Delayed reinduction
- Early and frequent CNS prophylaxis
- MRD-guided therapy
- Allo-HSCT for very high-risk patients

Kansagra A, et al. *Leuk Lymphoma*. 2018;59(3):526-541; Aldoss I, Stein AS. *Leuk Lymphoma*. 2018;59(5):1033-1050.

Poll to Audience

> Do you **REALLY** feel that adult patients with newly diagnosed Ph-negative ALL benefit from pediatric regimens?

A. Yes
B. No

Poll to Audience

> Have you **used** pediatric-inspired protocols in your clinical practice?

A. Yes
B. No

ALL Protocol in Less-Resourced Settings

- **Simple and easy** to follow
- **Less-toxic protocol**
- **Timely diagnosis** is critical to good outcome
- **Financial burden**
- Allogeneic SCT only for **very-high-risk subsets**
- **Few** options for salvage
- **Drugs** reimbursed by public system

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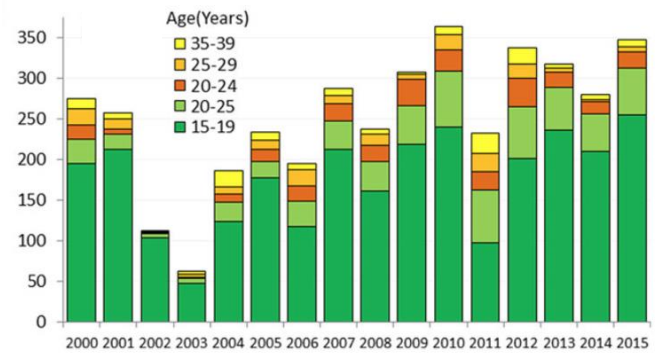
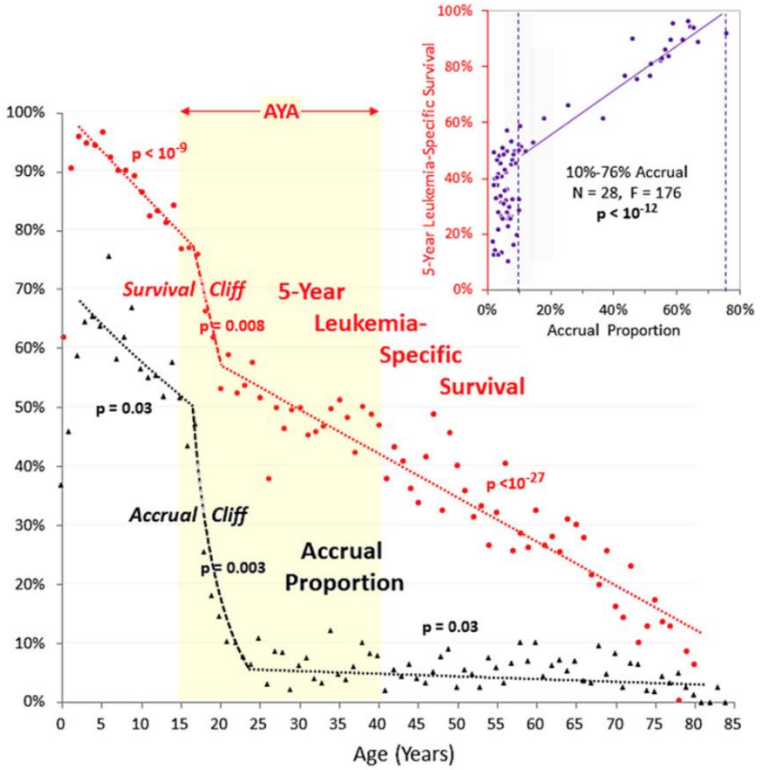
Adapted from Chagaluka G, et al. *Br J Haematol*. 2020;191(3):e87-e90.

The Role of Prospective Studies



- IC-APL initiative (2004) – multicenter Latin American study for APL – increase in OS
- ICAML (2016)
- BRALLA (2023) – NCT05959720



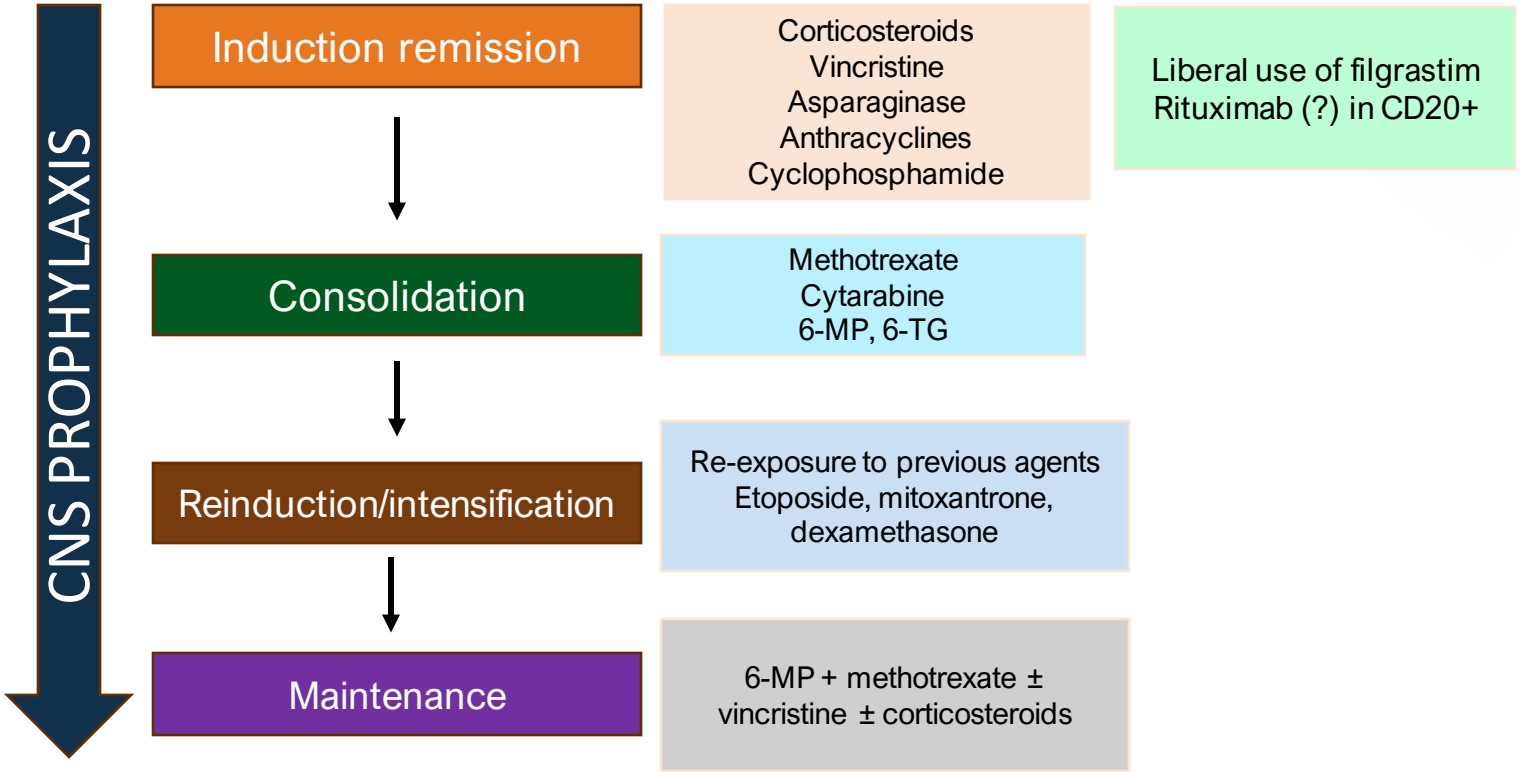
Bleyer A, et al. *Pediatr Blood Cancer*.2018;65:e27074; Corrêa de Araujo Koury L, et al. *Br J Haematol*. 2017;177(6):979-983.

Challenges of Starting Pediatric Protocols

- Small proportion of patients outside reference centers
- Perception of high toxicity from asparaginase
- Peculiar profile of side toxicities of asparaginase
- Need for outpatient care

Siegel SE, et al. *JAMA Oncol*. 2018;4(5):725-734; Aldoss I, Stein AS. *Leuk Lymphoma*. 2018;59(5):1033-1050.

Backbone of Pediatric Protocols



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Adapted from Estey EH, Faderl SH, Kantarjian HM. *Hematologic Malignancies: Acute Leukemias.* 1st ed. Heidelberg, Germany: Springer Berlin Heidelberg; 2008.

Remission Induction in ALL

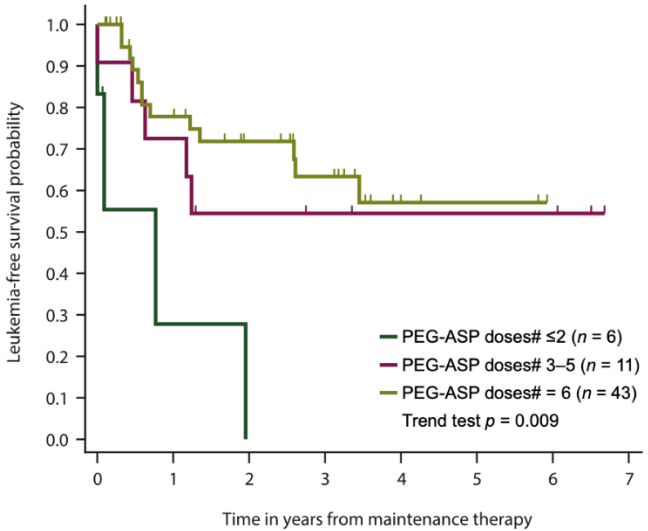
- Pre-phase – corticosteroids ± cyclophosphamide
  - Response to prednisone – prognostic factor in adults (Annino et al, GIMEMA, 2002) – <1000 blasts/µL
  - Crucial time for genetic characterization – Philadelphia chromosome
- Dexamethasone vs prednisone – decrease in CNS relapses in patients aged <10 yr (Bostrom et al, CCG-1922, 2003)
  - More toxicity of dexa in adults, no clear benefit in patients aged >10 yr → myopathy, glucose alterations, neurotoxicity, and osteonecrosis (Larsen E et al, CCO-AALL0232, 2016)
- Benefit of cyclophosphamide in induction – unclear (Annino et al, GIMEMA, 2002)

Simioni C, et al. *Hematol Oncol*. 2020;38(1):22-33; Paul S, et al. *Mayo Clin Proc*. 2016;91(11):1645-1666.

Role of Asparaginase

Formulation	Half-Life	Dosage
Native *E. coli* asparaginase	26–30 hours	6000 IU/m² 3 times/week
PEG-asparaginase	5.5–7 days	1000–2500 IU/m² every 2–4 weeks
Erwinia asparaginase	16 hours	6000–30000 IU/m² daily

- Small studies – overall benefit in terms of relapse and survival
- Retrospective comparisons – ASP-containing regimens vs hyper-CVAD – controversial results, trend to better survival with the former



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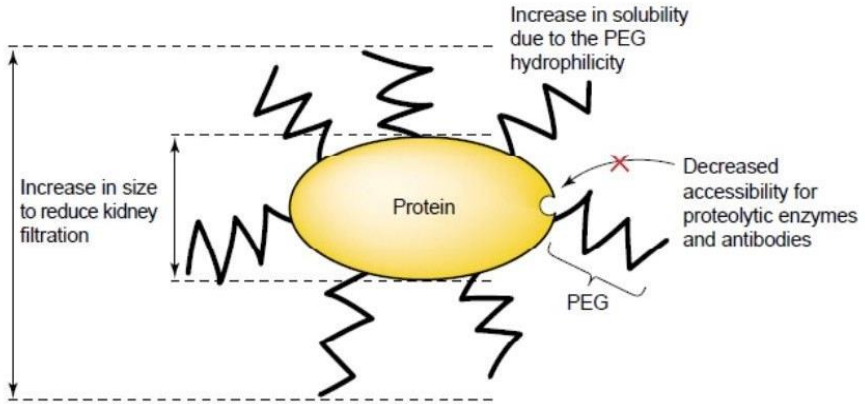
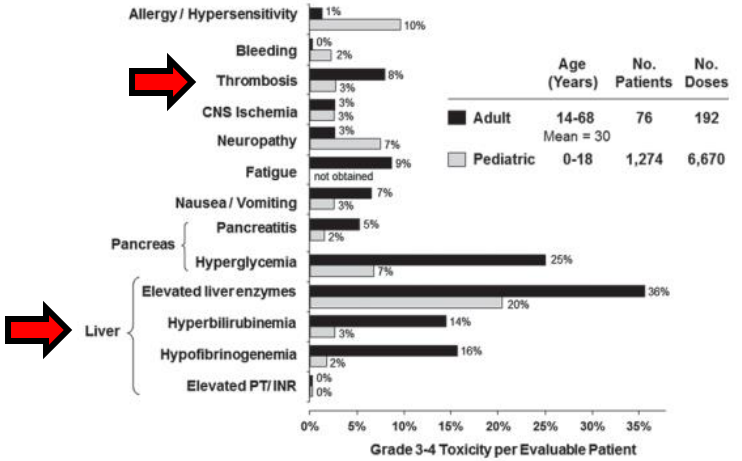
Simioni C, et al. *Hematol Oncol*. 2020;38(1):22-33; Aldoss I, et al. *Blood*. 2013;122(21):3915; Egler RA, et al. *J Pharmacol Pharmacother*. 2016;7:62-71.

Toxicity of Asparaginase





- Depletion of asparagine for 2–4 weeks
- Reduction in formation of antibodies
- Peak enzyme activity levels are attained within 5 days after intramuscular administration → **suggestion for intravenous route?**
- PEG-ASP penetrates poorly into the CSF → CSF depletion after plasm

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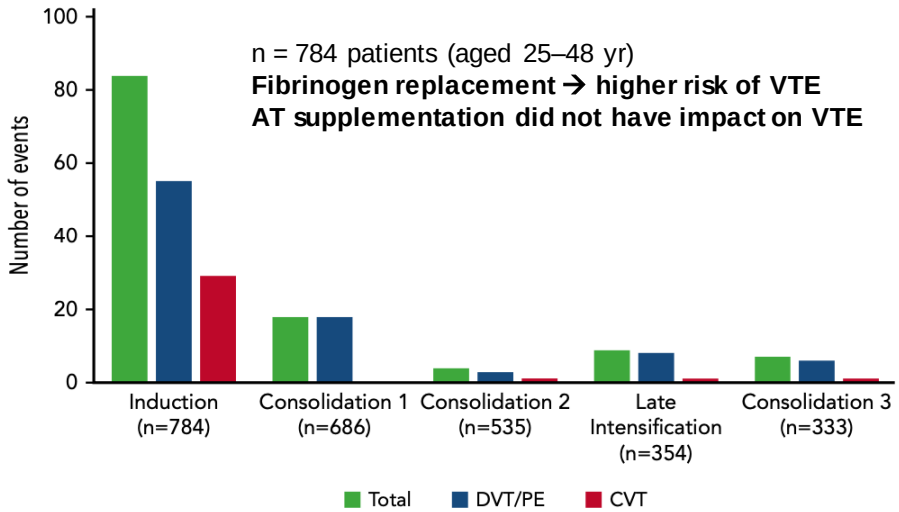
Douer D, et al. *Blood*. 2007;109(7):2744-2750; Shrivastava S, et al. *Crit Rev Oncol Hematol*. 2016;100:1-10; Stock W, et al. *Leuk Lymphoma*. 2011;52(12):2237-2253.

Thromboembolic Events With ASP

GRAALL-2005



THROMBOSIS (incidence of 5%–30%)

- **Replace fibrinogen if <50 mg/dL or only prior to invasive procedures**
- **Antithrombotic prophylaxis and antithrombin replacement – unclear**
- Recommended use of enoxaparin during induction if low risk of bleeding
- Occurrence of thrombosis does not preclude further use of ASP

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Rank CU, et al. *Blood*. 2018;131(22):2475-2484; Shrivastava S, et al. *Crit Rev Oncol Hematol*. 2016;100:1-10.

Thromboembolic Events With ASP

Thromboembolic event

↓

Discontinue ASP temporarily until resolution of symptoms
<u>Start anticoagulation</u>

LMWH → anti-Xa
Heparin → PTTa

- Maintain plaq >30–50 × 10^9/L;
- Stop LMWH 24 hr before lumbar punction

RE-EXPOSURE

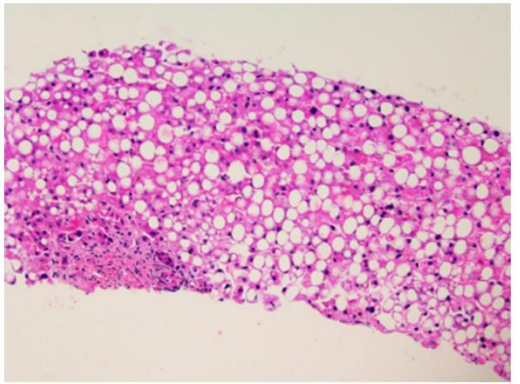
- **Screening for hereditary thrombophilias is not mandatory**
- **Grade 4 events (hemodynamic instability or cerebral venous thrombosis with permanent disability) should preclude further using of ASP**

Therapeutic: 0.7–1.2 UI/mL
Prophylactic: 0.1–0.3 UI/mL

Truelove E, et al. *Leukemia.* 2013;27(3):553-559; Payne JH, Vora AJ. *Br J Haematol.* 2007;138(4):430-445.

ASP-Induced Liver Toxicity

- Minor alterations in liver enzymes and bilirubin occur in the majority of patients
- Always reversible – might affect concurrent chemotherapy
- More common in adults and with PEG-asparaginase



Stock W, et al. *Leuk Lymphoma*. 2011;52(12):2237-2253; Patel B, et al. *Leukemia*. 2017;31(1):58-64; Gokbuget N, et al. ASH 2010.

ASP-Induced Liver Toxicity

Study	N	Age, Years	ASP Dose (IU/m²)	Number of Doses	Grade 3/4 Hepatotoxicity	Associated Factors	OS, %
CALGB 10403 *(Stock W et al, Blood 2019)*	295	17–39	2500 IM or IV each 3–4 weeks	8–9	Bilirubin: 18% Transaminitis: 28%		73 (3 yr)
City of Hope *(Aldoss I et al, Eur J Haematol 2015)*	152	23–47	2000 IV	9	Bilirubin: 24% Transaminitis: 54%	BMI, Hispanics, and higher cumulative dose	Not reported
USC *(Douer D et al, J Clin Oncol 2014, and Burke P et al, Leuk Res 2018)*	51	18–57	2000 (uncapped) IV each 4 weeks	6	Bilirubin: 31.4% Transaminitis: 64.7%	BMI	58 (7 yr)
University of Michigan *(Rausch CR et al, Leuk Lymphoma 2017)*	107	18–79	Variable	NI	Bilirubin: 21%	BSA, albumin, and platelet <50 × 10^9/L	Not reported
GMALL 07/2003 *(Goekbuget N et al, EHA 2016)*	2094	18–55	500–2000 (capped at 3750) each 3 weeks	2–6	Bilirubin: 16% Transaminitis: 30%	BMI, liver steatosis	58 (5 yr)
UKALL14 *(Patel B et al, Leukemia 2017)*	90	25–65	1000 IV each 2 weeks	2	Bilirubin: 24% Transaminitis: 36.5%	Aged >40 yr BMI	Not reported
University of São Paulo, Brazil *(Silva W et al, Clin Lymphoma Myeloma Leuk 2020)*	57	15–57	2000 (uncapped) IV each 2 weeks	2	Bilirubin: 28% Transaminitis: 44%	BMI	Not reported

ASP-Induced Liver Toxicity: Prevention and Management

2000 IU/m^2

↓

1000 IU/m^2

- Avoid doses greater than 2000 IU/m^2
- Capping at 3750 IU(?)

RISK FACTORS
- BMI ≥30 kg/m^2
- Hepatic steatosis
- Aged ≥35 years

Isolated transaminitis

Grade 3 or 4: Hold ASP until grade 1

Elevation of bilirubin

Direct B >3.0 mg/dL → hold until <2.0
DB >5 mg/dL or ascites, peripheral edema, encephalopathy → hold indefinitely

Vitamin B complex – 1 tablet PO twice day
L-carnitine 50 mg/kg/day IV in 6 doses

- After recovery, stepwise application of ASP
- Lower dose (500/1000 U) until full dose

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Stock W, et al. *Leuk Lymphoma*. 2011;52(12):2237-2253; Burke PW, et al. *ESMO Open*. 2020;5:e000858.

Consolidation

- Avoid unnecessary interruptions over these blocks
- Methotrexate toxicity
  1. High dose (2–5 g/m^2) in short infusions or continuous infusion with folinic acid rescue
  2. Capizzi (low doses 100–300 mg/m^2 along with ASP)

  (Sakura et al, JALSG, 2017) → randomized trial 3 g/m^2 vs 0.5 g/m^2 → 5-yr DFS 58% vs 32%

  - MTX serum level monitoring – not employed universally in many centers – similar kidney toxicity rates (Silva W et al, ASH 2022)
  - Vigorous hydration, urinary alkalinization, clinical e lab monitoring
- Probable universal benefit of blinatumomab even in MRD-neg patients (M Litzow et al, ASH 2022 – ECOG-ACRIN)

Gökbuget N, Hoelzer D. *Semin Hematol*. 2009;46(1):64-75; Paul S, et al. *Mayo Clin Proc*. 2016; 91(11):1645-1666.

Maintenance

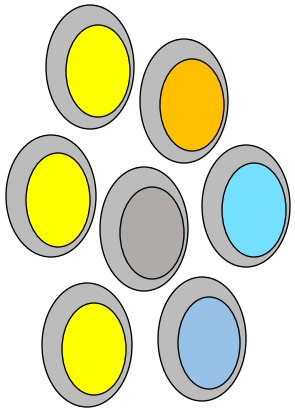
- Attempt at omitting maintenance – higher relapse rates
- Variable combination of 6-MP and MTX

WBC ~3000/µL

  - Addition of vincristine and corticosteroid pulses – without benefit in children (Conter V et al, *Lancet* 2007)
  - No clear benefit of intensive chemo during this period
  - Toxicities – pneumocystis, herpes, osteonecrosis

Gökbuget N, Hoelzer D. *Semin Hematol*. 2009;46(1):64-75; Paul S, et al. *Mayo Clin Proc*. 2016; 91(11):1645-1666.

Role of MRD in ALL



Diagnosis

MRD timepoint 1

MRD timepoint 2

INDUCTION PHASE

Corticosteroids
Vincristine
Asparaginase
Anthracyclines
± Cytarabine
± Cyclophosphamide

LONG-TERM SURVIVAL

CONSOLIDATION PHASE

Methotrexate
High-dose cytarabine
6-MP or 6-TG
± VP-16
± Cyclophosphamide

RELAPSE AND FAILURE

REINDUCTION AND MAINTENANCE

ALLO-SCT IN CR1

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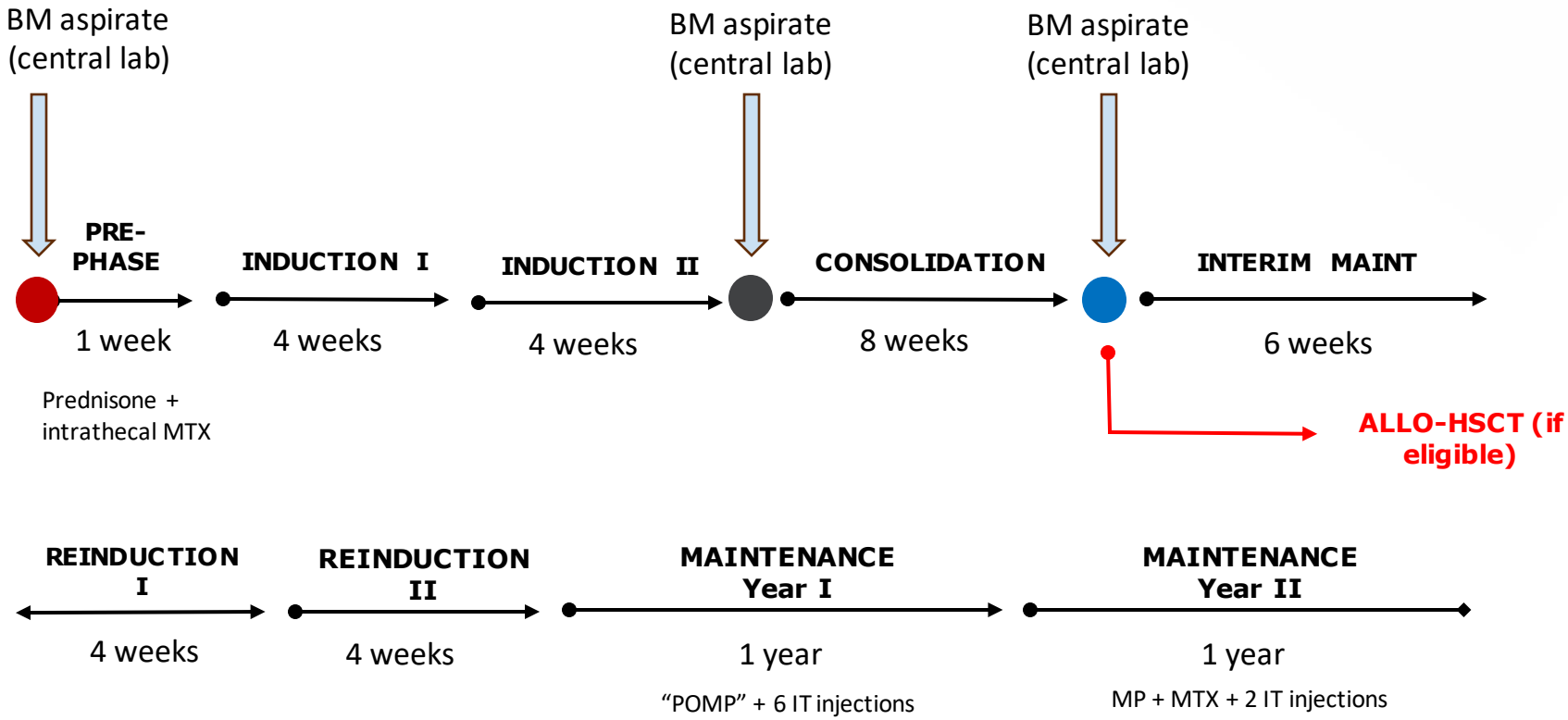
Adapted from Brüggemann M, Kotrova M. *Blood Adv.* 2017;1(25):2456-2466.

MRD Should Be Tracked Alongside Treatment



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BRALLA20 protocol

Allo-SCT in First CR According Different Protocols for Young Patients With Ph-Neg ALL

	Age	WBC	Phenotype	Cytogenetics	Genetics	MRD	BM Blasts	Late CR	Other
RALL (Russia)	>30			t(4;11), t(1;19)	*KMT2Ar*	Pos			
GMALL (Germany)		>30 (B)	Pro-B Early/mature-T		*KMT2Ar*	Pos		Yes	
HOVON (Netherlands)		>30 (B) >100 (T)		Adverse		Pos		Yes	
PALG (Poland)		>30 (B) >100 (T)			*KMT2Ar*	Pos			CNS+
FALL (Finland)		>100		abn11q23, hypodiploid		Pos	D15 >25%	Yes	
GIMEMA (Italy)		>100	Early/mature-T	Adverse	*KMT2Ar*	Pos			
UKALL (UK)		High count		Adverse		Pos			
SWALL (Sweden)				Hypodiploid	*KMT2Ar*	Pos	EOI >5%		
CELL (Czechia)						Pos			
PETHEMA (Spain)						Pos			
GRAALL (France)						Pos			

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Giebel S, et al. *Bone Marrow Transplant.* 2019;54(6):798-809.

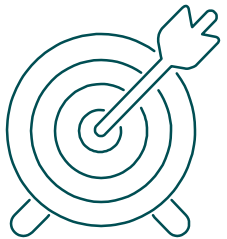
Allo-SCT in CR1: BRALLA20 Protocol

- 11q23 rearrangement (*KMT2A* or *MLL* gene) by FISH, karyotype, or molecular biology
- Hypodiploid karyotype (<40 chromosomes)
- Near-triploid karyotype (60–78 chromosomes)
- *CRLF2* rearrangement
- Complex (5 or more nonrelated abnormalities) for B-ALL
- Early T-cell precursor leukemia
- Late CR (after second cycle)
- MRD positive (≥0.1% EOI or ≥0.01% EOC)

BRALLA20 protocol. NCT05959720.

Current Issues in Brazil and Other Low- and Middle-Income Countries

- Lack of local studies
- No availability of blinatumomab, inotuzumab, and CAR T cell in public setting
- Lack of centralized laboratories and reliable prospective data on ALL
- No standardization and clinical validation of genetic findings and MRD for adults



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Personal communication.

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- Dra Fernanda Mendes
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Thanks!

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ALL case-based panel discussion

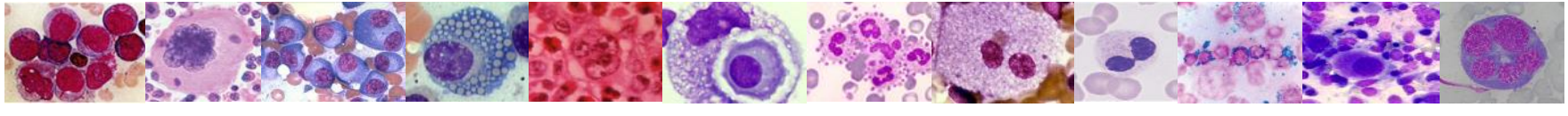
Roberta Demichelis

APTITUDE HEALTH®

ALL cases

Roberta Demichelis

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán



Disclosures

COI	COMPANY
RESEARCH	Novartis, American Society of Hematology
SPEAKER	AbbVie, AMGEN, Astellas, Pfizer
CONSULTING	AbbVie, AMGEN, Astellas, Gilead, Teva

Case 1: Adolescent and Young Adult

October 2018

28-year-old man
No previous medical history

90% blasts
CD34, CD10, CD19, CD22

Normal karyotype
FISH t(9;22) and t(v;11q23): both negative

Parameter	Value
Hemoglobin	6.9 g/dL
WBC	2.0×10^9/L
Blasts	**56%**
Platelets	13×10^9/L
LDH	173 U/L

Ph-negative B-cell ALL
AYA

Best frontline treatment?

Problems identified in Mexico

The highest incidence in adults is in AYA (67%)

Study GTLA 2015: poor otucomes. AYA 3-year OS: 25.7%

- **Modified CALGB 10403**
  - Significant improvement in outcomes
    2-year OS *72.1%*
  - Liver toxicity
  - Metabolic toxicity

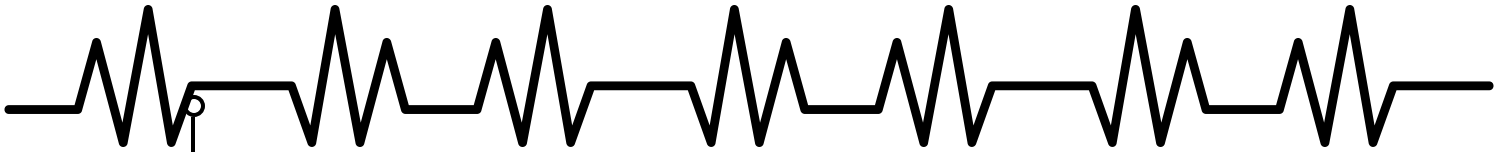
✓ Pharmacogenomics and metabolic toxicities
✓ Body composition assessment in adults with ALL

Crespo-Solis E, et al. *Cancer Med*. 2018;7(6):2423-2433; Rangel-Patiño J, et al. *Blood Adv.* 2023;7(18):5202-5209.

Ph-negative B-cell ALL
AYA

Modified CALGB 10403 + rituximab

Lumbar puncture: SNC1



Hypofibrinogenemia
No bleeding

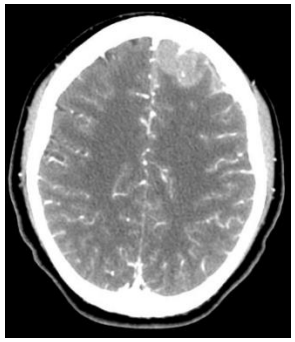
FibroScan
F0 S0

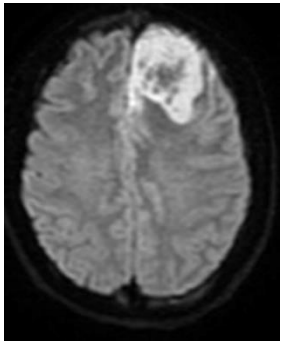
Day 28 BMA: no blasts
MRD by flow cytometry
<0.01%

Case 1: Adolescent and young adult

Surveillance since July 2021

May 2023: seizures with secondary fall and frontal trauma





- **<u>Systemic relapse</u>:** 76% blasts in bone marrow (same immunophenotype)
- **<u>CNS:</u>**

✓ Intraparenchymal tumor

✓ Lumbar puncture **CNS 2, flow cytometry with B-cell blasts** (no blasts in blood and no traumatic)

Questions for the audience

What would be the best treatment option at this time?

A. Repeat the initial regimen, since it was a late relapse
B. Regimen based on high doses of methotrexate or cytarabine
C. Blinatumomab
D. Inotuzumab ozogamicin
E. CAR T cells

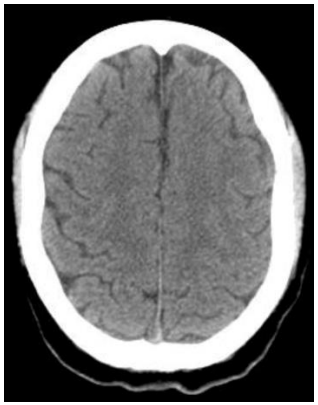
Questions for the panel

- ✓What is the **current role of flow cytometry** in the analysis of **cerebrospinal fluid**?

- ✓Hypothetical scenario: patient without CNS symptoms, with **CNS 2 and flow cytometry with blasts**. What to do?

Ph-negative B-cell ALL/AYA
Systemic + CNS late relapse

HyperCVAD (phase B: HDMTX and cyatarabine)



June 2023 (after 2 cycles, B and A): Encephalomalacia and residual dural thickening

Neutropenic fever
Stable

Levetiracetam

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

Lumbar puncture 2 to 7: SNC1

Questions for the audience

Second complete remission
3 cycles of HDMTX and cytarabine
2 cycles of hyper-CVAD (phase A)

1 matched sibling donor

Now, he is ready for transplant.
Does the patient need cranial radiotherapy?

A. Yes, because there is an intraparenchymal lesion
B. No, because he is already in complete remission with intrathecal and systemic chemotherapy
C. Only if he did not receive total body irradiation as part of the conditioning regimen
D. I don´t know

Questions for the panel

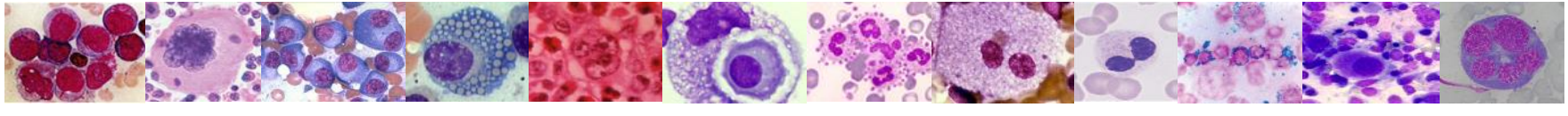
- ✓ In which patients do you indicate **cranial radiotherapy**?
- ✓ Do you think that every adult with ALL who receives an allo-transplant should receive conditioning with **total body irradiation**?

Case 2: Elderly

Juan Luis Ontiveros Austria, MD

Hematology Resident

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán



Disclosures

- Nothing to declare

Clinical case

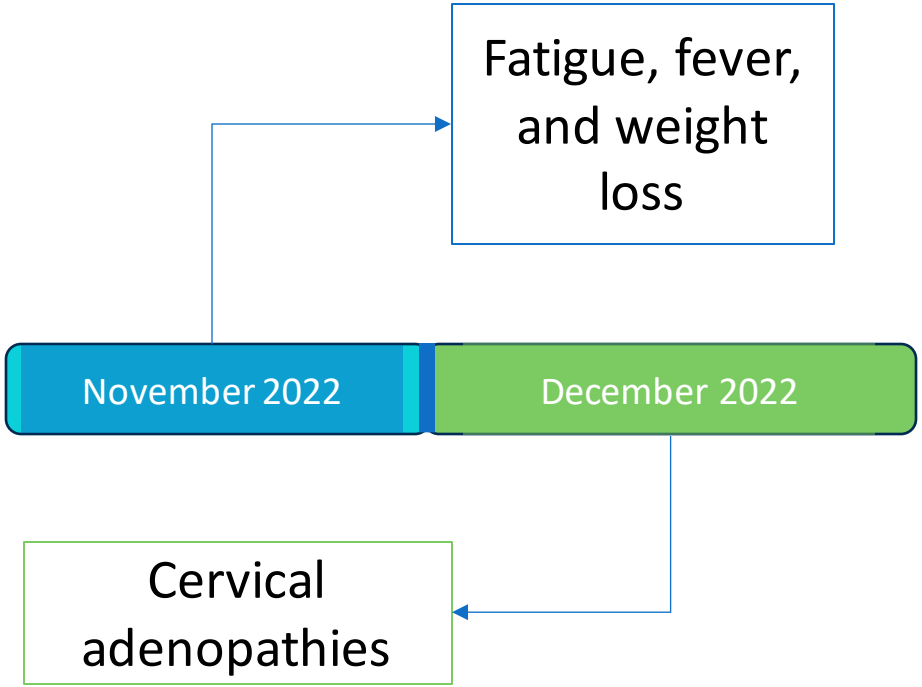
73-year-old woman

Active professor/investigator

Cancer family history: father lung cancer, mother cervical cancer, son acute lymphoblastic leukemia

- Type 2 diabetes (6 years)
- Systemic hypertension (6 years)
- Osteoarthritis (4 years)

Disease history



Parameter	Value
Hemoglobin	10.5 g/dL
WBC	20.5×10^9/L
Neutrophils	1.16×10^9/L
Lymphocytes	19.0×10^9/L
Blasts	**50%**
Platelets	133×10^9/L

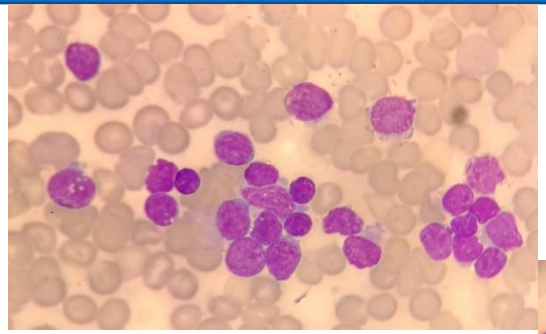
Parameter	Value
Glucose	159 mg/dL
Creatinine	0.70 mg/dL
Lactate dehydrogenase	694 U/L

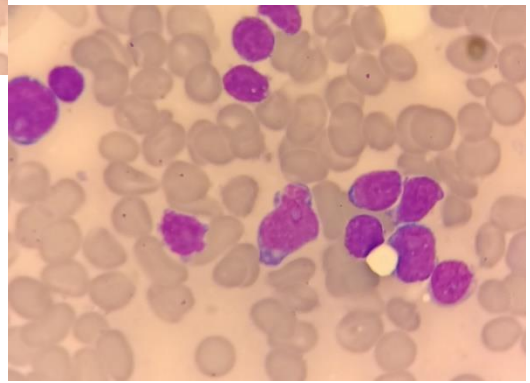
Geriatric evaluation: pre-frail

Bone marrow analysis

65% blasts

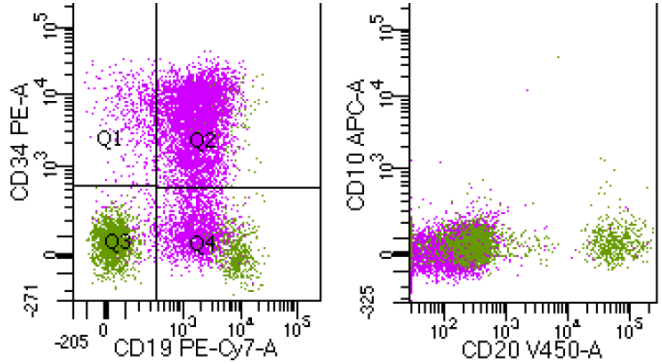
Bone marrow aspirate





Flow cytometry: blasts 68%, CD34, CD19, CD22 **positive**, CD10, IgM **negative**.

Flow cytometry



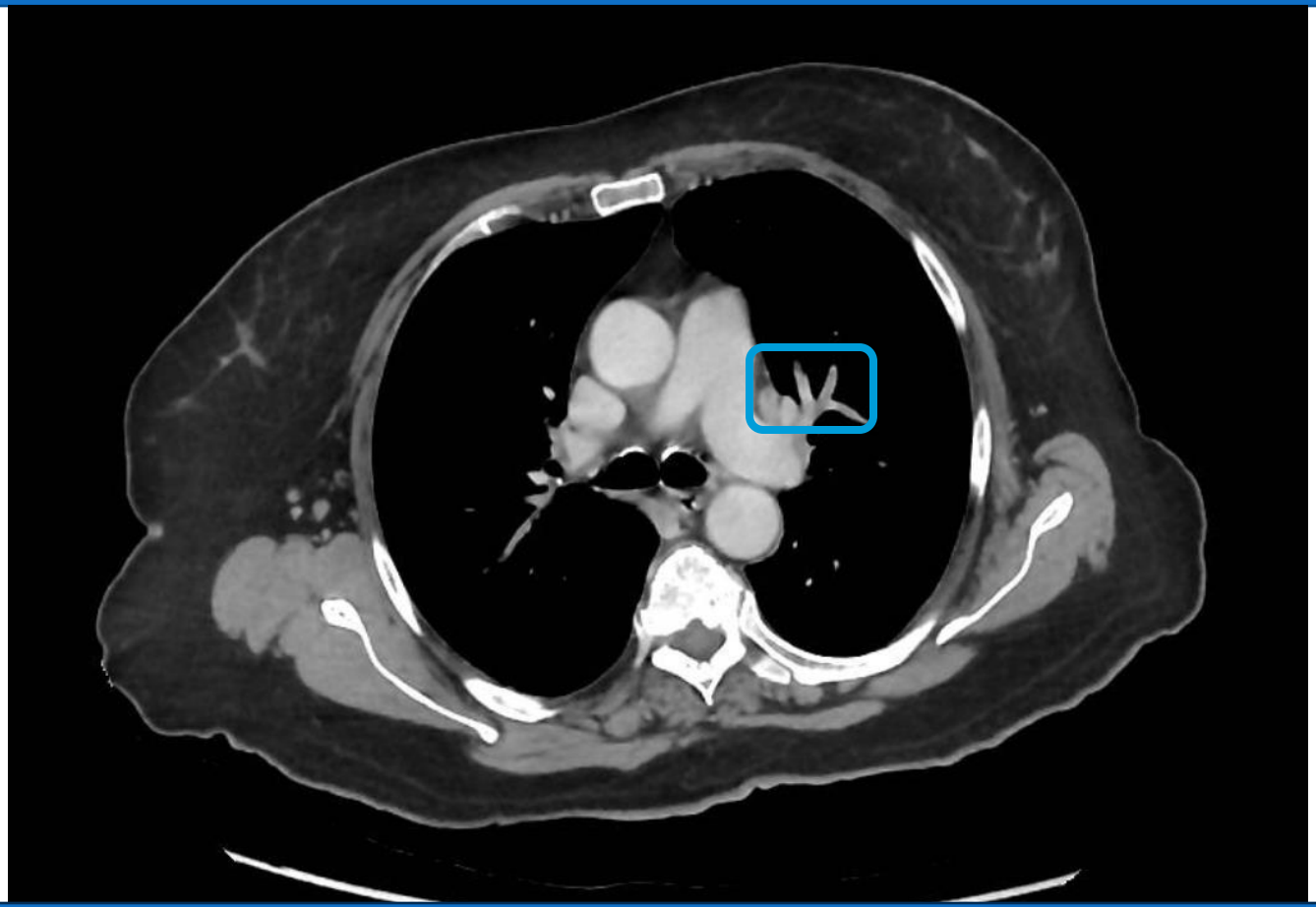
Genetics

Karyotype: 46, XX
FISH t(9;22) and 11q23: **NEGATIVE**

Clinical case evolution

Sudden dyspnea and supplementary oxygen requirement

Contrast tomography: filling defect on principal right pulmonary artery and filling defects on both femoral common veins



Elderly patients with ALL have worse outcomes

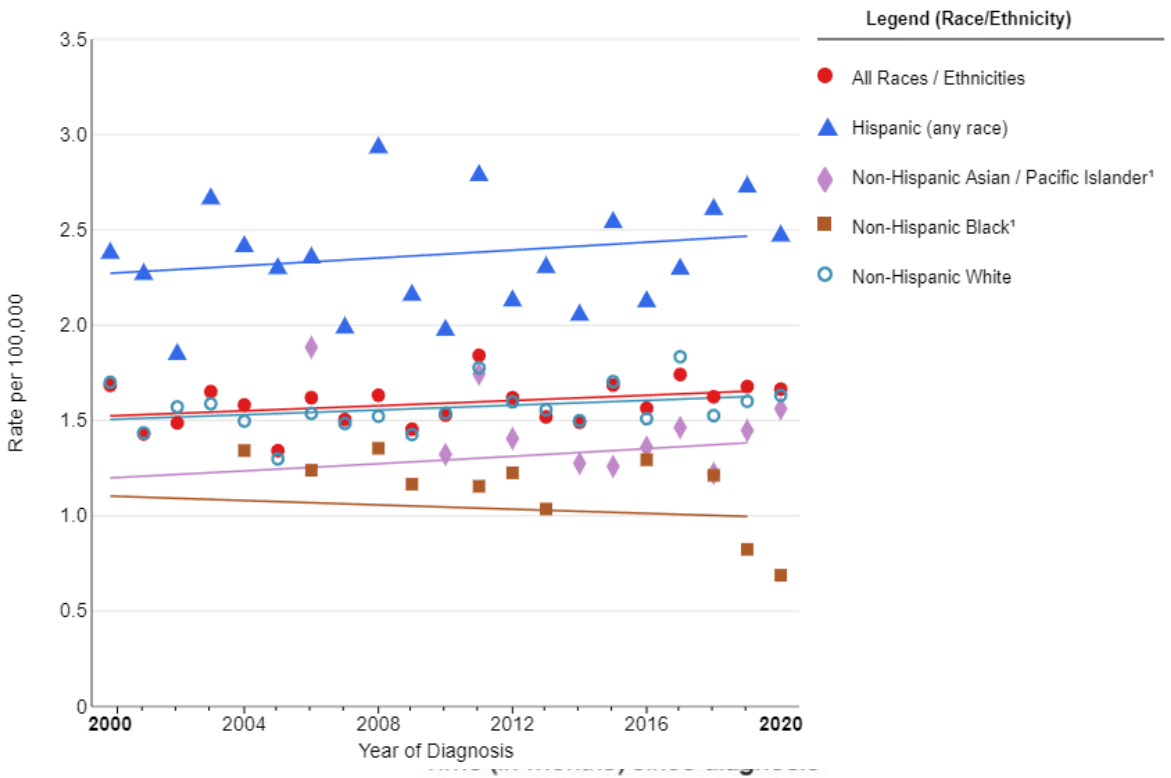
Median OS: 23.2 months with intensive chemotherapy[1]

3-year (OS): 16%[2]

Philadelphia-like phenotype: predominant in Hispanic population[4]

Acute Lymphocytic Leukemia (ALL)
Recent Trends in SEER Age-Adjusted Incidence Rates, 2000-2020
Observed SEER Incidence Rate By Race/Ethnicity, Both Sexes, Ages 65+

3

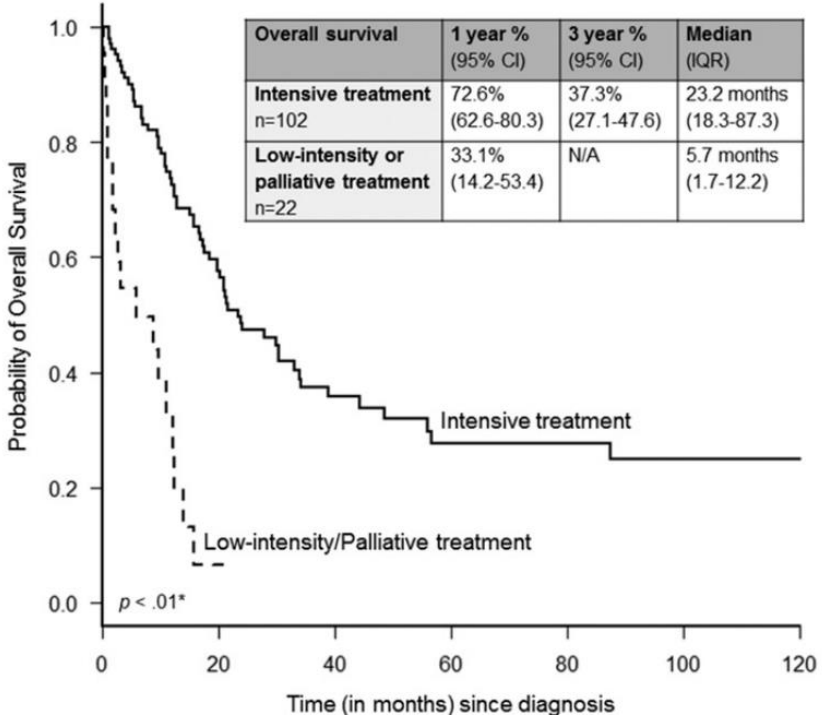


1. Miller KC, et al. *Leuk Lymphoma*. 2019;60(4):990-999; 2. Luskin MR. *Hematol Am Soc Hematol Educ Progr*. 2021;2021(1):7-14; 3. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. Updated 2023 Jun 8; 4. Short NJ, et al. *Leukemia*. 2021;35(11):3044-3058.

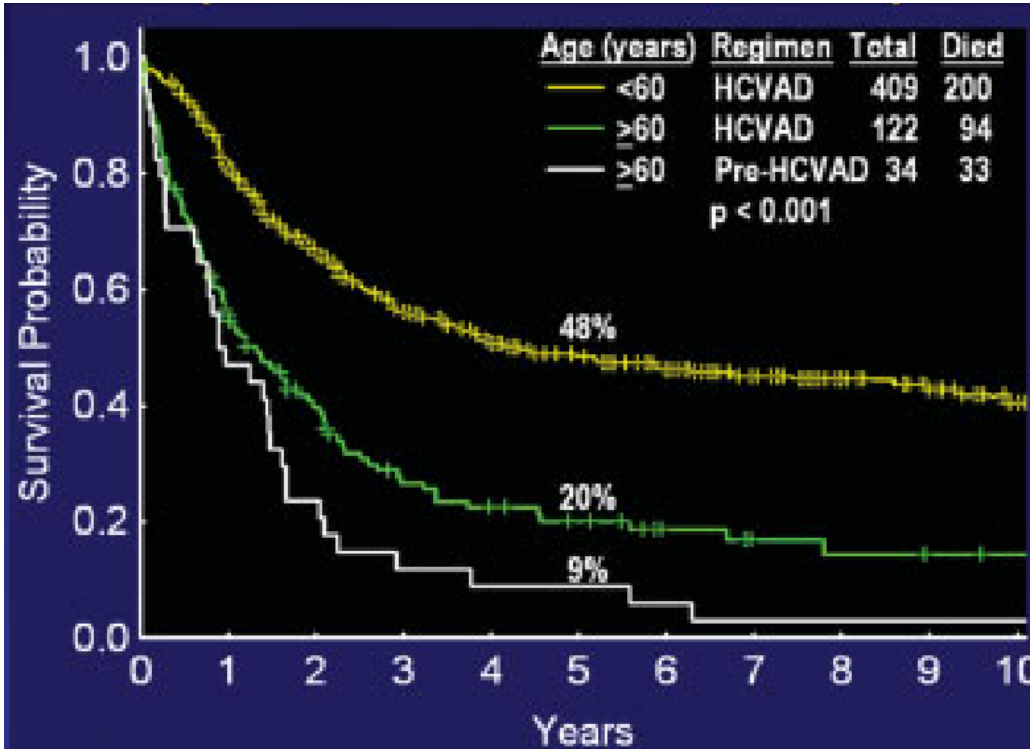
Elderly patients have lower survival rates

Mayo Clinic: median OS 23.2 months vs 5.7 months

Overall survival	1 year % (95% CI)	3 year % (95% CI)	Median (IQR)
Intensive treatment n=102	72.6% (62.6-80.3)	37.3% (27.1-47.6)	23.2 months (18.3-87.3)
Low-intensity or palliative treatment n=22	33.1% (14.2-53.4)	N/A	5.7 months (1.7-12.2)



Hyper-CVAD mortality according to age



Miller KC, et al. *Leuk Lymphoma*. 2019;60(4):990-999.

Question for the audience

In your practice, which treatment would you choose for this patient, considering her age and frailty status?

A. Hyper-CVAD
B. Mini–hyper-CVD
C. Blinatumomab-containing regimen
D. Inotuzumab-containing regimen
E. Adjusted pediatric regimen
F. Other

Question for the panelists

- What would be your choice in your daily practice?

Reduced intensity + immunotherapy increases survival rates

Regimen	Phase	N	Line	Age, y	Regimen-Related Deaths	Response	Survival
InO + mini–hyper-CVD ± Blina consolidation[1]	II	125	First	≥60	0% early mortality 34% mortality in remission	99% ORR 89% CR (94% MRD negative)	CR 3 years: 79% Median OS: 45 months 5-year PFS: 44% 5-year OS: 46%
InO induction CC consolidation (INITIAL-1)[2]	II	45	First	≥55	0% early mortality	100% CR/CRi (74% MRD negative after third)	EFS 1 year: 87% OS 2 years: 77%
Blina induction Blina consolidation (SWOG 1318)[3]	II	29	First	≥65	0%	66% CR/CRi (92% MRD negative)	DFS 1 year: 37% OS 3 years: 37%
InO induction Blina consolidation (A041703)[4]	II	33	First	≥60	0%	CR course I: 85% CR course II: 97%	EFS 1 year: 75% OS 1 year: 84%

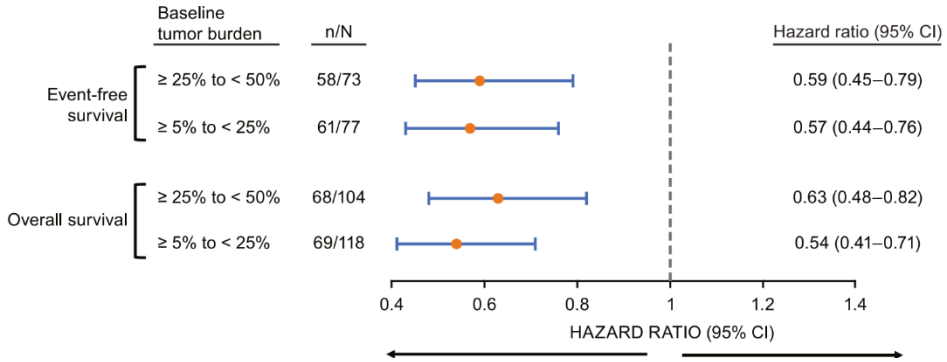
1. Jabbour E, et al. *Lancet Haematol*. 2023;10(6):e433e444; 2. Stelljes M, et al. *Blood*. 2021;138(suppl 1):abstract 2300; 3. Advani AS, et al. *J Clin Oncol*. 2022;40(14):1574-1582;
4. Wieduwilt MJ, et al. *J Clin Oncol*. 2023;41(16 suppl):abstract 7006.

Cytoreduction prior to blinatumomab consolidation may improve outcomes

For only MRD: MRD^{neg} 78%; OS 36.5 months[1]

More blasts → worse OS

Fewer blasts → better responses



OS <50% vs ≥50% blasts: 38.3% vs 23.6%
EFS <50% vs ≥50% blasts: 89.4% vs 79.3%
(HR 0.58; 95%CI, 0.47-0.72; *P* <.001)[2]

1. Kantarjian H, et al. *N Engl J Med*. 2017;379(9):836-847; 2. Queudeville M, et al. *Cancer*. 2023;129(9):1384-193.

Sequential RI ChT + Blina may improve response outcomes

ALL08 trial

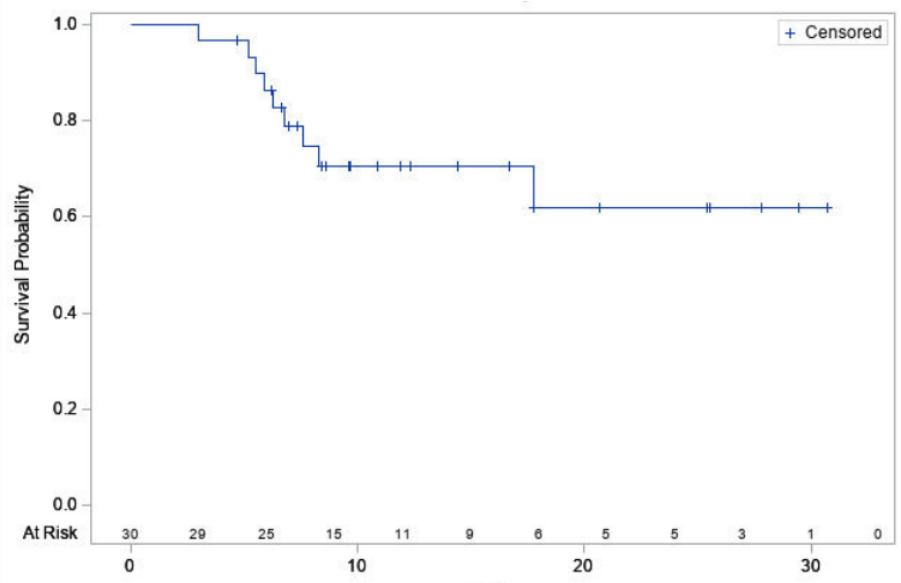
Mini–hyper-CVD → Blinatumomab → Phase B hyper-CVAD→ Blinatumomab alternated with phase B hyper-CVAD (3) → POMP

Mortality during induction: 0%

CR: 100%; **negative MRD**: 70% after **IB**, 83% after **IIB**

24-month EFS: 61.8%

24-month OS: 68.6%



Fleming S, et al. B*lood.* 2021;138(suppl 1):abstract 1234.

Treatment

Phase A Mini–Hyper-CVD	
Cyclophosphamide	150 mg/m^2 BID D1-3
Vincristine	1 mg D4 and 11
Dexamethasone	2 mg D1-4 and 11-14

Phase B Mini–Hyper-CVD	
Methotrexate	750 mg/m^2 D1
Cytarabine	500 mg/m^2 D2-3

Response

Bone marrow aspirate:

Blasts flow cytometry

40%

Response

Bone marrow aspirate:

Blasts flow cytometry

11%

Intrathecal chemotherapy: CNS 1

Question for the audience

What to do next?

A. The patient is refractory, so I will change to a more intensive chemotherapy regimen
B. She had a partial response, so I will continue with the same regimen
C. Blinatumomab
D. Inotuzumab ozogamicin
E. The patient is refractory and not a candidate for transplant, so I will continue with supportive care

Treatment continuation

Blinatumomab	
Cycle 1	9 µg D1-7, 28 µg D8-28
Cycles 2-4	28 µg D1-28
Intrathecal chemotherapy	Intrathecal methotrexate + dexamethasone

Response

Bone marrow aspirate: no blasts

MRD: 0.08%

Maintenance (POMP)

Oral methotrexate 15 mg/m^2

6-mercaptopurine 100 mg (escalated dose)

Vincristine 1 mg each month

To take home . . .

- Elderly patients are a hard-to-treat population
  - Performance status
  - Comorbidities
  - Adverse genetic profiles
  - Deaths during induction
- Few clinical trials take into consideration patients over 60 years. Including this group may improve treatment options
- Lessening tumor burden with reduced-intensity chemotherapy prior to blinatumomab could enhance responses
- Consider treatment!
  - Nearly 20% of patients are offered palliative treatment regardless of performance status[1]

1. Miller KC, et al. *Leuk Lymphoma*. 2019;60(4):990-999.

Question for the panelists

- What would be your choice for this patient?
- Should we continue blinatumomab? How many cycles would be necessary?
- Would you prefer blinatumomab alternated with POMP maintenance?

Global Leukemia Academy

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®

Question 5

Which of the following factors are important in assessing AML patients at diagnosis? Select all that apply.

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

Optimizing and Personalizing Frontline Therapy in Fit AML: Incorporating Genomics and Targeted Therapies

GLA LATAM
October 2023

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Department of Leukemia
MD Anderson Cancer Center

Disclosures

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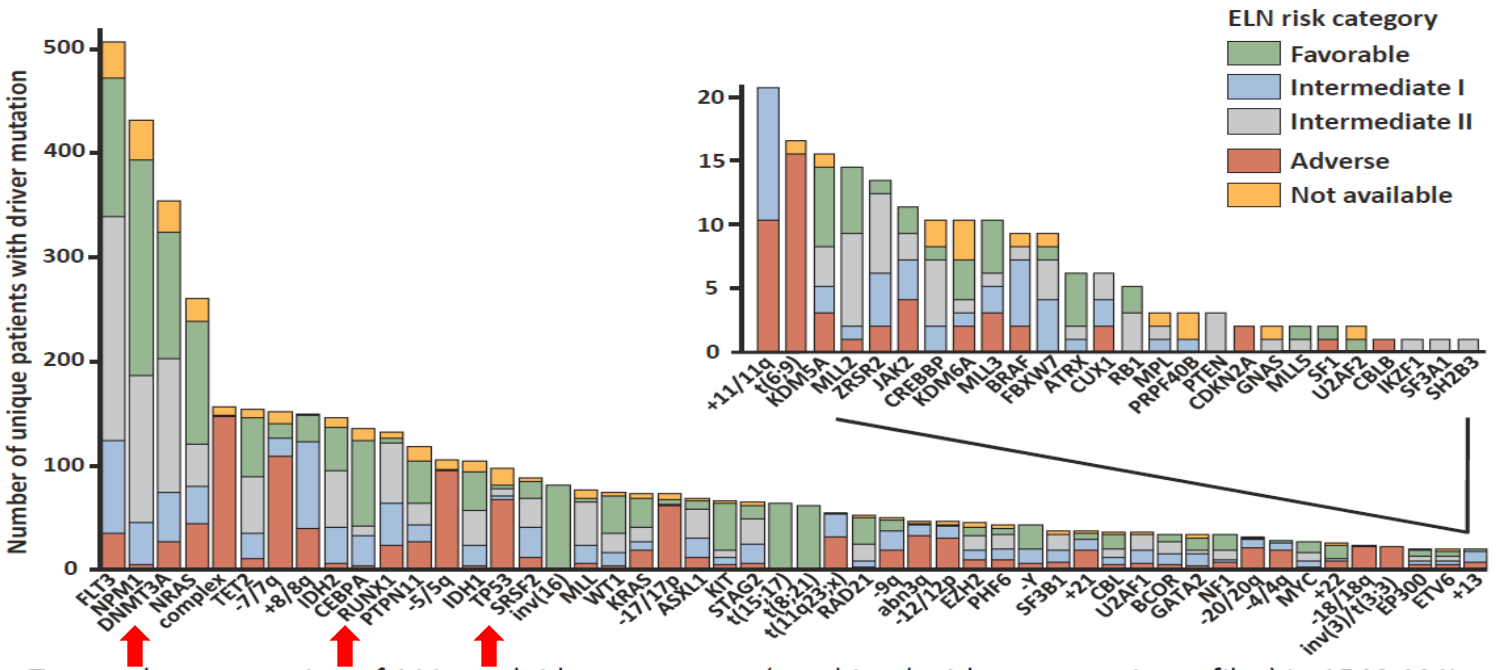
Advisory/Consulting: Pfizer, BMS, Daiichi Sankyo, Novartis, Jazz, Astellas, AbbVie, Genentech, Agios, Servier, ImmunoGen, Forty Seven, Gilead, Syndax, Trillium, Kite, Shattuck Labs, STAR Therapeutics, Arcellx, Glycostem

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

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 Allo-SCT Decisions

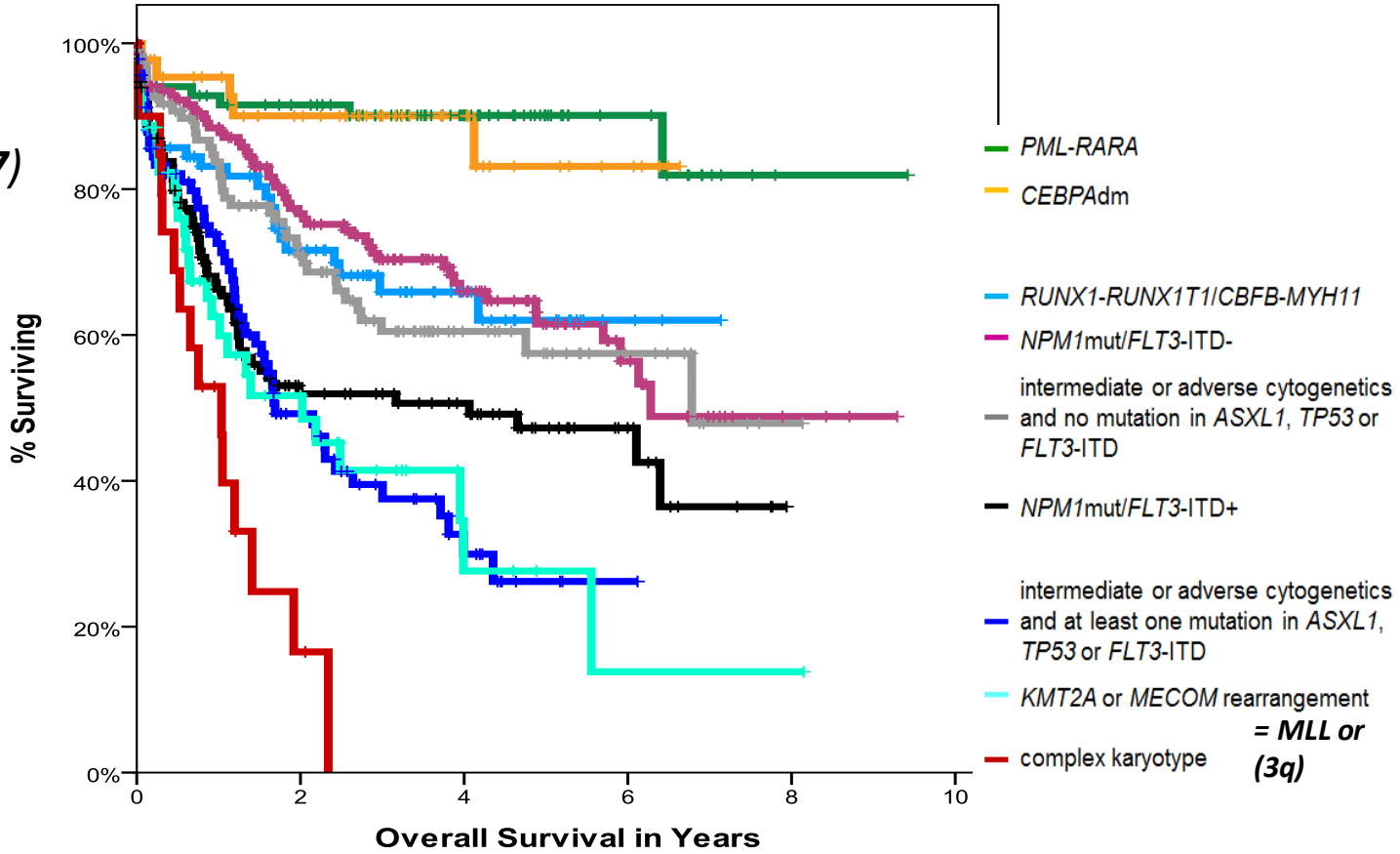
APL

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;128:286.

2022 ELN Risk Categorization

Risk Category	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* • Mutated *NPM1* without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1* with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*,*MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2* • Mutated *TP53*

Note

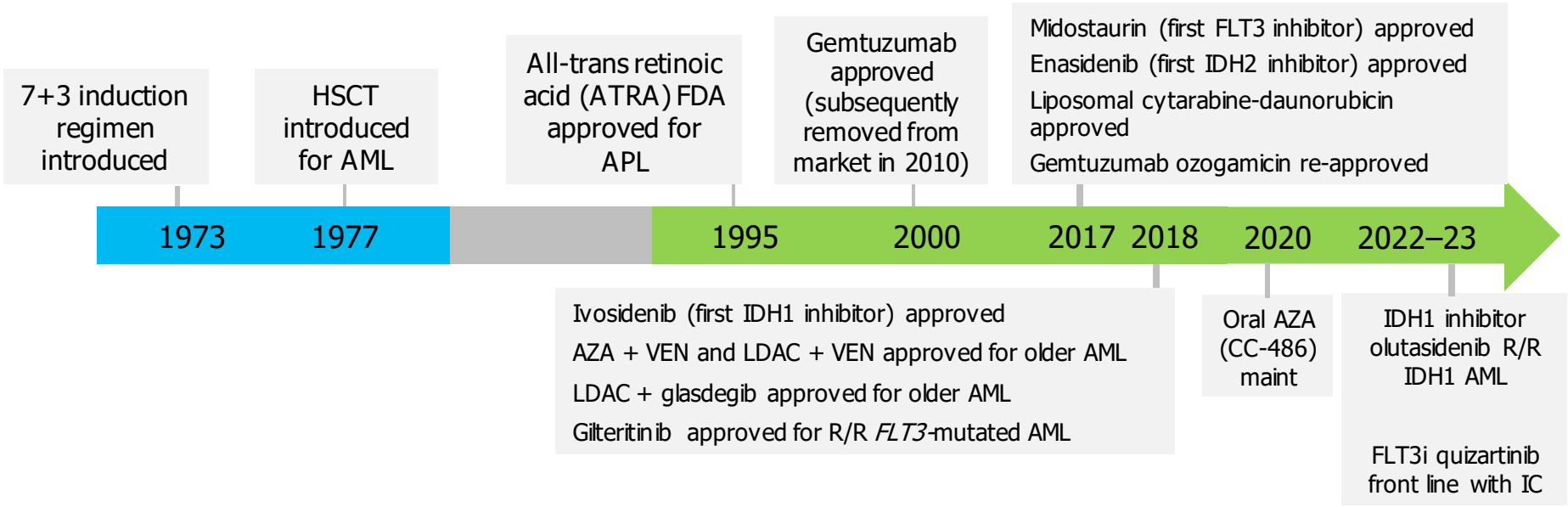
- The ELN AML risk classification has been developed on the basis of data from intensively treated patients and may need modifications for patients receiving less-intensive therapies
- Initial risk assignment may change during the treatment course on the basis of results from MRD analyses

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**

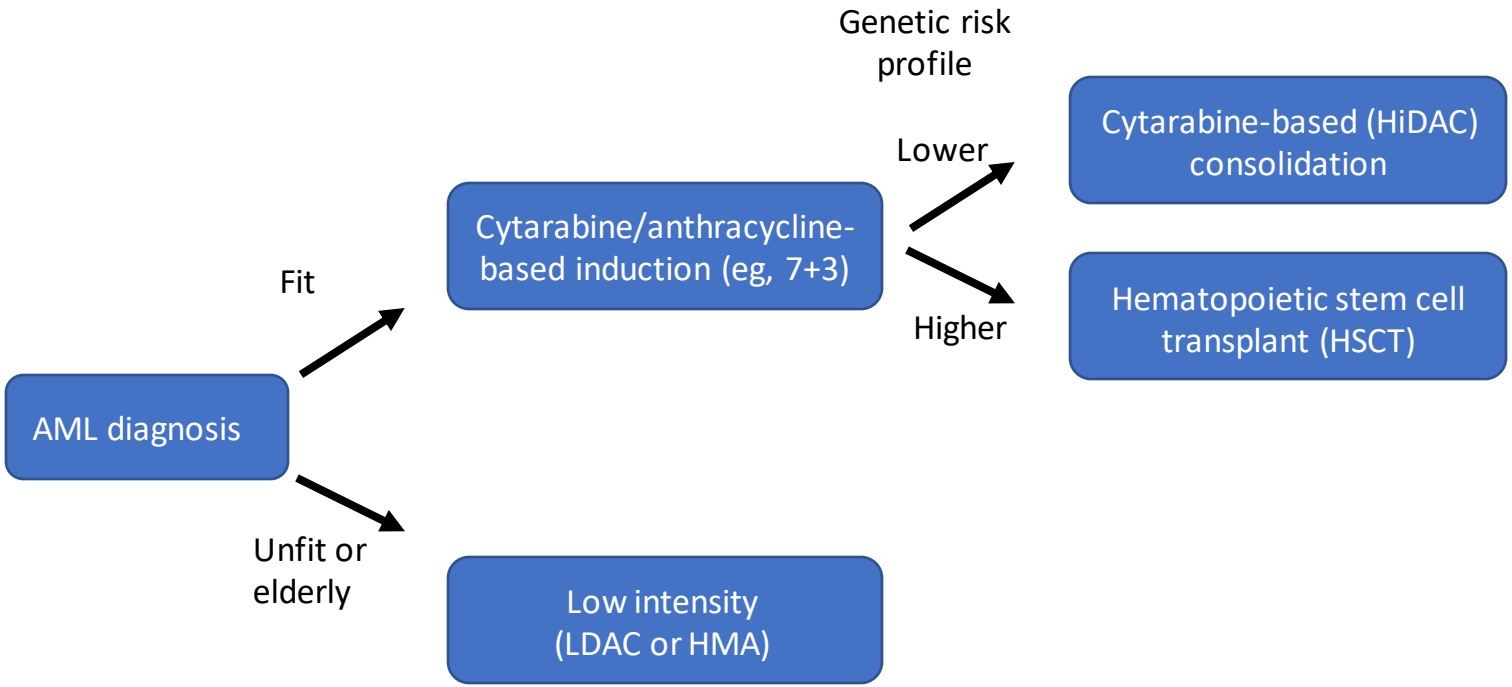
Treatment of AML (accelerated progress 2017–2023): 12 Drug Approvals

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

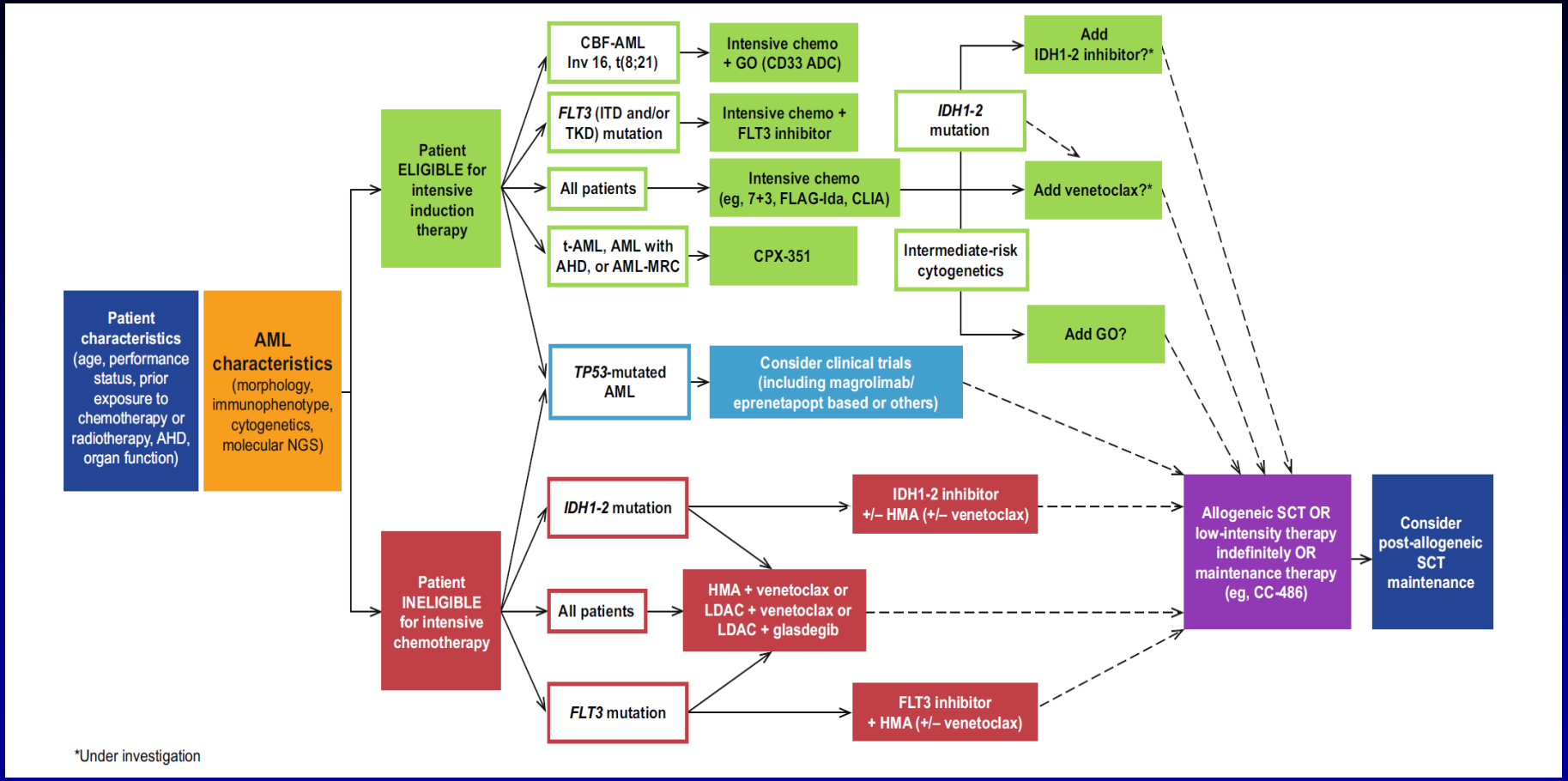


Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	33% → ?

The Pre-2017 Paradigm



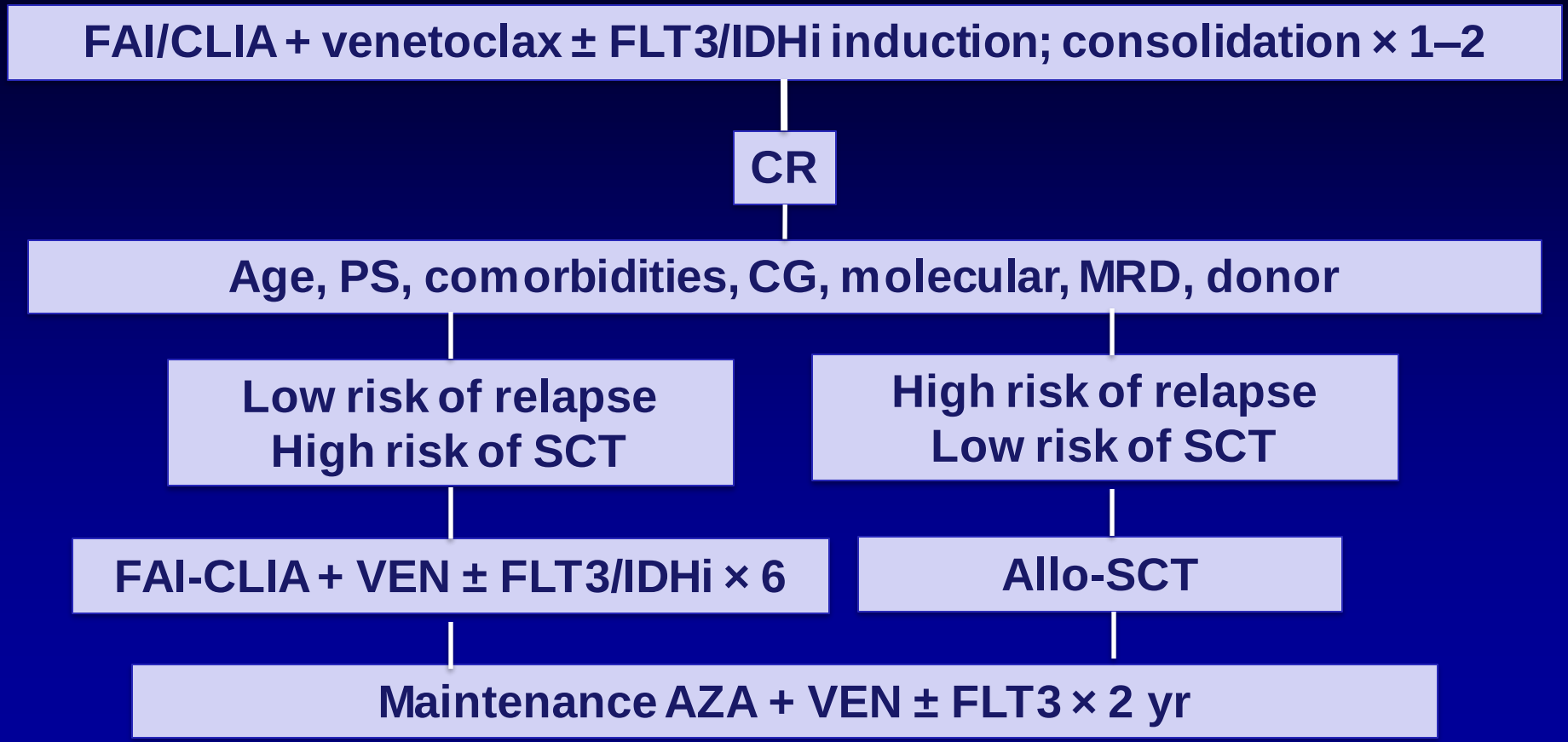
Evolving Diagnostic and Treatment Paradigm for Newly Dx AML



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

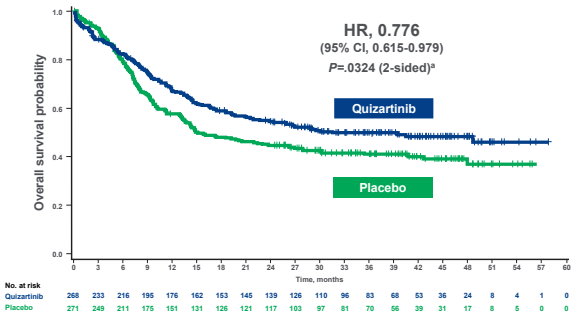
IC Is Still a Key Modality, at Least for Now

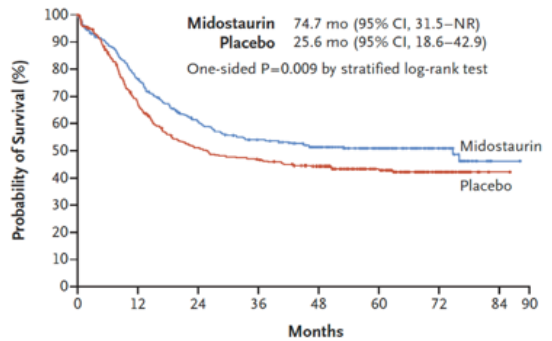
Therapy of Younger AML at MD Anderson in 2020+ (FLT3, CBF, others)



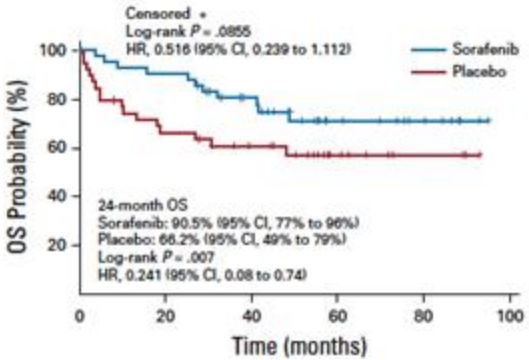
1. *FLT3*m AML: FLT3 Inhibition Improves Survival in Fit Patients Across the Treatment Spectrum

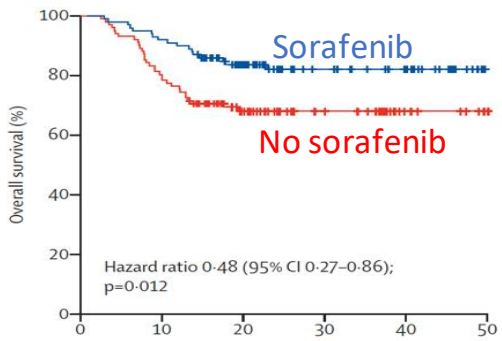
Newly diagnosed, intensive chemotherapy + TKI/placebo



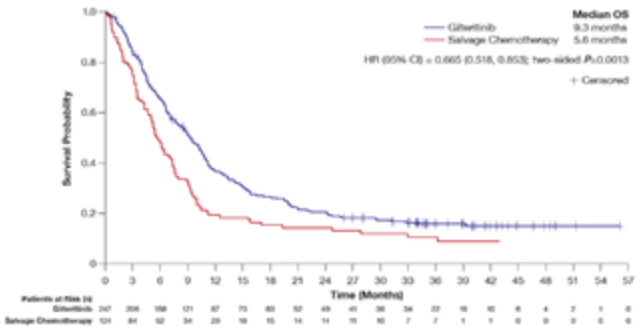


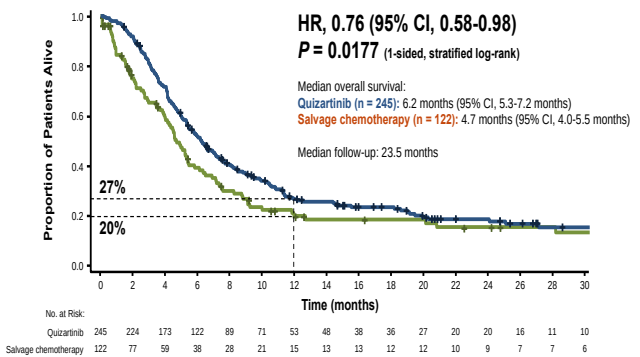
TKI maintenance after allo-HSCT (sorafenib 2 studies)





Relapsed/refractory Single-agent TKI vs chemotherapy

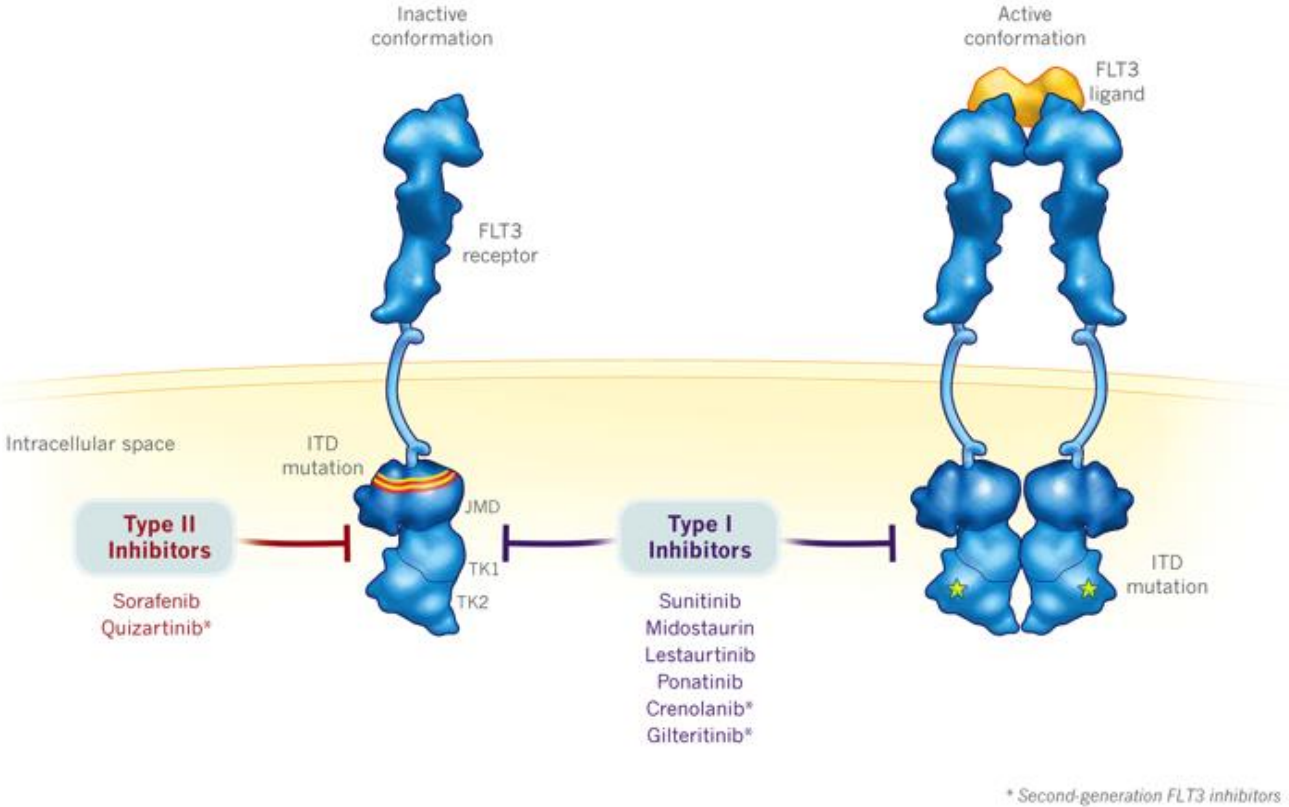




Erba HP, et al. EHA 2022. Abstract S100; Stone RM, et al. *N Engl J Med.* 2017;377:454-464; Burchert A, et al. *J Clin Oncol*. 2020;38:2993-3002; Xuan Y, et al. *Lancet Oncol*. 2020;21:1201-1212; Perl AE, et al. *Blood.* 2022;139:3366-3375; Cortes JE, et al. *Lancet Oncol*. 2019;20:984-997.

Type 1: Bind Receptor "Active" Conformation Near ATP Pocket or Activation Loop: ITD and TKD

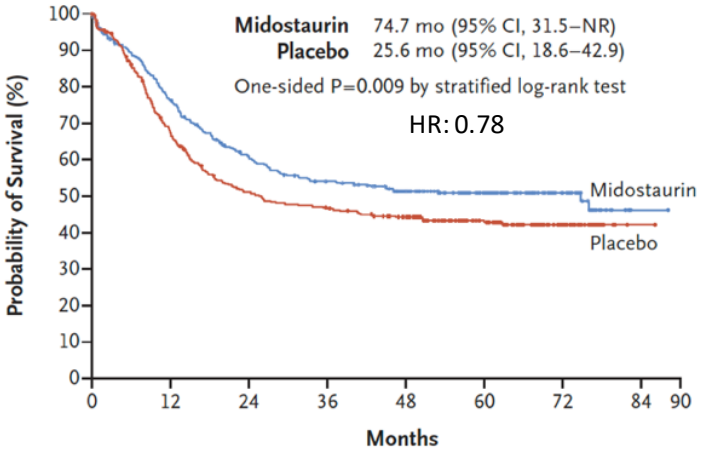
Type 2: Bind Receptor "Inactive" Conformation Near ATP Pocket – ITD Only



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

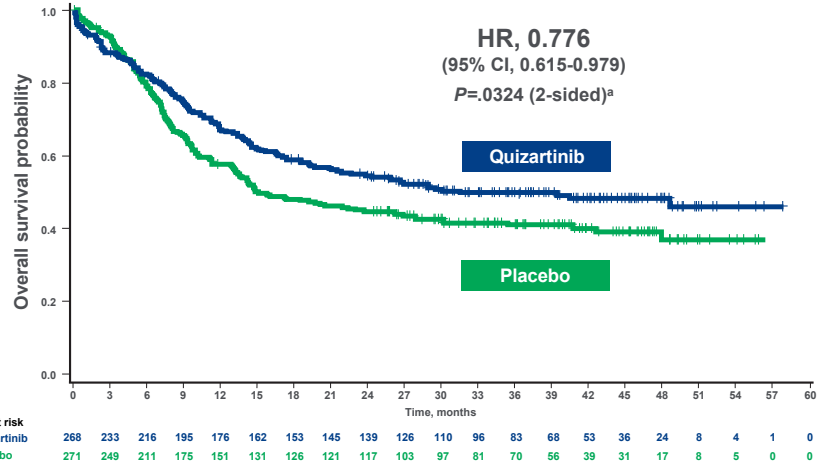
Comparing RATIFY and QuANTUM-First

	CR
Midostaurin	68%
Placebo	61%



- 60-day mortality: not reported

	CR	CR/CRi
Quizartinib	54.9%	71.6
Placebo	55.4%	64.9

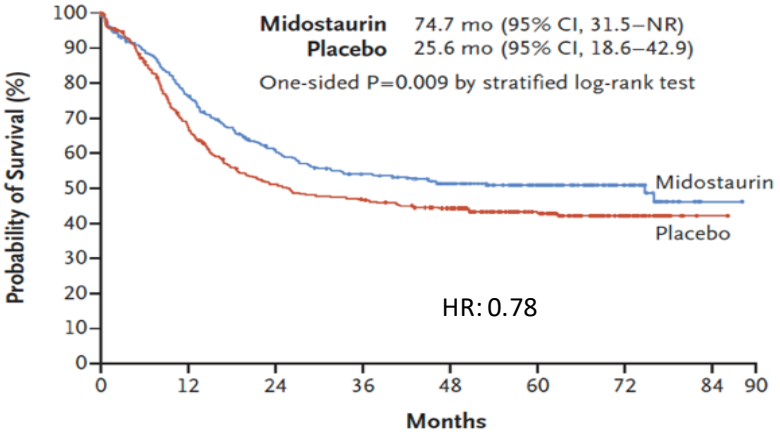


- 60-day mortality: quizartinib 7.5%, placebo 4.9% (mostly infections)
- ANC recovery was 7 days longer in quiz arm; platelets 2 days longer in quiz arm
- Any grade QT prolongation: quizartinib 13.6%, placebo 4.1%
- 2 cases of cardiac arrest or VT in quiz arm (none in placebo)

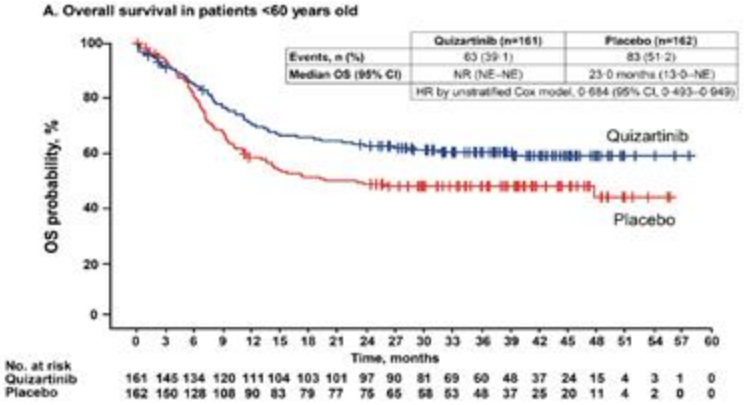
Stone RM, et al. *N Engl J Med.* 2017;377:454-464; Erba HP, et al. *Lancet*. 2023;401:1571-1583.

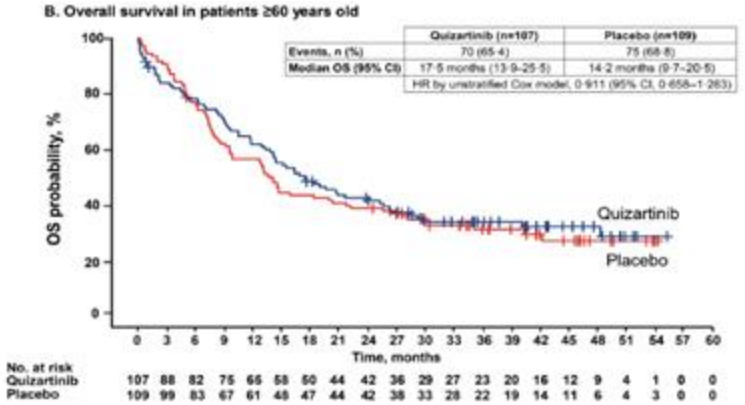
Younger Patients Particularly Benefit From Quizartinib

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



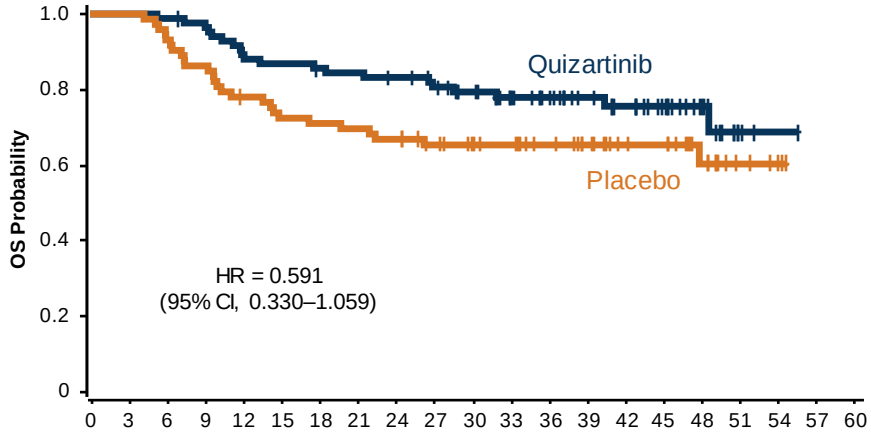
QuANTUM First: <60 years old and all *FLT*-ITD: 4-yr OS 60%





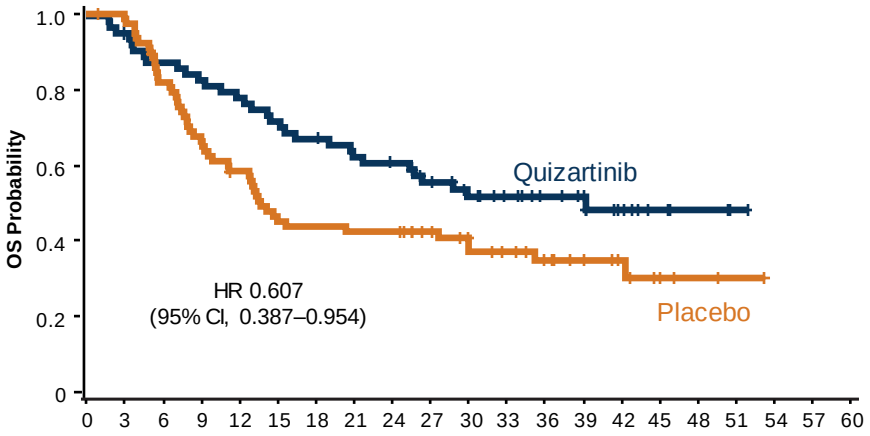
QuANTUM-First: Overall Survival in Patients Who Had CR[1]

Patients with CR who received allo-HCT in CR1



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

Patients with CR NOT receiving allo-HCT in CR1



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

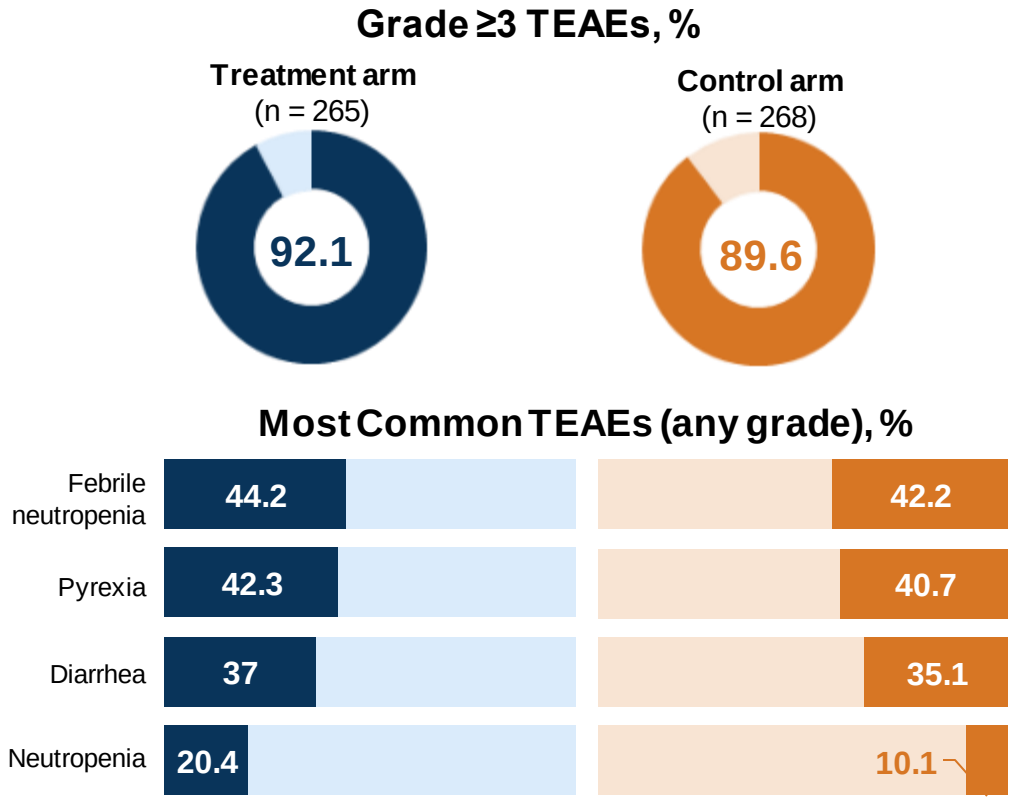
Patients receiving quizartinib had longer OS irrespective of allo-HCT in CR1[1,2]

1. Erba H, et al. *Lancet*. 2023;401:1571-1583; 2. Schlenck R, et al. EHA 2023. Abstract S137.

QuANTUM-First: Adding Quizartinib Was a Tolerable Strategy in ND *FLT3* AML[1,2]

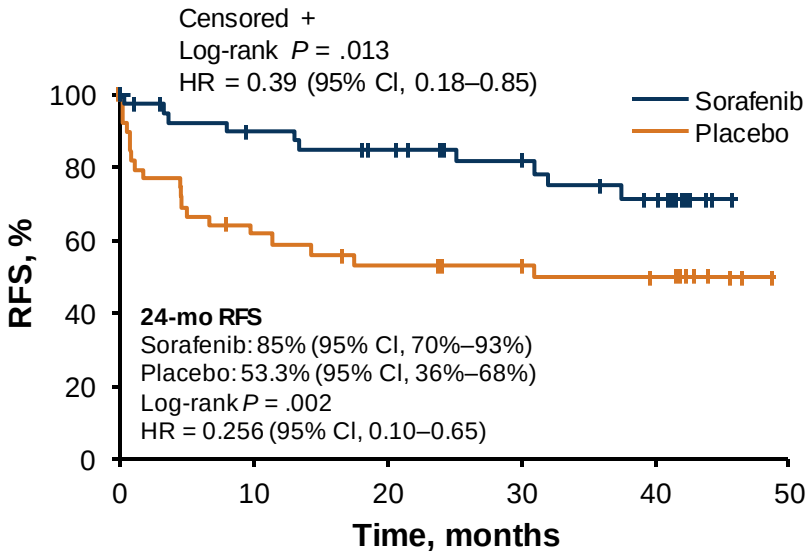
- Overall, combining quizartinib with intensive chemotherapy and as continuation monotherapy was found to be manageable[1]
- No new safety signals were reported
- 30-day mortality: Q 5.7%, P 3.4%
- 60-day mortality: Q 7.5%, P 4.9%
- Grade 3 QT ↑ : Q 2.3%, P 0.7%

July 2023: FDA approval of quizartinib with standard chemotherapy induction and as maintenance monotherapy following consolidation for *FLT3*-ITD–mutated AML; not indicated as maintenance monotherapy following allo-HCT

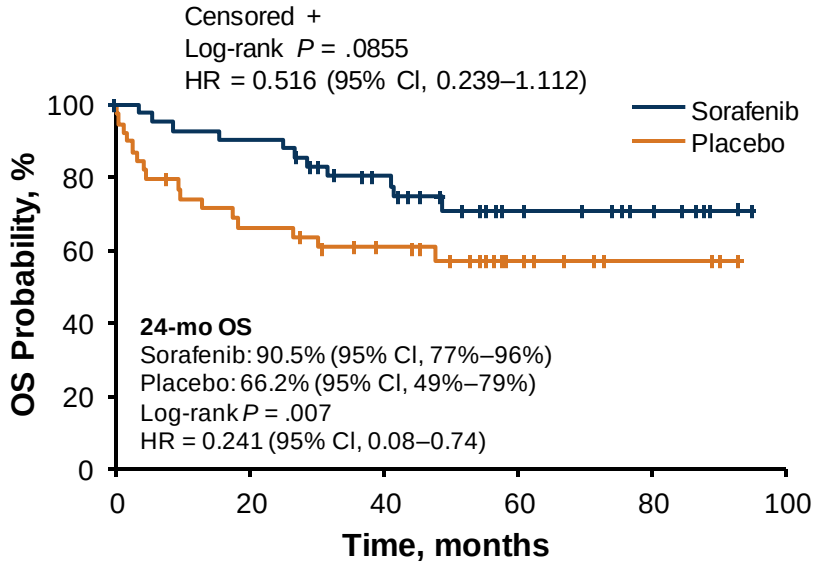


1. Erba H, et al. *Lancet*. 2023;401:1571-1583; 2. Vanflyta (quizartinib) [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216993s000lbl.pdf.

FLT3i Maintenance Post-SCT: RFS and OS in *FLT3*+ AML in CR After HSCT Treated With Sorafenib vs Placebo (SORMAIN)



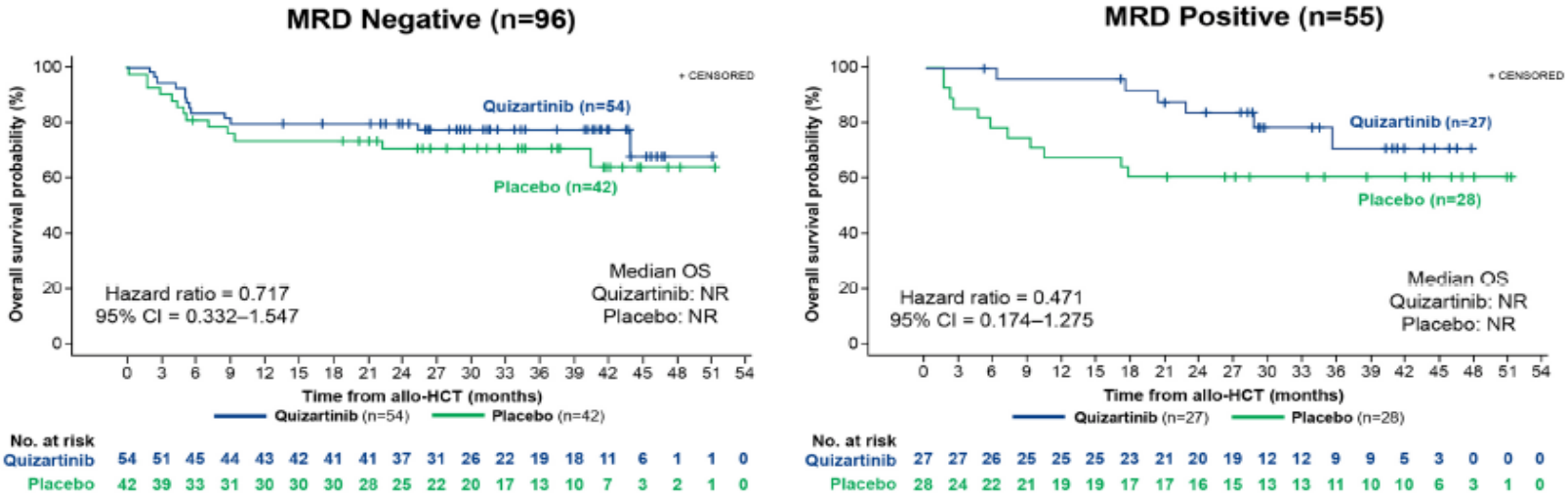
No. at Risk						
Placebo	40	24	19	17	14	0
Sorafenib	43	35	31	25	18	0



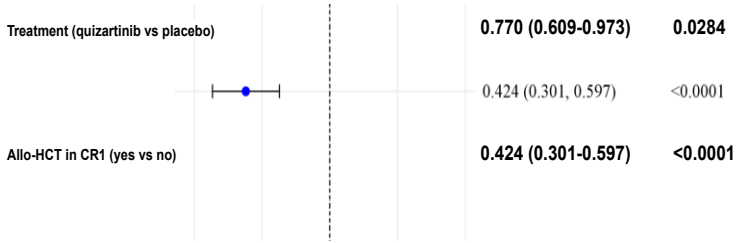
No. at Risk						
Placebo	40	25	19	9	3	0
Sorafenib	43	38	28	12	7	0

Burchert A, et al. *J Clin Oncol*. 2020;38:2993-3002.

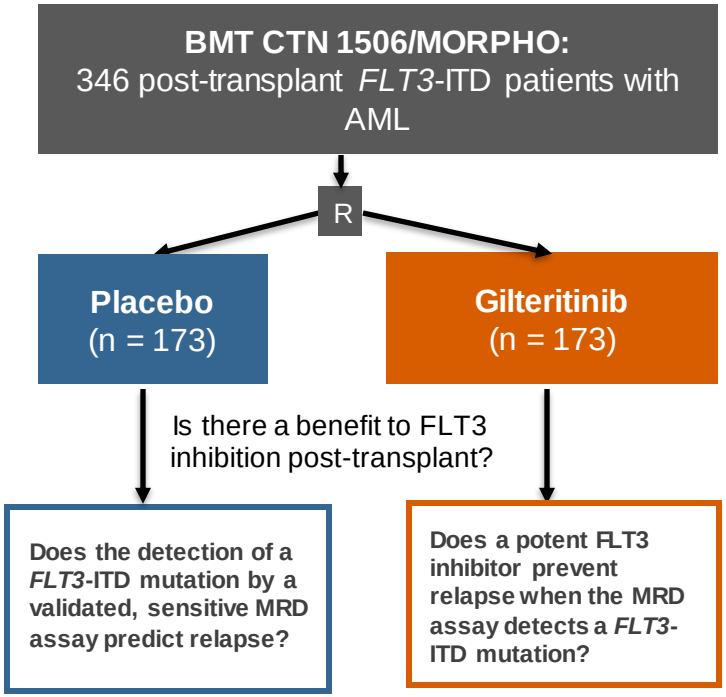
OS in Patients Undergoing Allo-HCT in CR1 by Latest Pre–Allo-HCT MRD Status (cutoff 10^{-4})[a]



Analysis using Kaplan-Meier plots.
Note that of the 157 patients (84 in the quizartinib arm and 73 in the placebo arm) who underwent allo-HCT in CR1, 151 with MRD data were analyzed (81 in the quizartinib arm and 70 in the placebo arm).



Phase III Randomized Study of Gilteritinib – *MORPHO*



Astellas and BMT CTN Announce Topline Results from Phase 3 MORPHO Trial of Gilteritinib

astellas

NEWS PROVIDED BY
Astellas Pharma Inc.; BMT CTN
Mar 09, 2023, 01:00 ET

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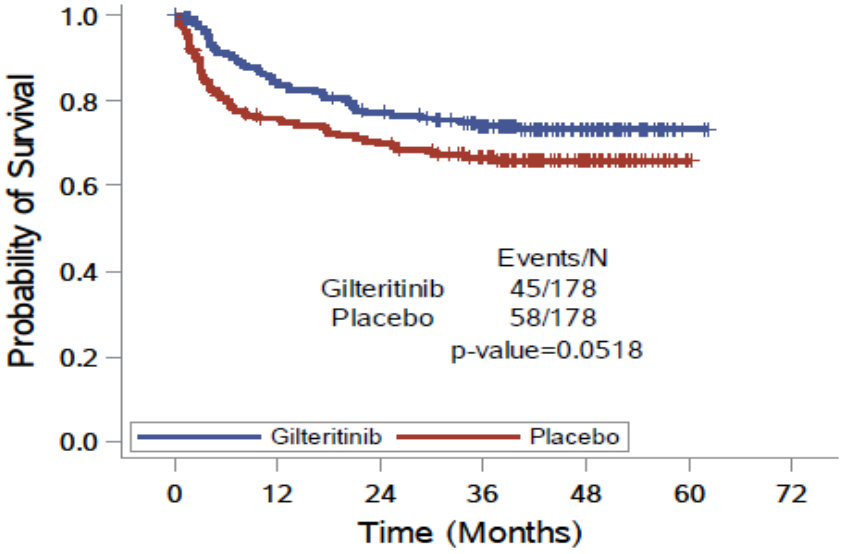
TOKYO and ROCKVILLE, Md., March 9, 2023 /PRNewswire/ -- Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) today announced topline results from the Phase 3 MORPHO clinical trial evaluating gilteritinib as a maintenance therapy following allogeneic hematopoietic stem cell transplantation (HSCT) for patients with FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) mutated acute myeloid leukemia (AML). Based on the data, the study did not meet its pre-defined primary endpoint of relapse-free survival (RFS) for patients treated with gilteritinib compared to placebo. The study was conducted in collaboration with BMT CTN.

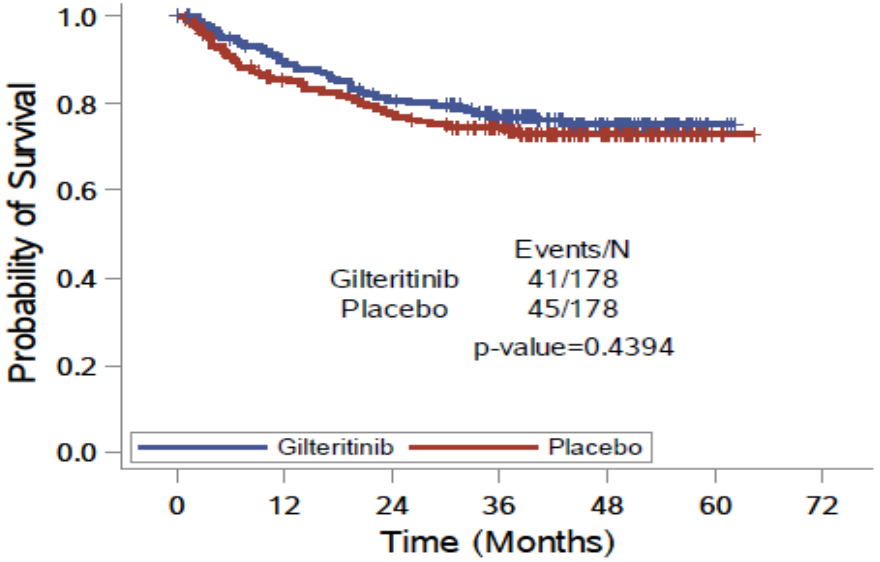
Levis MJ, et al. *Blood.* 2019;134(suppl 1):4602.

BMT CTN 1506 (MORPHO): Efficacy Outcome

Primary objective:
Relapse-free survival
HR = 0.679 (0.459–1.005)
P = .0518

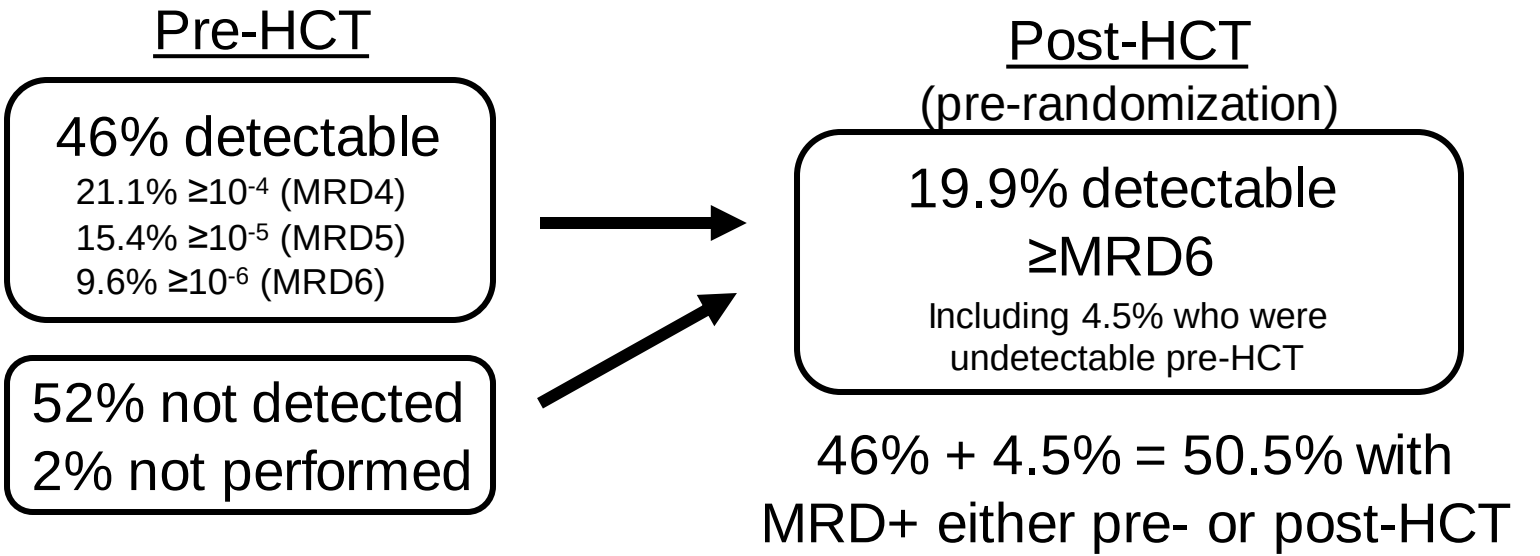


Key secondary objective:
Overall survival
HR = 0.846 (0.554–1.293)
P = .4394

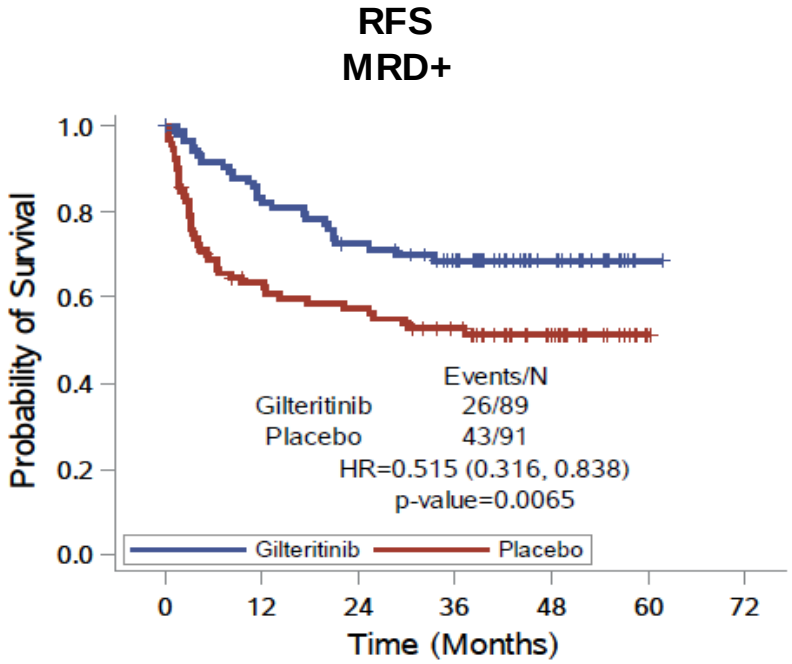


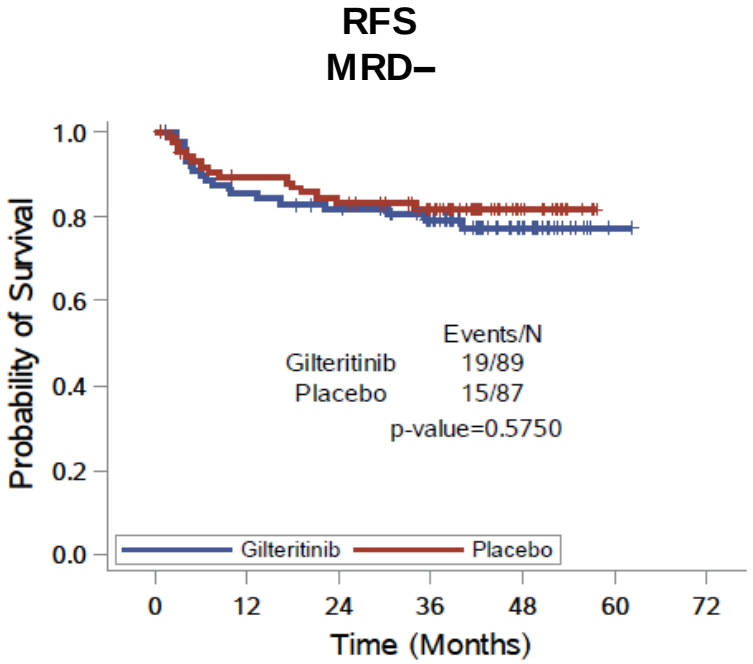
Measurable Residual Disease (MRD)

- PCR-NGS assay
  - 2-step assay
    - PCR of juxtamembrane region, amplicons analyzed by NGS
    - *Genes Chromosomes Cancer.* 2012;1:689-695; *Blood Adv.* 2018;8:825-831
  - Detects *FLT3*-ITD mutation with sensitivity of ~1 × 10^{-6}
- MRD analyzed in 350/356 (98.3%) pre-HCT and 347/356 (97.5%) in post-HCT
  - First 2 cc aspirate collected for MRD



Effect of Detectable MRD on RFS by Study Arm (51% had peri-HSCT MRD detectable using 10e6 *FLT3* assay)

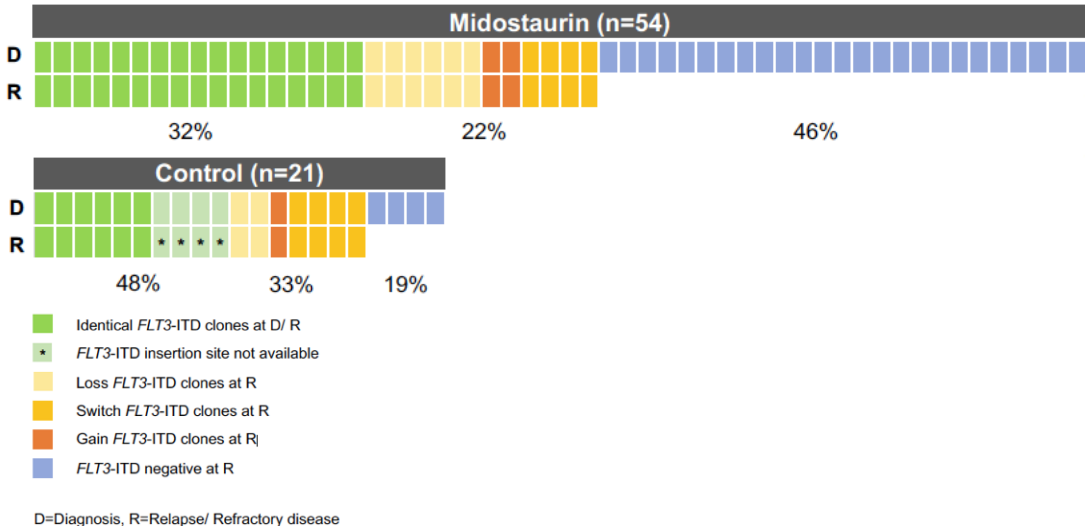




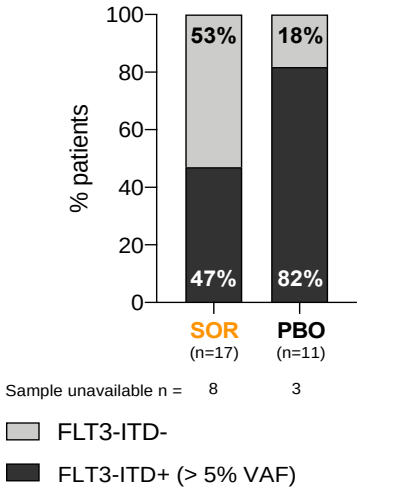
Levis M, et al. EHA 2023. Abstract LB2711.

Why May Maintenance Not Work as Optimally as Initially Hoped?
FLT3 Lost at Relapse After Frontline IC + FLT3 TKIs in 45%–55% of Patients: Data From 3 Studies

RATIFY



3+7 ± Sorafenib (ALLG AMLM16)



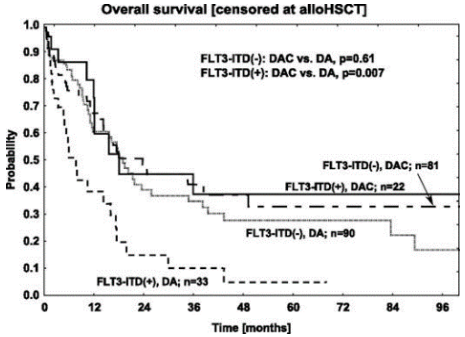
Additionally, 8/11 (73%) patients experiencing relapse after intensive chemotherapy + crenolanib had only wild-type *FLT3* in the relapsing AML cells

Data from other frontline randomized trials (QUANTUM-1, HOVON GILT) are forthcoming

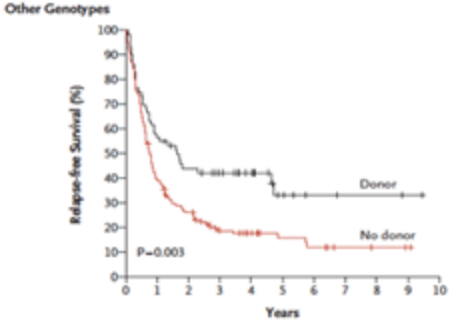
Schmalbrock LK, et al. *Blood*. 2021;137:3093-3104; Anstee NS, Wei AH, et al. ASH 2020. Abstract 272; Wang ES, et al. ASCO 2022. Abstract 7007.

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%

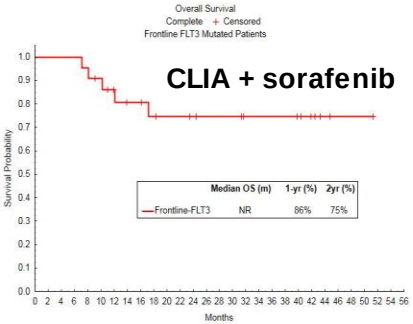
Adding purine analogue to DA (DAC)



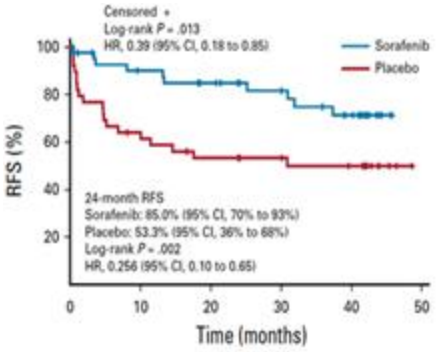
First remission allo-HSCT



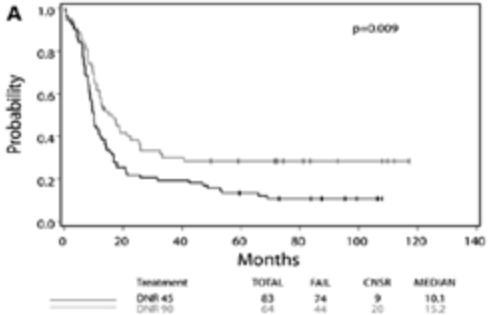
FLT3 inhibitors



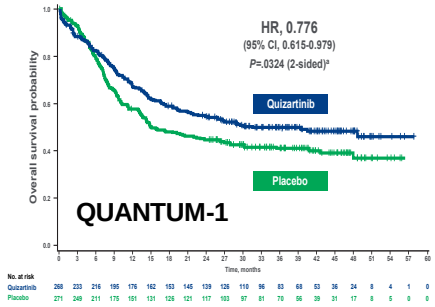
After allo-SCT sorafenib

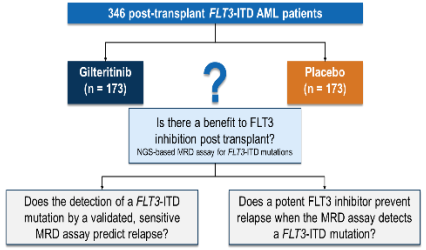


High-dose daunorubicin



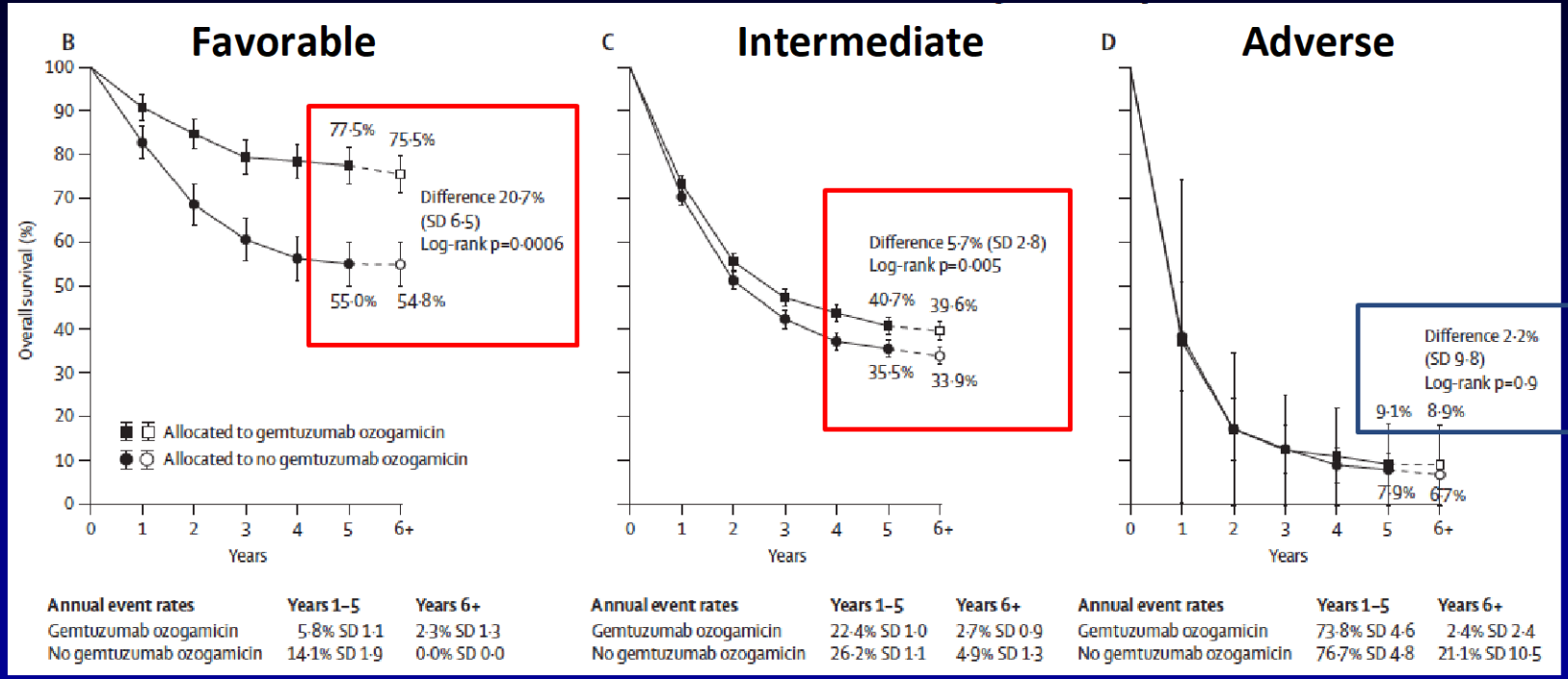
GILT maintenance Ph III





Would AZA + GILT be better?

2. Gemtuzumab Benefit Most Prominent in CBF-AML



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

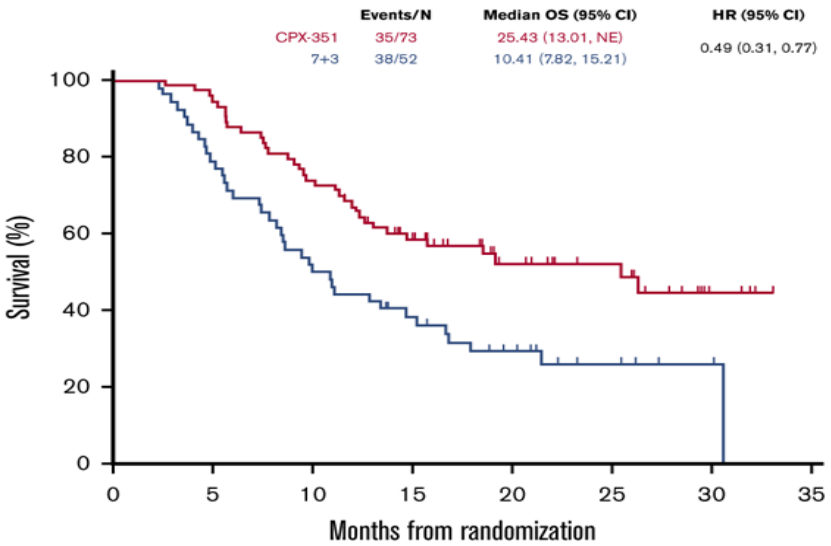
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Meta-analysis of overall survival of 3,325 patients with AML stratified by cytogenetic risk

Hills RK, et al. *Lancet Oncol*. 2014;15:986-996.

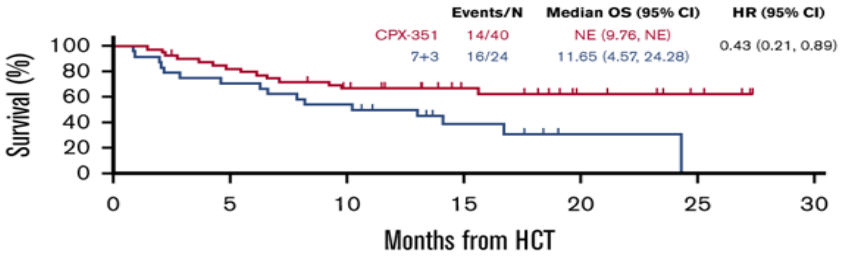
3. Older adults with newly diagnosed high-risk/secondary AML who achieved remission with CPX-351 versus 7+3: *post hoc* analyses of outcomes from a phase 3 study

Overall survival benefit in patients who achieved CR or CRi with CPX-351 versus 7+3 regimen



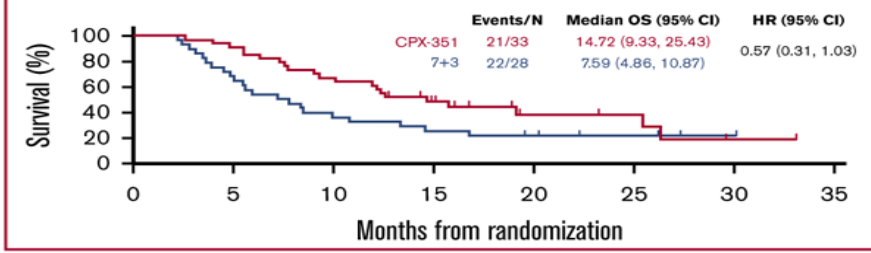
Proceeded to transplant

Landmarked survival benefit in patients who achieved CR or CRi with CPX-351 versus 7+3 regimen



Did not proceed to transplant

Overall survival benefit in patients who achieved CR or CRi with CPX-351 versus 7+3 regimen



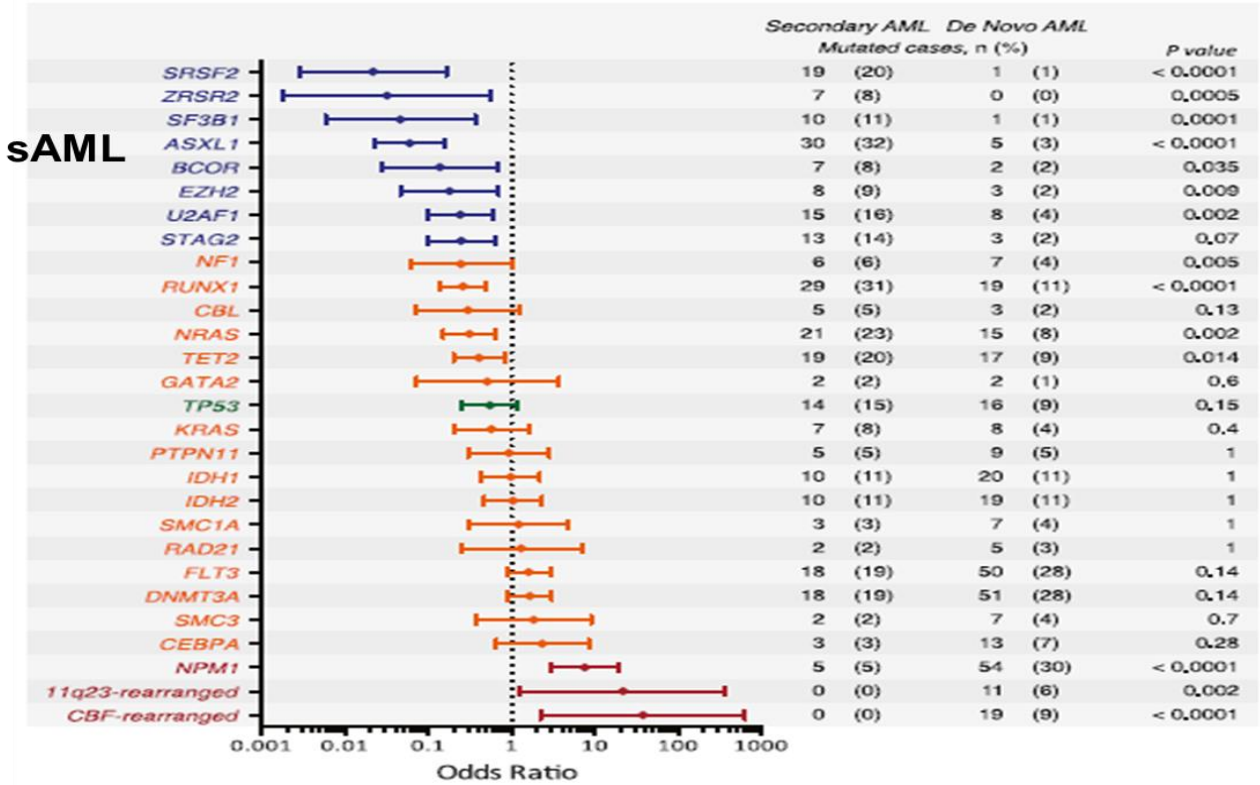
Conclusion:

Survival was longer for patients who achieved remission (CR or CRi) with CPX-351 versus conventional 7+3 chemotherapy

7+3 CR+CRi ≠ CPX-351 CR+CRi

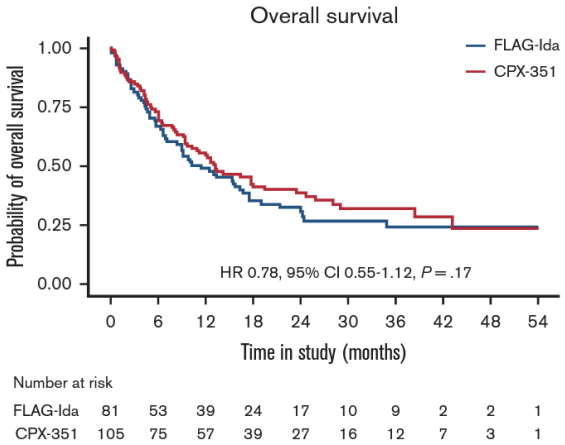
Lin TL, et al. *Blood Adv*. 2021;5:1719-1728.

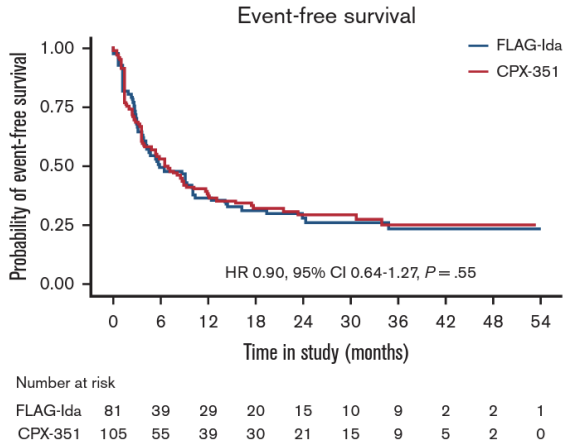
AML Ontogeny Can Be Mutationally Defined



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

Intensive Approaches for High-Risk (cyto-)Genetics





- NCRI AML-19 randomized comparison of 2 cycles of FLAG-IDA vs CPX-351 in ND AML or MDS-EB with 10%–19% blasts or IPSS-R INT or higher if lower blasts (n = 189 randomized for this question)
  - High-risk genetics by karyotype
  - MRD+ post-induction C1
  - MRD+ post-induction C2)
- Aged 18–70 but fit for intensive chemo

Othman J, et al. *Blood Adv*. 2023;7:4539-4549.

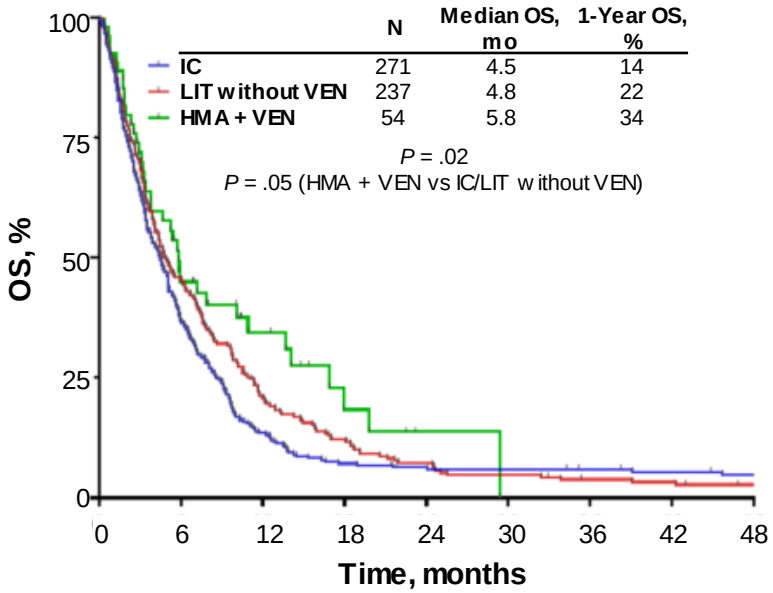
Use of HMA + Venetoclax Platforms May Improve Outcomes in sAML With Prior HMA Exposure, Particularly in Non–Adverse-Risk Karyotype

Retrospective Analysis, N = 562 Patients With sAML

From Preceding MDS or CMML, Pretreated With HMA

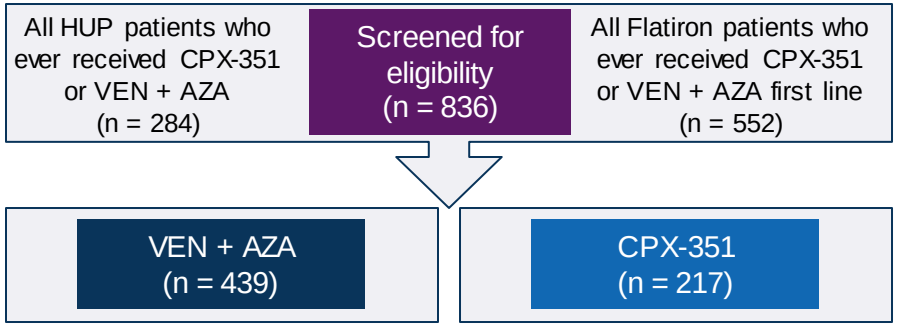
Compared with intensive chemotherapy or lower-intensity therapy without venetoclax, HMA + venetoclax resulted in

- Higher CR/CRi rates (39% and 25%, respectively; *P* = .02)
- Superior OS (1-year OS 34% and 17%, respectively; *P* = .05)
- Benefit of HMA + venetoclax was restricted to patients with non-adverse risk karyotype

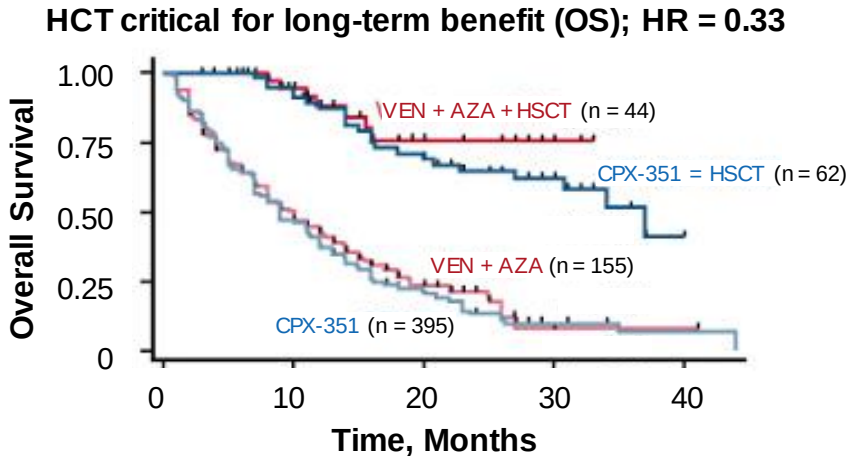


Short NJ, et al. *J Hematol Oncol*. 2022;15:12.

Further Real-World Evidence Suggests Efficacy of CPX-351 and Venetoclax Regimens in ND AML



	VEN + AZA	CPX-351
Median OS, mo	13	11
Median OS with allogeneic transplant, mo	NR	37
Median OS without allogeneic transplant	10	9



Take-Homes

1. First-line treatment with CPX-351 or venetoclax + azacitidine resulted in similar OS
2. **Use of HCT critical for OS benefit (tx choice did not influence OS when controlling for HCT)**
3. Similar early mortality with either option; infection, neutropenic fever, and inpatient LOS higher with CPX-351

Matthews AH, et al. *Blood Adv*. 2022;6:3997-4005.

4. Improving Cytotoxic Therapy, Non-*FLT3*, Non-CBF Approaches With the Addition of Venetoclax to Frontline IC

Induction

- **Cladribine 5 mg/m²** IV daily for 5 days on D1–5
- **Idarubicin 10 mg/m²** IV daily for 3 days on D1–3
- **Cytarabine 1500 mg/m²** (1000 mg/m² for patients aged ≥60) IV daily for 5 days on D1–5

Consolidation

- Cladribine **5 mg/m²** IV daily for 3 days on D1–3
- Idarubicin **8 mg/m²** IV daily for 2 days on D1–2
- Cytarabine **1000 mg/m²** (750 mg/m² for patients aged ≥60) IV daily for 3 days on D1–3

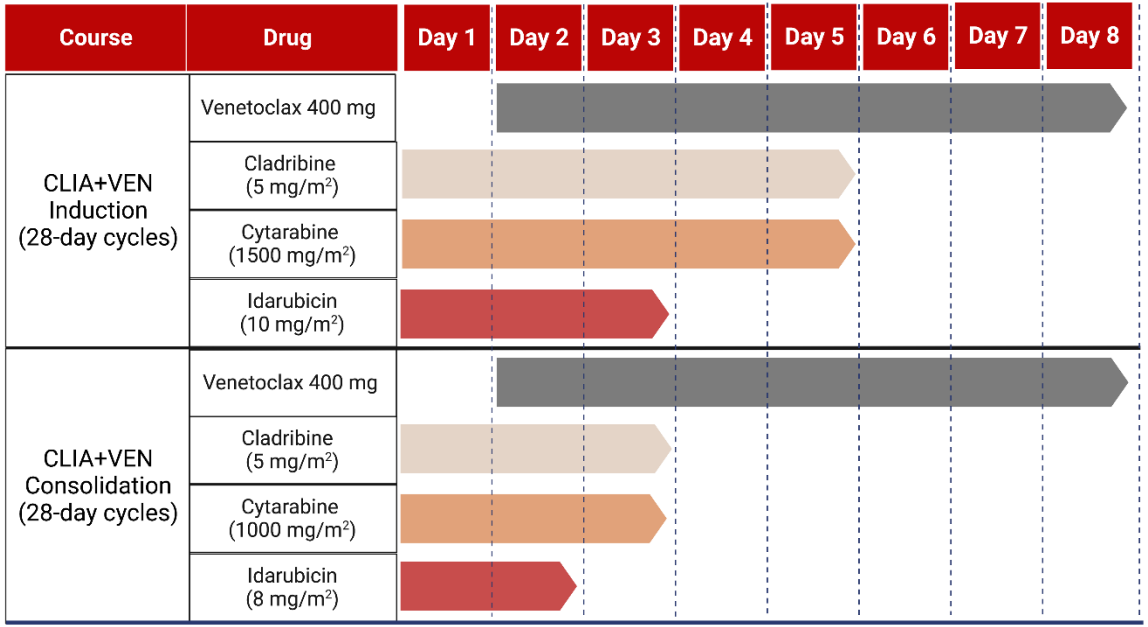
Venetoclax dosing

- 400 mg daily (modifications made for CYP3A4i)
- Given on days 2–8 of each cycle

Cytoreduce to WBC <20,000 prior to venetoclax

TLS monitoring per institutional standard

Antimicrobial prophylaxis in all patients: antibacterial, antiviral, antifungal



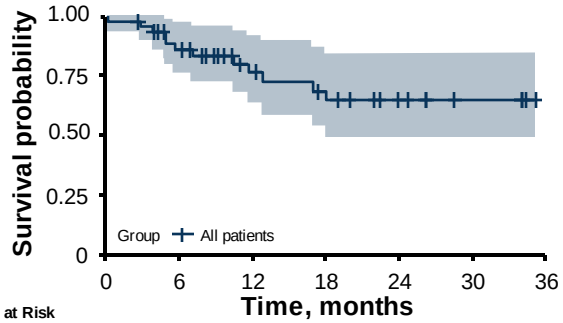
Response

N = 67	n / N (%); Median [Range]
Composite CR rate (CR + CRi)	**64 / 67 (96)**
Best response	
CR	**57 / 67 (85)**
CRi	**7 / 67 (10)**
NR	2 / 67 (3)
Died	1 / 67 (1.5)
MRD negative at first response assessment (by flow)	47 / 61 (**77**)
MRD-negative 10e4 on study (by flow)	55 / 61 (**90**)
Positive	6 / 61 (10)
Total number of courses given, median (IQR)	2.0 [2.0–3.0]
Responders who received allo-SCT	45 / 64 (**70**)
Mortality rate at 4 weeks	1 / 67 (1.5)
Mortality rate at 8 weeks	2 / 67 (3)

FLAG-Ida/CLIA + Venetoclax

FLAG-IDA + Venetoclax[1]

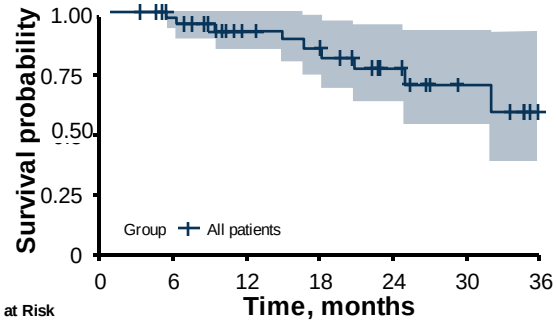
Event-Free Survival



No. at Risk

All patients	45	35	20	15	8	4	0

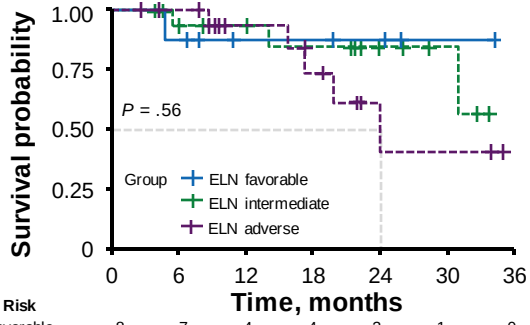
Overall Survival



No. at Risk

All patients	45	39	25	20	11	6	0

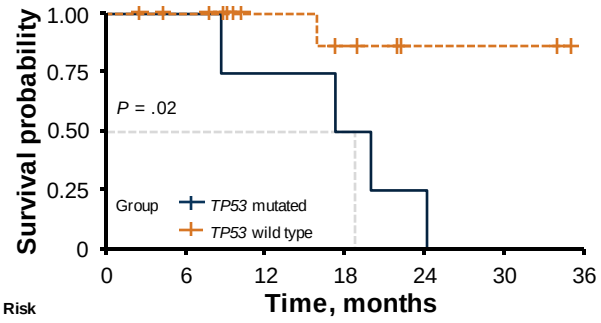
Overall Survival



No. at Risk

ELN favorable	8	7	4	4	3	1	0
ELN intermediate	18	15	11	9	5	3	0
ELN adverse	19	17	10	7	3	2	0

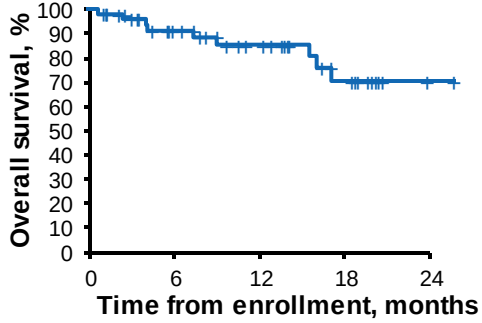
Overall Survival ELN Adverse Risk



No. at Risk

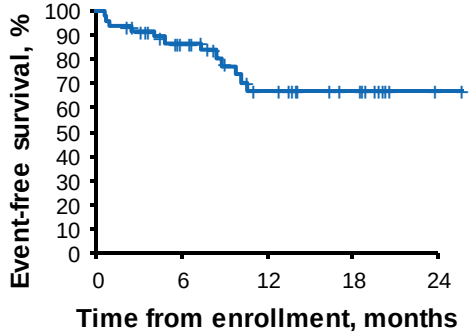
TP53 mutated	4	4	3	2	1	0	0
TP53 wild type	15	13	7	5	2	2	0

CLIA + Venetoclax[2]



No. at Risk (No. Censored)

All	50 (0)	35 (11)	24 (20)	13 (28)	1 (40)	

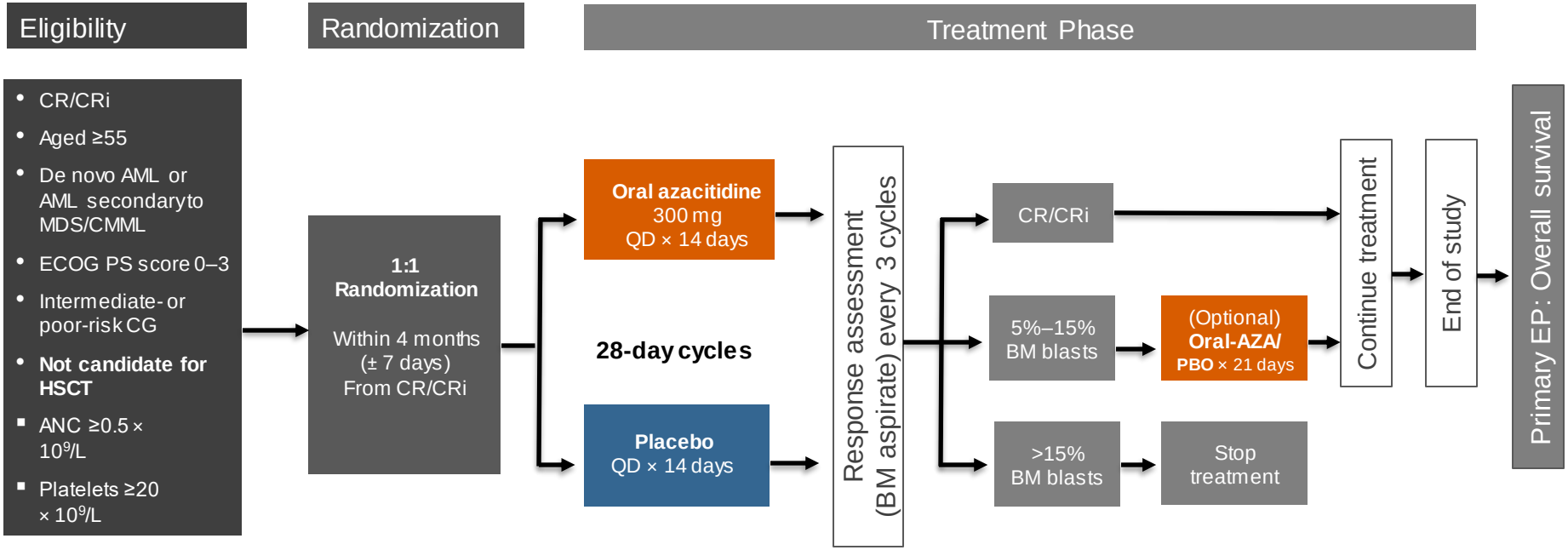


No. at Risk (No Censored)

All	50 (0)	35 (11)	19 (19)	12 (26)	1 (37)

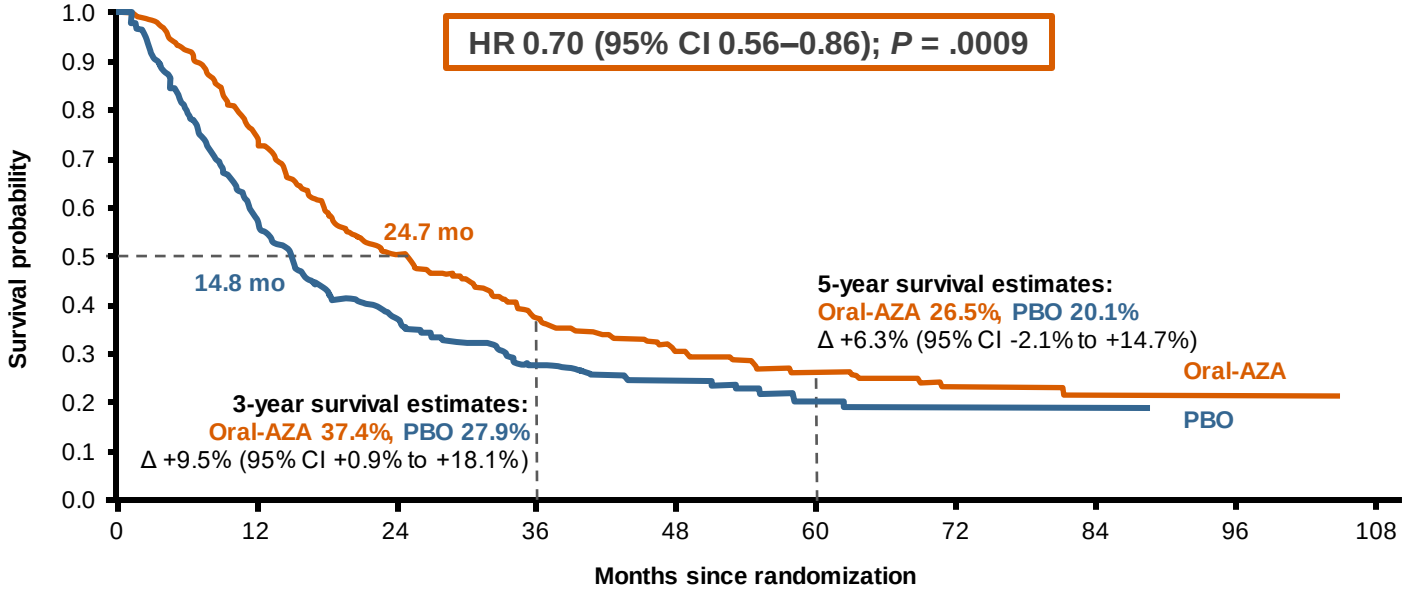
1. DiNardo CD, et al. *Am J Hematol*. 2022:1035-1043; 2. Kadia TM, et al. *Lancet Haematol*. 2021;8:e552-e561.

Oral AZA as Maintenance – *QUAZAR AML-001: Study Overview*



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

Oral AZA as Maintenance – *QUAZAR AML-001: Updated OS March 2023*



Number at Risk

Oral-AZA	238	168	116	83	60	40	19	9	5	0
PBO	234	127	82	57	33	20	9	3		

Wei AH, et al. *Am J Hematol*. 2023;98:E84-E87.

How to Manage Side Effects of Oral AZA Maintenance Therapy? *QUAZAR AML-001*

	Oral AZA (n = 236)		Placebo (n = 233)	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Event	*Number of Patients, %*			
Any adverse event	231 (98)	169 (72)	225 (97)	147 (63)
Nausea	153 (65)	6 (3)	55 (24)	1 (<1)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhea	119 (50)	12 (5)	50 (21)	3 (1)
Neutropenia	105 (44)	97 (41)	61 (26)	55 (24)
Constipation	91 (39)	3 (1)	56 (24)	0
Thrombocytopenia	79 (33)	53 (22)	63 (27)	50 (21)
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Asthenia	44 (19)	2 (1)	13 (6)	1 (<1)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (<1)
Arthralgia	32 (14)	2 (1)	24 (10)	1 (<1)
Abdominal pain	31 (13)	2 (1)	16 (7)	0
Upper respiratory tract infection	31 (13)	1 (<1)	32 (14)	0
Decreased appetite	30 (13)	2 (1)	15 (6)	2 (1)
Cough	29 (12)	0	39 (17)	0
Febrile neutropenia	28 (12)	27 (11)	18 (8)	18 (8)
Back pain	28 (12)	3 (1)	23 (10)	2 (1)
Leukopenia	25 (11)	18 (8)	19 (8)	14 (6)
Pain in extremity	25 (11)	1 (<1)	12 (5)	0
Dizziness	25 (11)	0	21 (9)	0
Headache	23 (10)	0	26 (11)	1 (<1)
Peripheral edema	21(9)	0	24(10)	1 (<1)

Nausea/vomiting/diarrhea

- GI AEs were primarily managed with standard supportive care measures and oral azacitidine dosing modifications
  - Administer an antiemetic 30 minutes before each dose for at least the first 2 cycles
  - For first interruption, attempt to restart at same dose
  - For second interruption, reduce dose
- The use of concomitant medications for nausea, vomiting, and diarrhea decreased over time in parallel with rates of GI AEs as therapy continued

Cytopenias

- If ANC <500/µL or platelets <50,000/µL on day 1 of a cycle, delay start of the cycle until the ANC >500/µL and platelets >50,000/µL
- For first interruption, attempt to restart at same dose
- For second interruption, reduce dose

Dose reduction

Starting dose: 300 mg for days 1–14

- Step 1: 200 mg for days 1–14
- Step 2: 200 mg for days 1–7
- Step 3: Stop

ANC, absolute neutrophil count

Wei AH, et al. *N Engl J Med*. 2020;383:2526-2537. Ravandi et al. *J Hematol Oncol*. 2021;14:133.

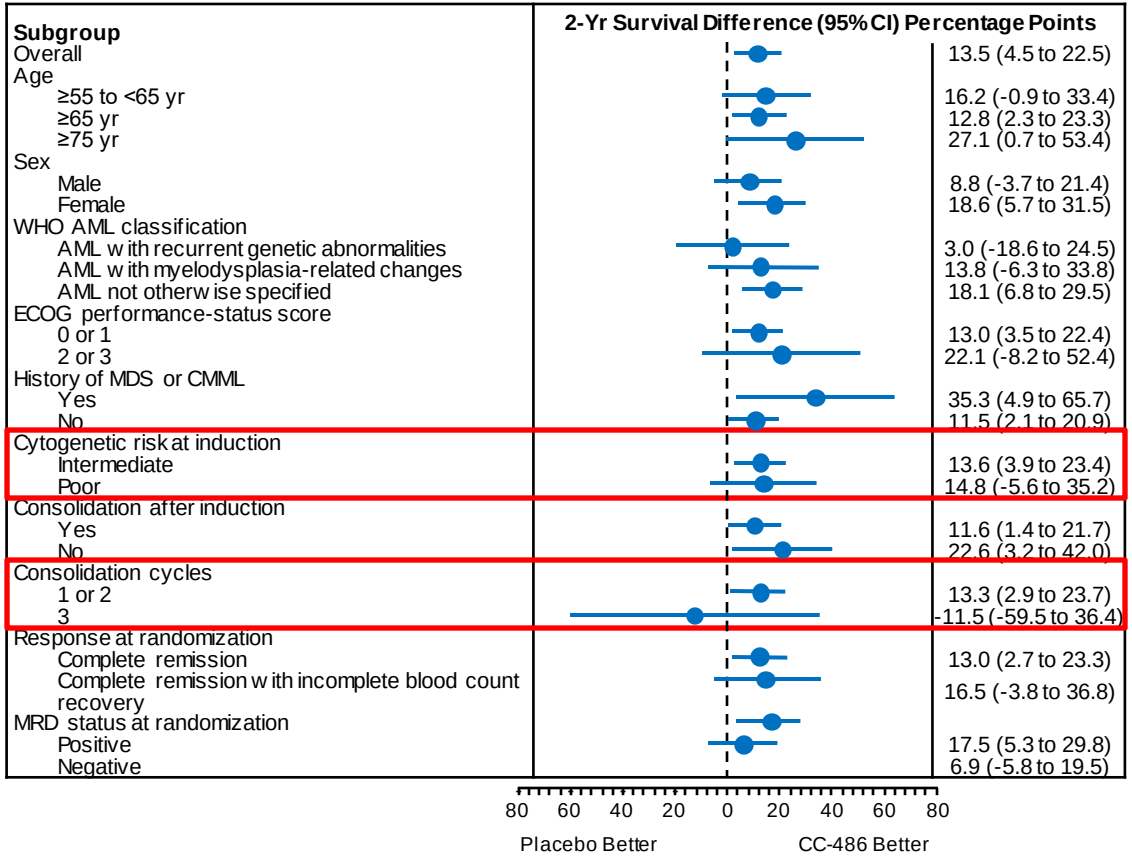
Who Should Get Maintenance Therapy?
QUAZAR AML-001

Inclusion criteria for QUAZAR study

- *Intermediate/poor risk (NOT cytogenetic favorable risk)*
- *CR1 or CRi1 after induction chemotherapy*
- *NOT azacitidine + venetoclax*
- *NOT candidate for ASCT*

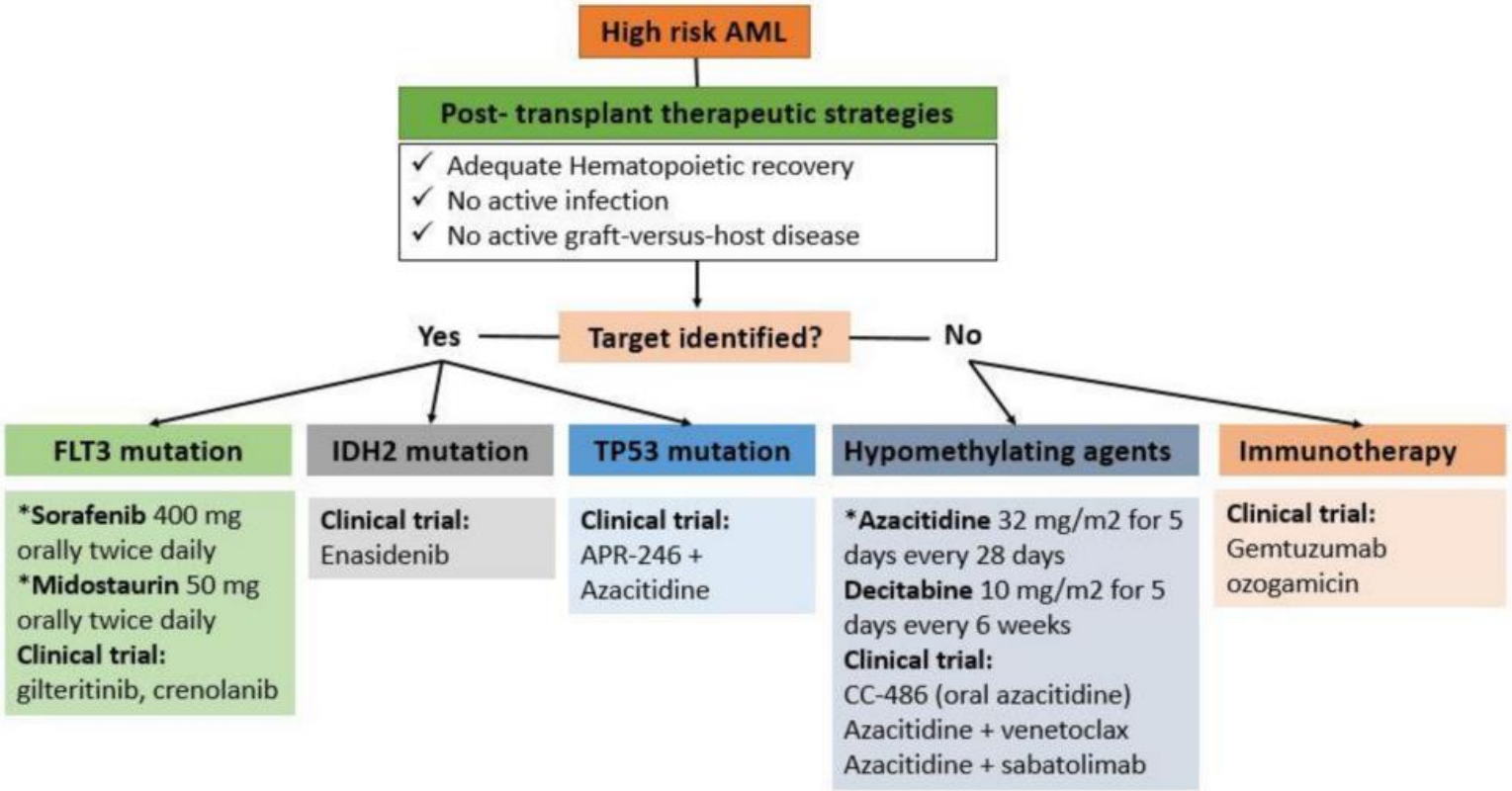
Niche use of maintenance therapy

- *Not fit enough for ASCT (and full number of consolidation cycles?)*
- *Fit enough to have received induction chemotherapy (otherwise azacitidine + venetoclax)*



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

Maintenance Therapy After Allogeneic Transplantation



Dalle IA, et al. *Cancers (Basel).* 2022;14:1490.

Leukemia Questions?

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- Cell: 832-573-7080
- Office: 713-794-4392

Global Leukemia Academy

Therapeutic approaches in high-risk and frail AML patients

Phillip Scheinberg

Head, Division of Hematology
Hospital A Beneficência Portuguesa
São Paulo, Brazil

APTITUDE HEALTH

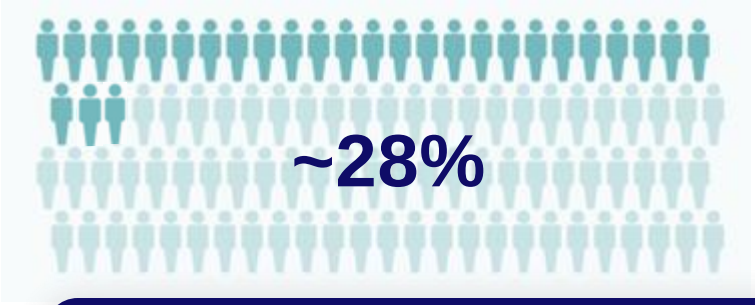
Disclosures

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

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

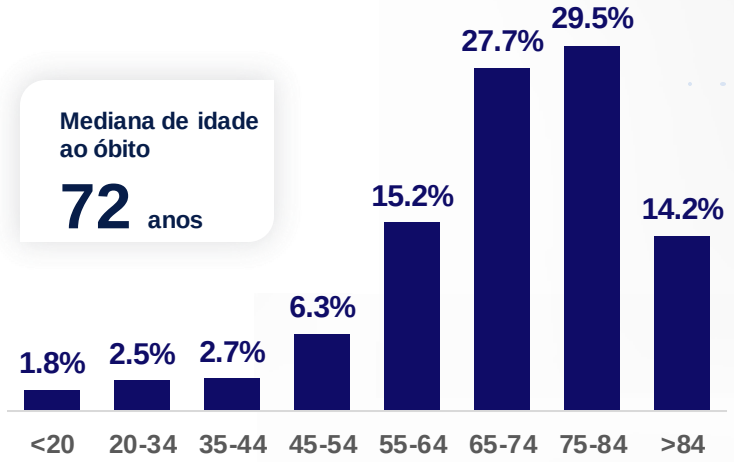
Sobrevida do paciente e idade de mortalidade

Pacientes que sobrevivem em 5 anos, %



Os piores resultados em pacientes idosos, em comparação com aqueles com menos de 60 anos de idade, foram associados a problemas de tolerabilidade ao tratamento e alterações cromossômicas associadas ao prognóstico desfavorável.

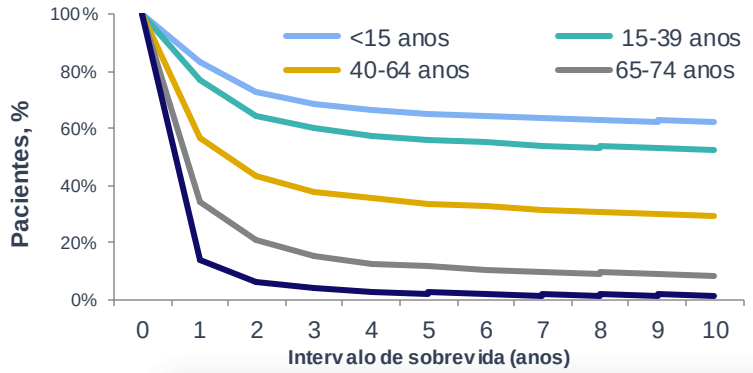
Óbitos por LMA por faixa etária, %



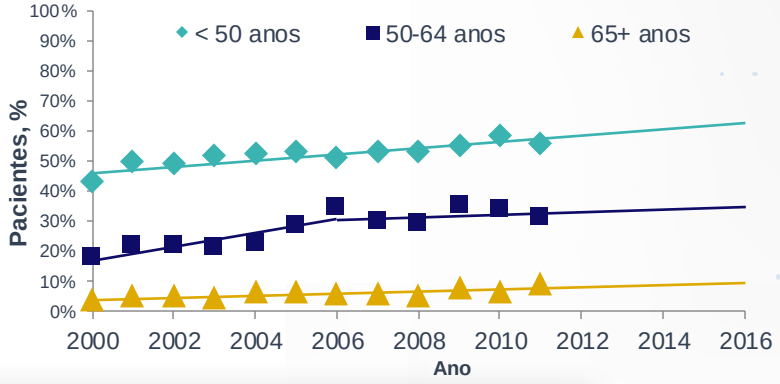
1. National Cancer Institute. Cancer Stat Facts: Acute Myeloid Leukemia (AML). https://seer.cancer.gov/statfacts/html/amyl.html. Acesso em julho de 2019.
2. Ma E, et al. Clin Lymphoma Myeloma Leuk. 2016;16:625-636. 3. Almeida AM et al. Leuk Res Rep. 2016;6:1-7.

Sobrevivência por idade

Tempo relativo de sobrevivência do diagnóstico à morte em pacientes com LMA, 2000-2015



Sobrevida de 5 anos por ano de diagnóstico (2000-2016)



Embora a sobrevida de pacientes mais jovens com LMA tenha melhorado na última década, os pacientes idosos continuam com prognóstico ruim.

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

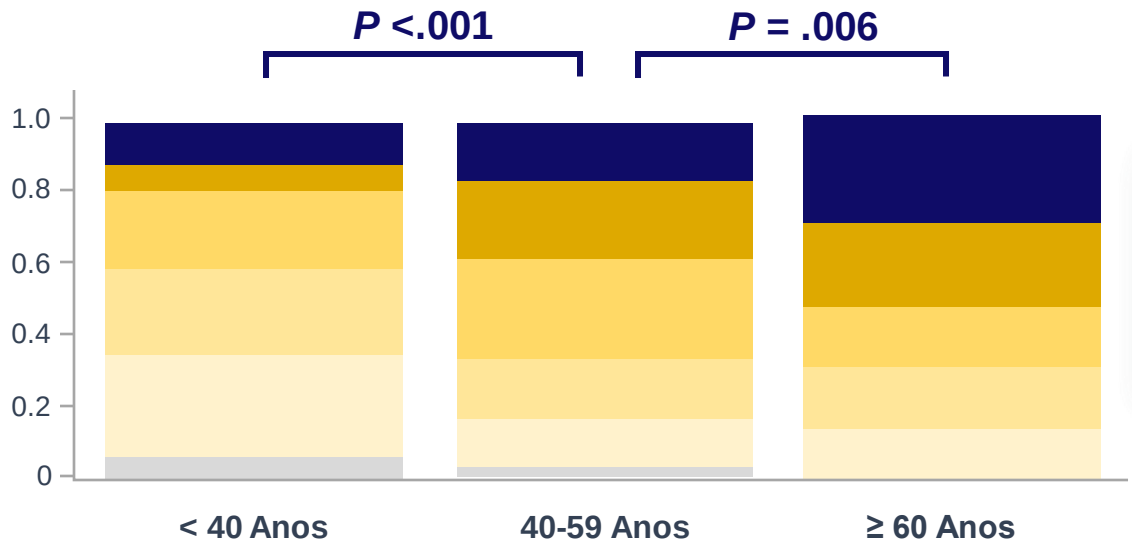
Desafios Clínicos dos Pacientes Idosos com LMA

- Menor performance status
- Maior incidência de comorbidades
- Baixa contagem de leucócitos no diagnóstico
- Baixo percentual de blastos medulares
- Maior probabilidade de resistência multi drogas
- Menor incidência de citogenética “favorável”
- Menor probabilidade de atingir remissão
- Maior probabilidade de morbidade/ mortalidade relacionada ao tratamento
- Menor probabilidade de sobrevida
- Maior incidência de LMA secundária (s-LMA) e relacionada ao tratamento (t-LMA)

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

Número de mutações aumenta com a idade nos pacientes com LMA

Nº genes mutados por Pt, por faixa etária



Nº Genes Mutados

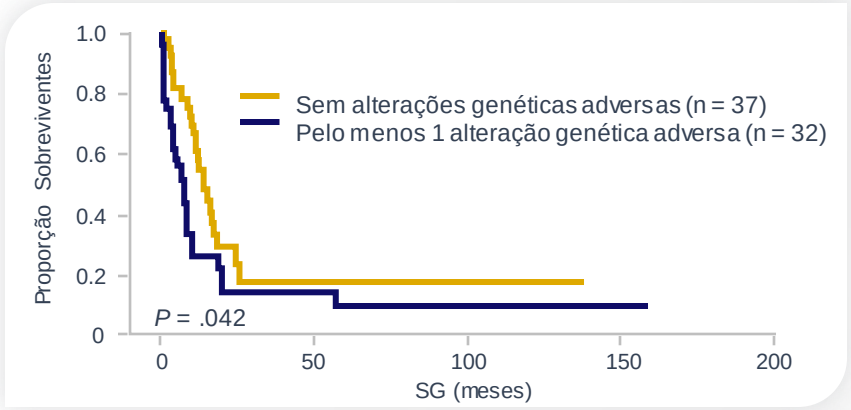
0 | 1 | 2 | 3 | 4 | ≥ 5

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

Mutações de pior prognóstico são mais prevalentes em Pacientes Idosos com LMA

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

Variáveis*	Pts com Alterações, %			*P* Value
	Todos	Idosos	Jovens	
TET2	14.3	24.3	8.1	<.001
DNMT3A	15.2	20.9	11.6	.008
TP53	7.6	13.0	4.2	.001
Cohesin	10.0	9.6	10.2	>.999



*Para todas as variáveis, exceto *Cohesin*, n = 462; for *Cohesin*, n = 411.
Tsai CH, et al. Leukemia. 2016;30:1485-1492.

Critérios de Inelegibilidade – Ferrara

Critérios para definir a não elegibilidade à quimioterapia intensiva em LMA

- Idade >75 anos
- Insuficiência cardíaca congestiva ou cardiomiopatia documentada com FE ≤50%
- Doença pulmonar documentada com DLCO ou VEF1 ≤65%, dispneia ou qualquer neoplasia pleural
- Em diálise e idade >60 anos ou carcinoma renal não controlado
- Cirrose hepática Child B ou C, ou doença hepática com elevação acentuada de transaminases e >60 anos, ou qualquer carcinoma hepático ou hepatite viral aguda
- Infecção ativa resistente à terapia anti-infecciosa
- Doença mental que requer hospitalização, institucionalização ou tratamento ambulatorial intensivo ou dependência
- Status de desempenho do ECOG ≥3 não relacionado à leucemia
- Qualquer outra comorbidade que o médico julgue incompatível com quimioterapia intensiva

DLCO = Capacidade de Difusão Pulmonar para o Monóxido de Carbono. VEF=Volume Expiratório Forçado.
Ferrara F. et al. Leukemia. 2013;27:997-999.

Opções para os inelegíveis a QT intensiva até 2018

EXPECTATIVAS DO TRATAMENTO:

RC, SG e
Qualidade de vida

ATÉ 2018

- BSC
- LDAC
- HMA monoterapia

RESULTADOS

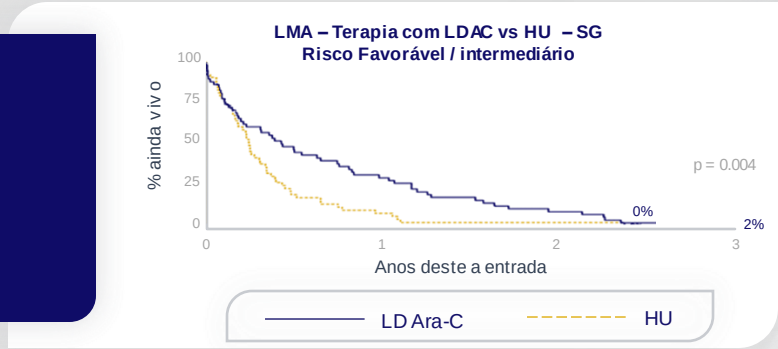
Burnett AK Cancer 2007;109:1114–24
Kantarjian HM. J Clin Oncol 2012;30:2670-7
Dombret H, et al. Blood. 2015/ 36126(3)?291-299

LDAC vs Hidroxiureia

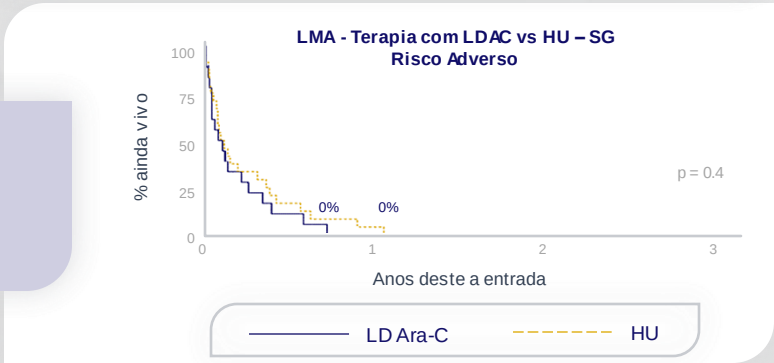
Estudo com 217 pacientes inelegíveis a QT randomizados para LDAC / HU (com e sem ATRA)

Modesto benefício na população de risco favorável e intermediário

- RC 18% vs 1%
- SG 4m vs 3m



Na população de alto risco, <u>não houve</u> benefício na SG

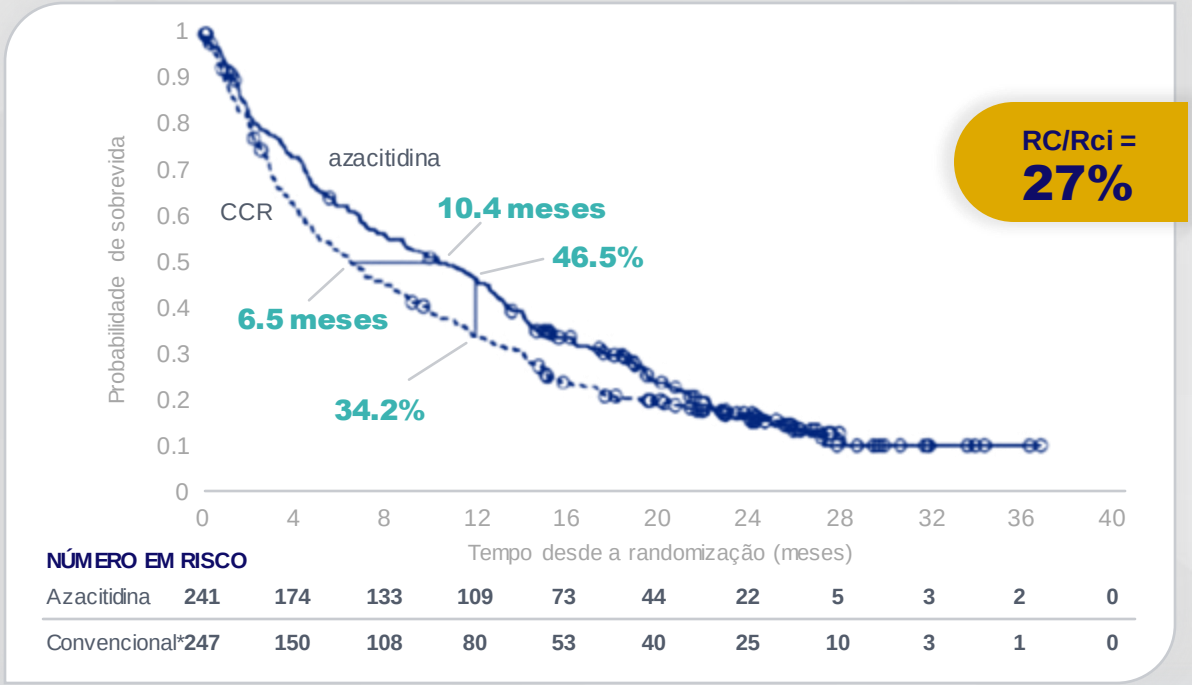


Burnett AK et al, Cancer 2007;109:1114–24

Dombret H, et al, 2015

AZA em monoterapia para pacientes idosos com LMA

Azacitidina monoterapia tem taxa de RC/RCi modestas quando comparados ao tramento convencional (QT/LDAC/BSC)



NÚMERO EM RISCO

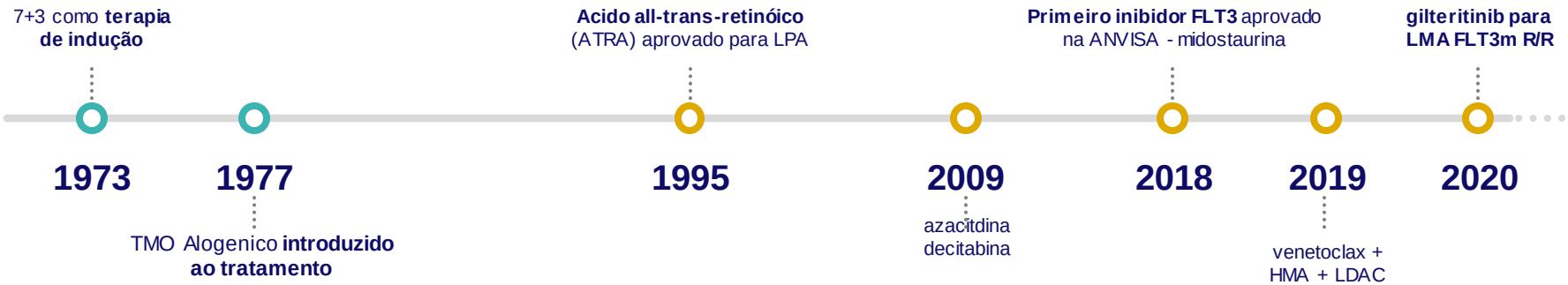
Azacitidina	241	174	133	109	73	44	22	5	3	2	0
Convencional*	247	150	108	80	53	40	25	10	3	1	0

*Convencional: regime de suporte convencional (QT intensiva de indução, LDAC ou suporte paliativo)
Dombret H, et al. Blood. 2015/ 36126(3)?291-299

Tratamento da LMA (Progresso acelerado 2018-2020): História

Desde a sua introdução nos anos 70, a **terapia com 7+3** tem sido o **standard of care na LMA**

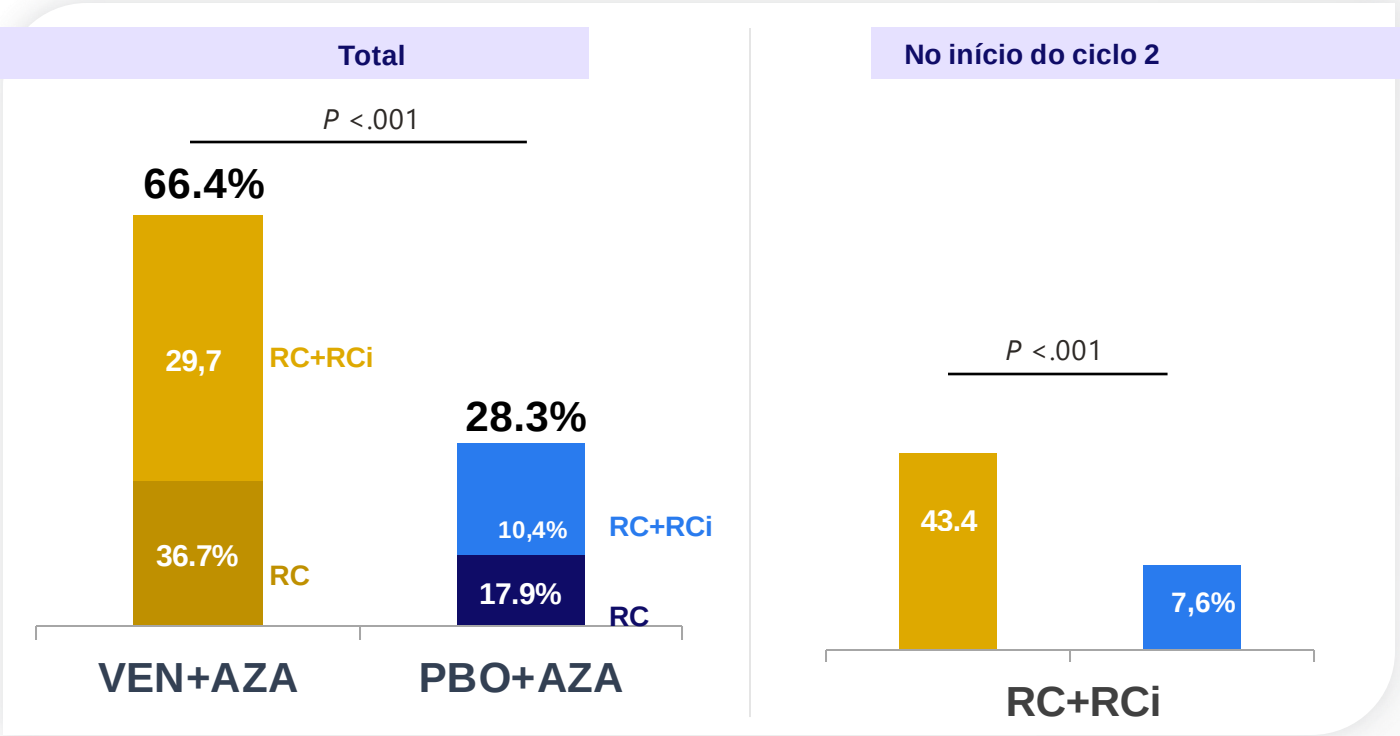
Aprovações na ANVISA



Ano	1975	1980	1990	1995	2000	2005	2009	2013	2022
Sobrevida em 5 anos (%)	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

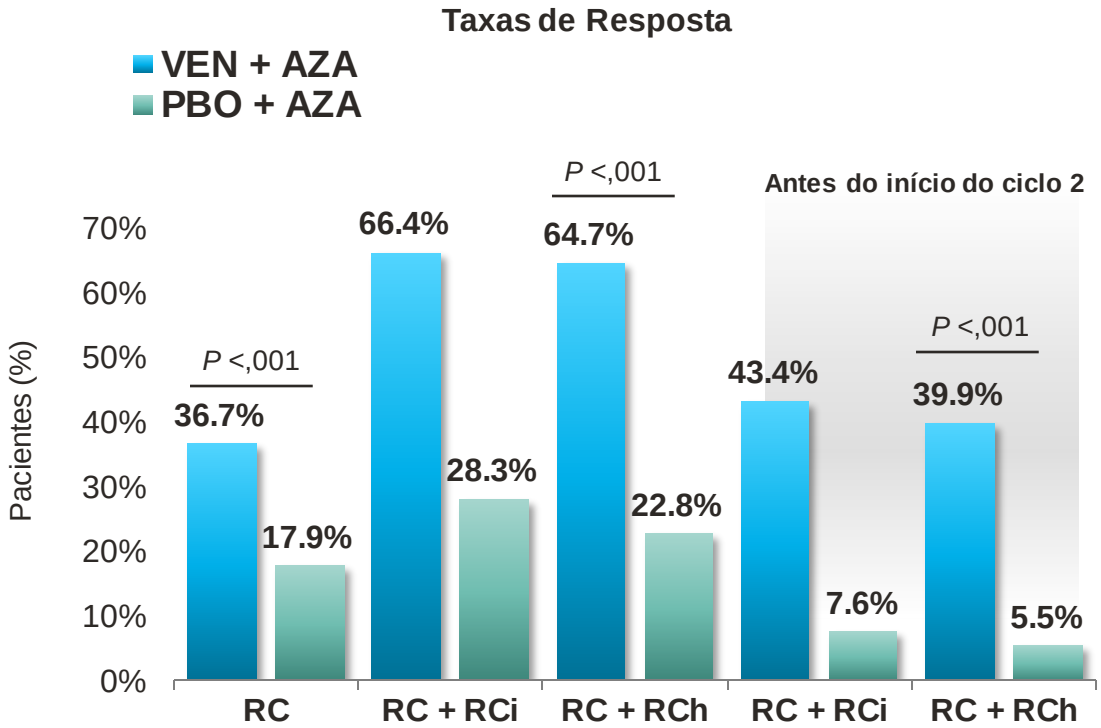
Portal ANVISA - https://consultas.anvisa.gov.br acessado em Abril 2021

VIALE-A: Taxa de resposta RC / RCi



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

Taxas de Resposta e Tempo de Resposta



Mediana de meses (faixa)	VEN + AZA (N=286)	PBO + AZA (N=145)
Tempo para a primeira resposta (RC ou RCi)	**1,3** (0,6-9,9)	**2,8** (0,8-13,2)

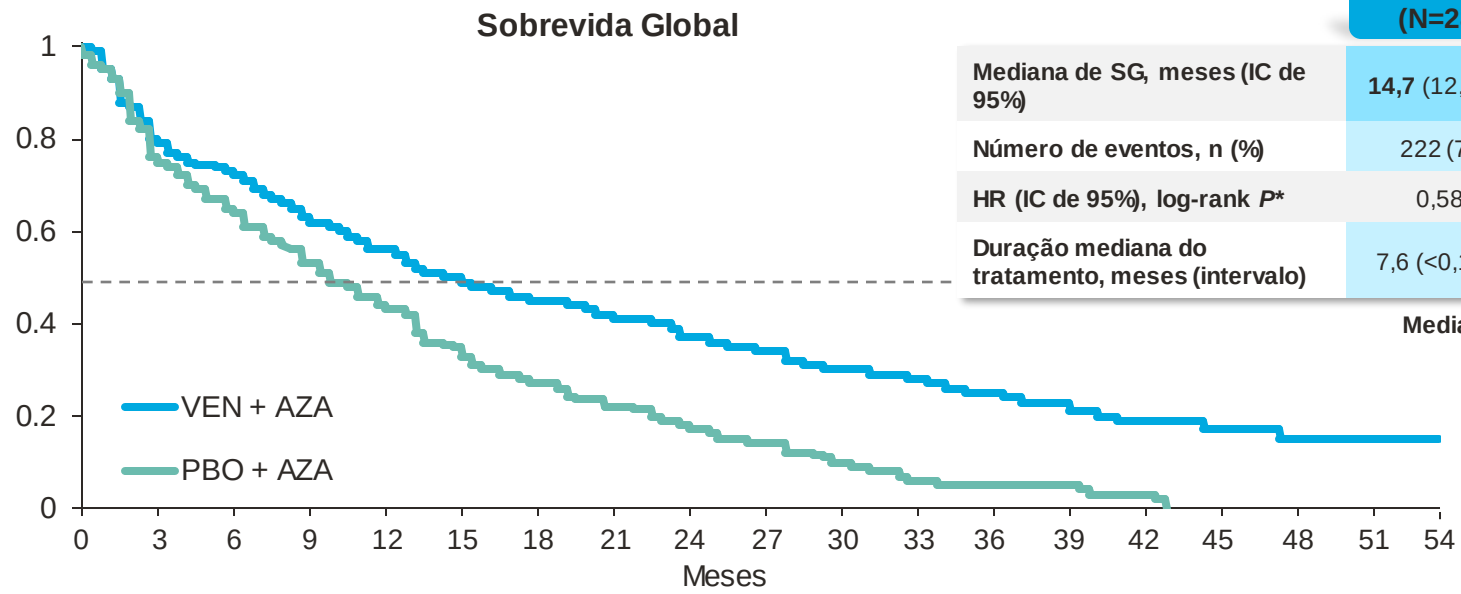
Em pacientes com RC + RCi, a negatividade da DRM ocorreu em:

- **23,4%** recebendo VEN + AZA vs
- **7,6%** recebendo PBO + AZA

AZA=Azacitidina. IC=Intervalo de Confiança. RC=Remissão Completa. RCi=RC com Recuperação Incompleta do Hemograma. RCh=RC com Recuperação Hematológica Parcial. DRM=Doença Residual Mensurável. NR=Não Alcançado. PBO=Placebo. VEN=Venetoclax.

Desfecho Primário
Data de corte de dados: 4 de janeiro de 2020.
DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29.

Acompanhamento de Longo Prazo: Sobrevida Global



	VEN + AZA (N=286)	PBO + AZA (N=145)
Mediana de SG, meses (IC de 95%)	**14,7** (12,1-18,7)	**9,6** (7,4-12,7)
Número de eventos, n (%)	222 (77,6)	138 (95,2)
HR (IC de 95%), log-rank *P**	0,58 (0,465-0,723), *P* <,001	
Duração mediana do tratamento, meses (intervalo)	7,6 (<0,1-30,7)	4,3 (0,1-24,0)

Mediana de acompanhamento:

43,2 meses
(intervalo <0,1 – 53,4)

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

Análise de 100% de SG
360/431 eventos de sobrevida

*As distribuições foram estimadas para cada braço de tratamento usando a metodologia Kaplan-Meier e comparadas usando o teste log-rank estratificado por idade (18-<75, ≥75 anos) e risco citogenético (risco intermediário, risco alto). A HR entre os braços de tratamento foi estimada usando o modelo de riscos proporcionais de Cox com os mesmos fatores de estratificação usados no teste de log-rank. AZA=Azacitidina. IC=Intervalo de Confiança. HR=Razão de Riscos. SG=Sobrevida Global. PBO=Placebo. VEN=Venetoclax.

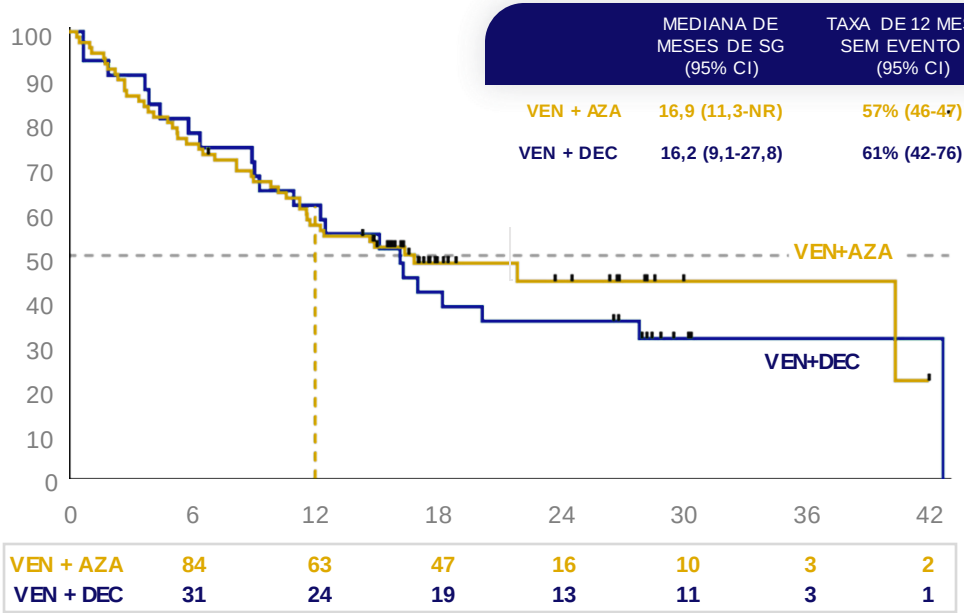
Desfecho Primário
Corte de dados: 1 de dezembro de 2021.
Pratz KW, et al. Oral 219. 64th ASH. Dec 10-13, 2022. New Orleans, LA.6

M14-358: Sobrevida Global – Análise combinada

MEDIANA DE SG

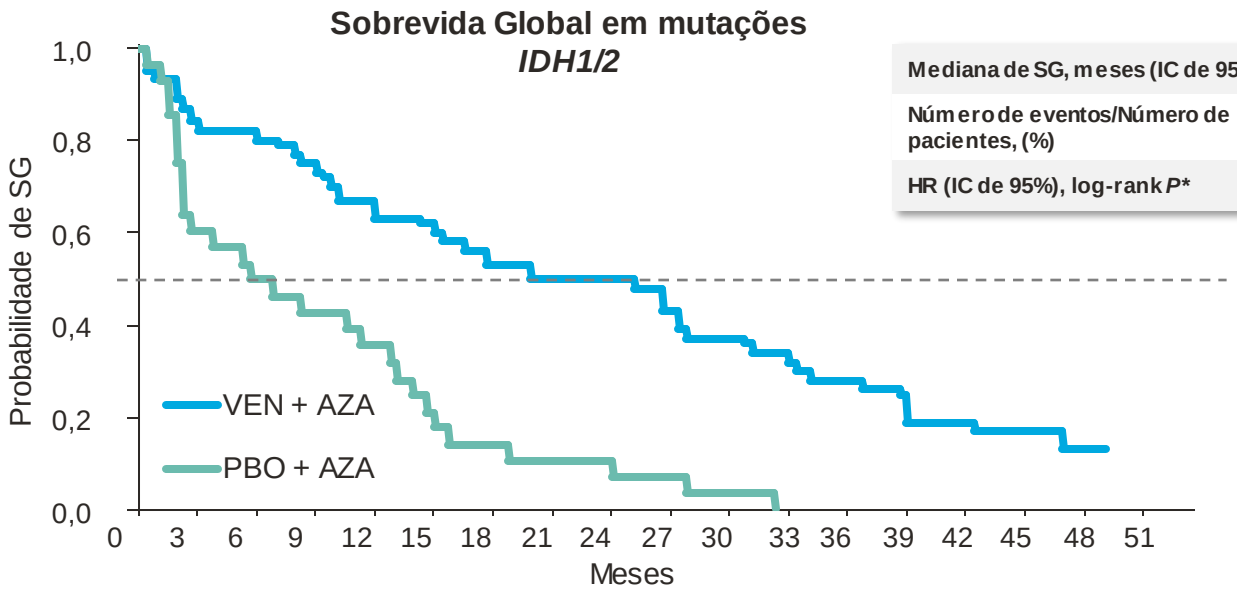
venetoclax + azacitidina
14,9 meses (0,4–42,0)

venetoclax + decitabina
16,2 meses (0,7–42,7)



1. Pollyea DA, et al. ASH 2018. Abstract285; 2. DiNardo CD, et al. Blood. 2018;133:7-17.

Acompanhamento de Longo Prazo: Pacientes com mutações *IDH1/2* alcançaram mediana de SG na análise de 100% de SG



	VEN + AZA (N=286)	PBO + AZA (N=145)
Mediana de SG, meses (IC de 95%)	**19,9** (12,2-27,7)	**6,2** (2,3-12,7)
Número de eventos/Número de pacientes, (%)	49/61 (80,3)	28/28 (100)
HR (IC de 95%), log-rank *P**	0,314 (0,189-0,522), *P* <,001	

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

Análise *Post-hoc*

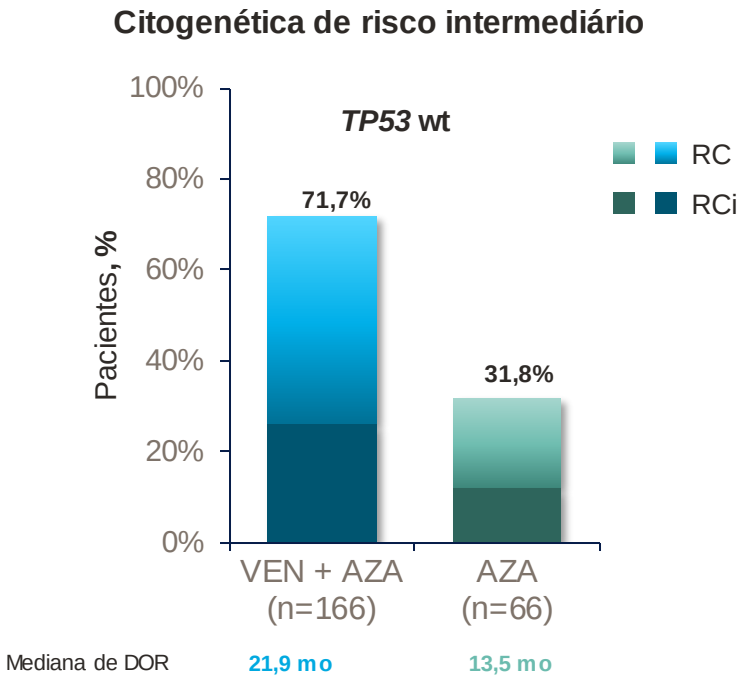
As análises de subgrupo não foram desenvolvidas para demonstrar uma diferença estatisticamente significativa na SG ou nas taxas de resposta. Pequenos números de pacientes nesses subgrupos podem ser uma limitação dessa análise. Nenhuma conclusão de eficácia ou segurança pode ser tirada desses dados.

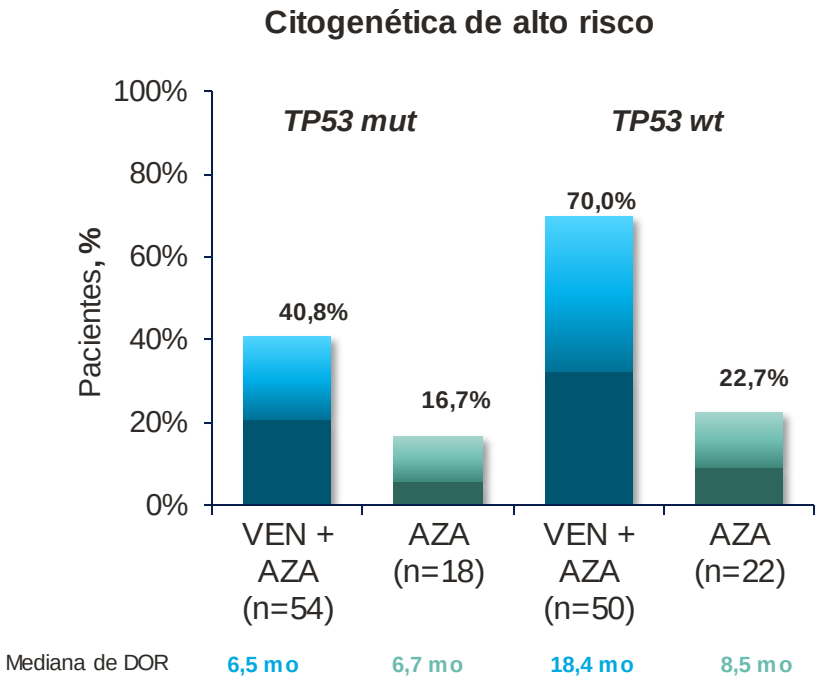
Corte de dados: 1 de dezembro de 2021.

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

*As distribuições foram estimadas para cada braço de tratamento usando a metodologia Kaplan-Meier.
O teste de log-rank não estratificado e a razão de riscos foram estimados usando o modelo de Cox não estratificado. Os dados IDH1/2 são provenientes do método CDX.
AZA=Azacitidina. IC=Intervalo de Confiança. HR=Razão de Riscos. SG=Sobrevida Global. PBO=Placebo. VEN=Venetoclax.

Em uma análise agrupada de pacientes do VIALE-A e do estudo de fase 1b, as taxas de remissão foram altas em citogenética de risco intermediário ou alto e pacientes com *TP53*^{wt} tratados com VEN + AZA

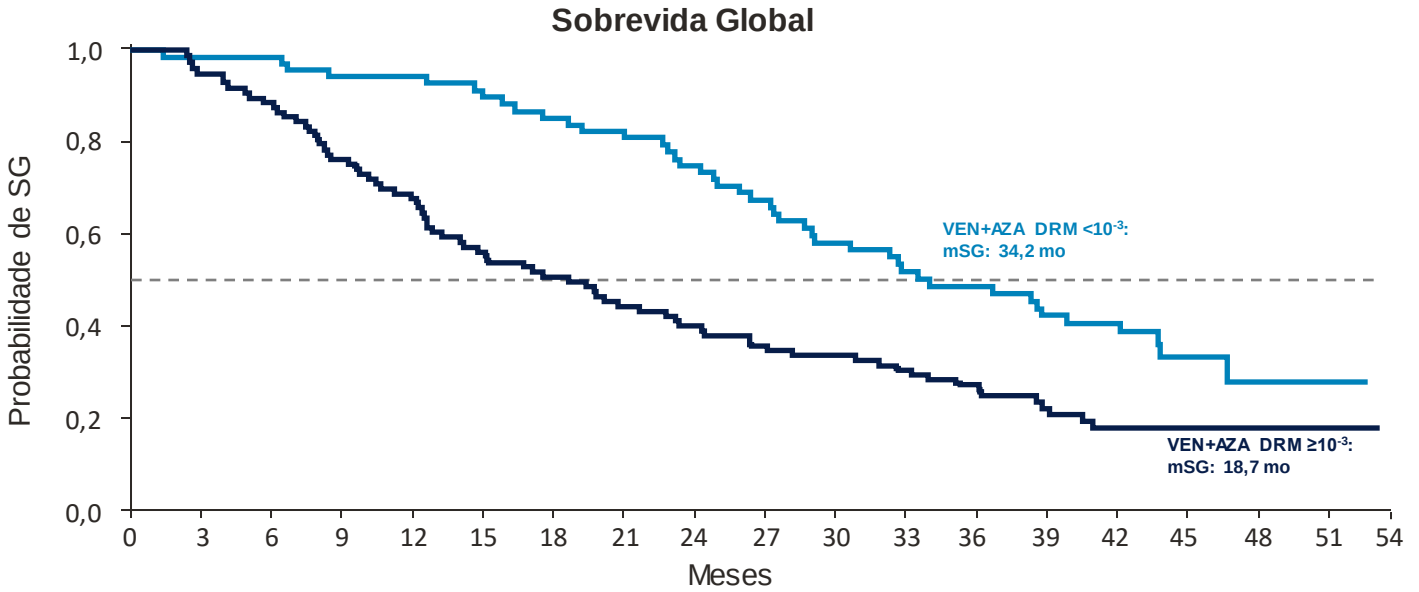




Análise *Post-hoc*
As análises de subgrupo não foram desenvolvidas para demonstrar uma diferença estatisticamente significativa na SG ou nas taxas de resposta. Pequenos números de pacientes nesses subgrupos podem ser uma limitação dessa análise. Nenhuma conclusão de eficácia ou segurança pode ser tirada desses dados.
Pollyea DA, et al. Clin Cancer Res. 2022 Aug 25;CCR-22-1183. doi: 10.1158/1078-0432.CCR-22-1183. Online ahead of print.

Aza=Azacitidina. RC=Remissão Completa.
RCi=RC com Recuperação Hematológica Incompleta. Mut=Mutação. Ven=Venetoclax. wt=Selvagem.

Acompanhamento de Longo Prazo: Sobrevida Global por Resposta DRM

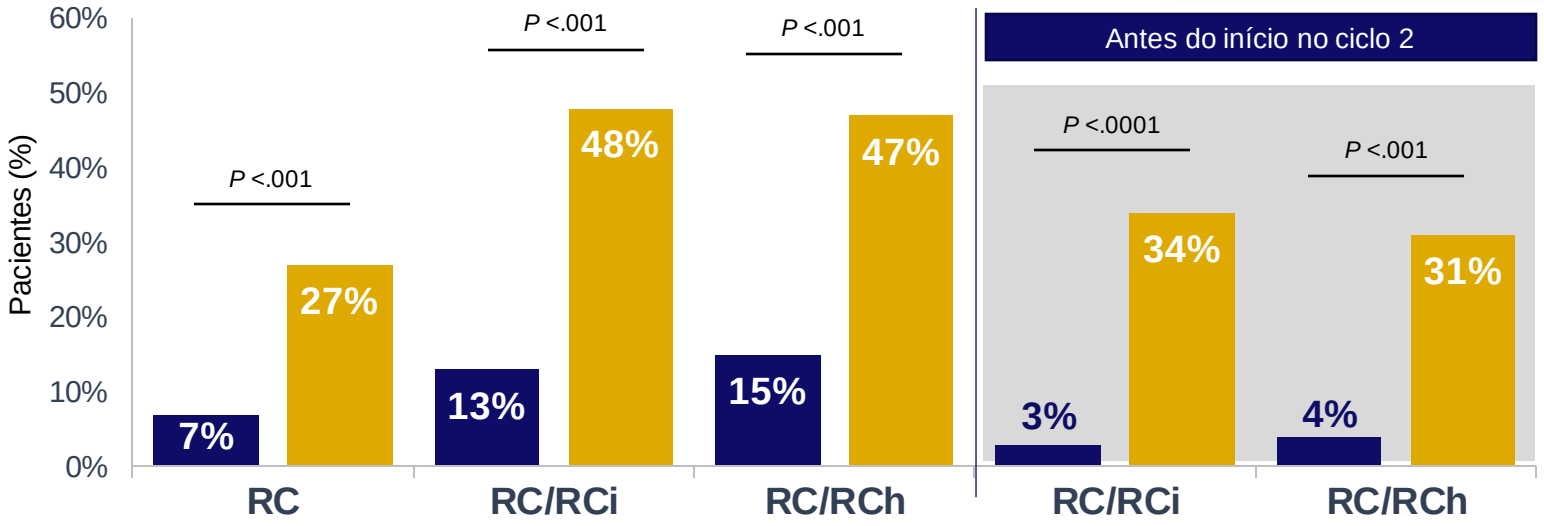


Pacientes em risco																			
<10^{-3} VEN	69	68	67	64	64	61	57	55	50	43	37	34	31	26	22	10	4	1	0
≥10^{-3} VEN	96	91	85	73	63	52	47	41	37	33	31	28	23	17	10	7	2	1	0

*As distribuições foram estimadas para cada braço de tratamento usando a metodologia Kaplan-Meier.
AZA=Azacitidina. IC=Intervalo de Confiança. HR=Razão de Riscos. SG=Sobrevida Global. PBO=Placebo. VEN=Venetoclax.

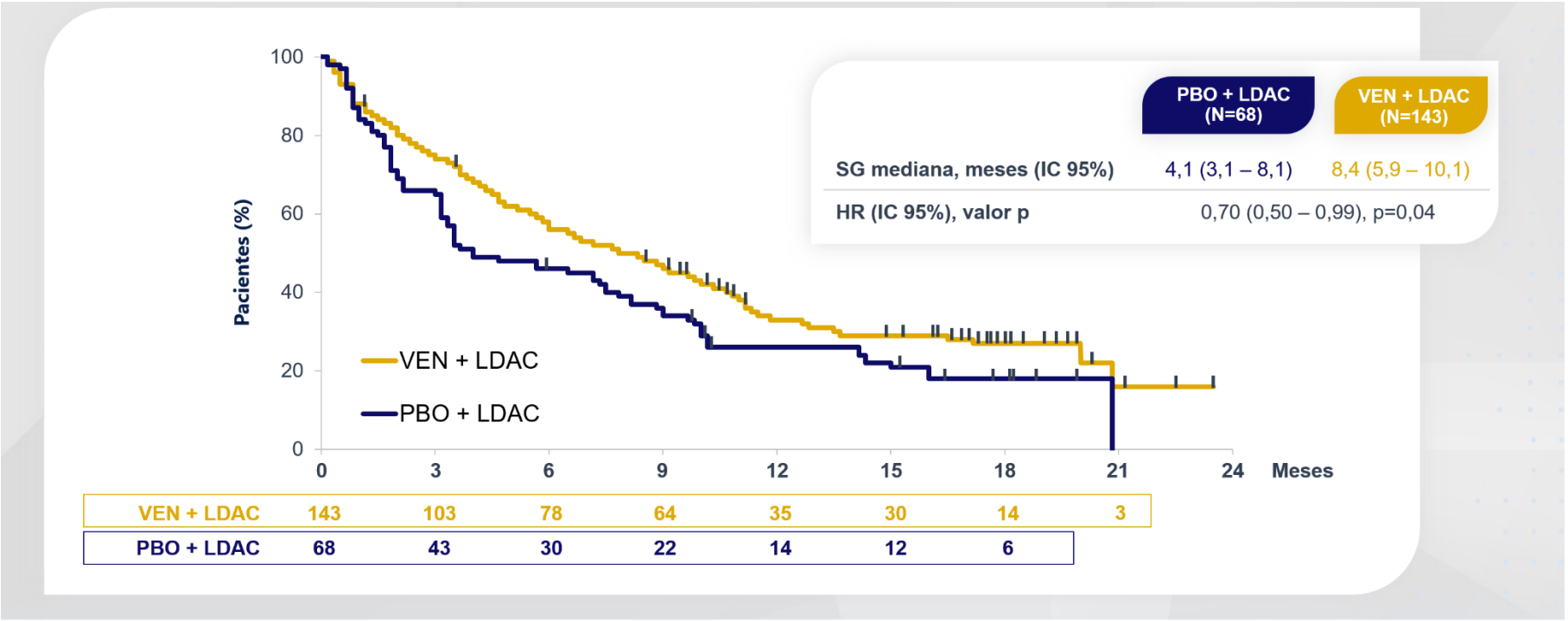
Corte de dados: 1 de dezembro de 2021.
Pratz KW, et al. Oral 219. 64th ASH. December 10-13, 2022. New Orleans, LA.

VIALE-C: Taxas de Resposta



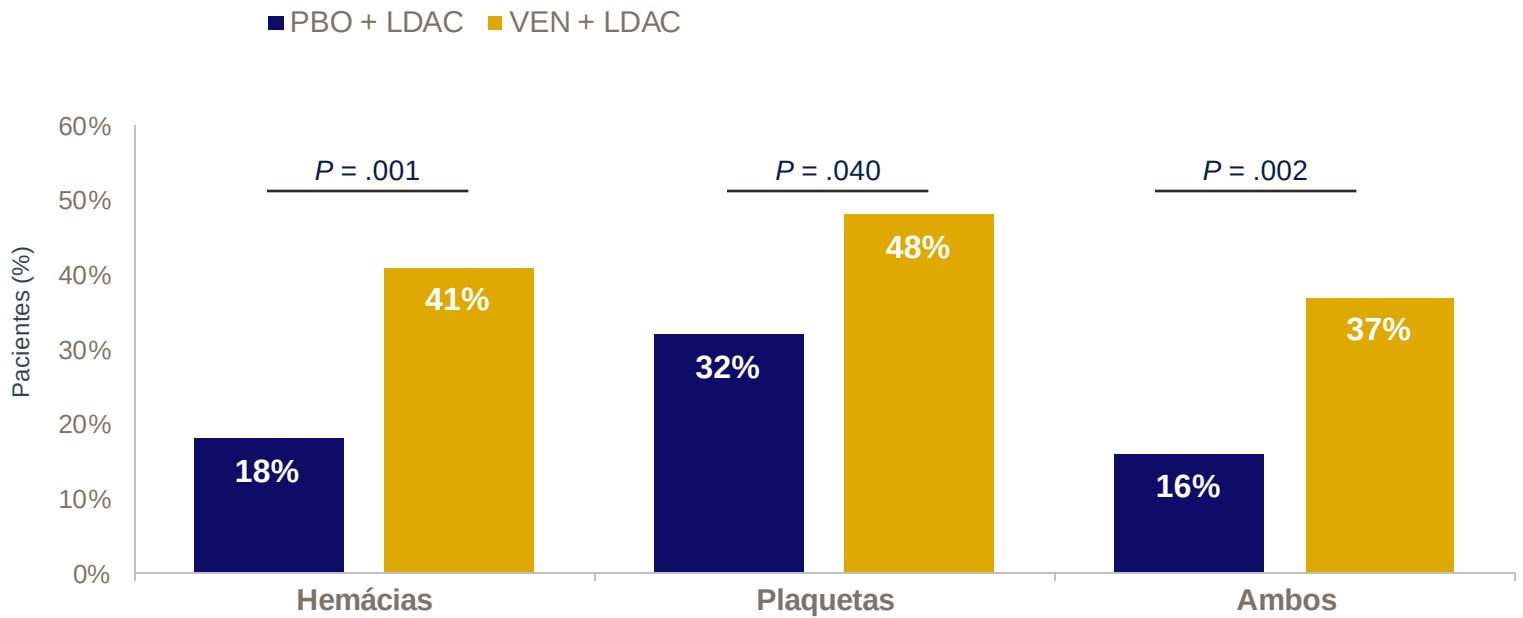
Wei AH et al, Blood 2020 Jun 11;135(24): 2137-2145. doi: 10.1182

VIALE-C: Sobrevida global na Análise Primária Pré-planejada



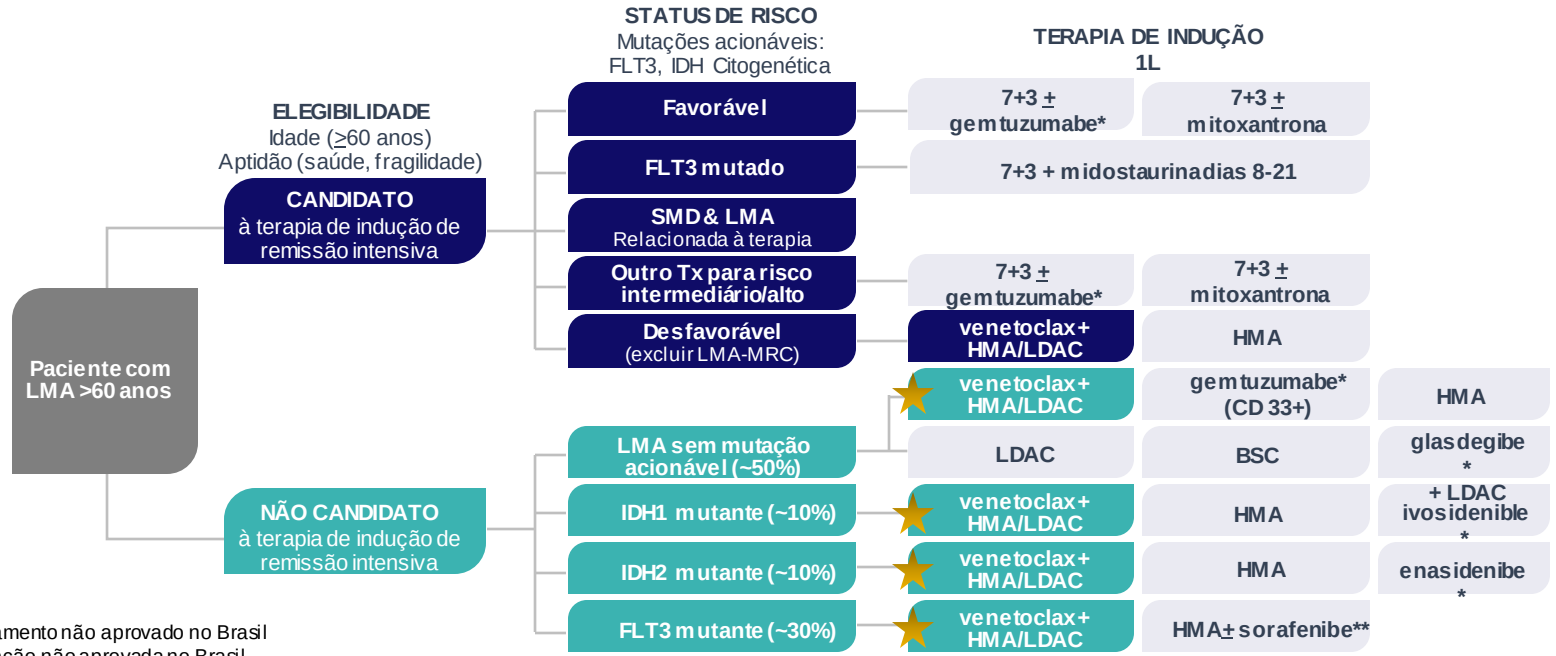
Wei AH et al, Blood 2020 Jun 11;135(24): 2137-2145. doi: 10.1182

VIALE-C: Independência transfusional*



*Definido como ≥56 dias consecutivos sem hemograma ou transfusão de plaquetas entre o primeiro e o último dia de tratamento
Wei AH et al, Blood 2020 Jun 11;135(24): 2137-2145. doi: 10.1182

As Diretrizes da NCCN priorizam as combinações de venetoclax como primeira linha de tratamento para pacientes inelegíveis a QT



*Medicamento não aprovado no Brasil
** Indicação não aprovada no Brasil

★ **Categoria 1 – venclexta (venetoclax) + azacitidina:** baseado em evidências de alto nível, há um consenso uniforme do NCCN que esta **intervenção é apropriada.**

Nota: Com base nas diretrizes da NCCN v3-2020 (dez 2019)
NCCN: National Comprehensive Cancer Network; aHSCT: transplante alogênico de células-tronco hematopoiéticas;

Estratificação de risco – ELN 2022

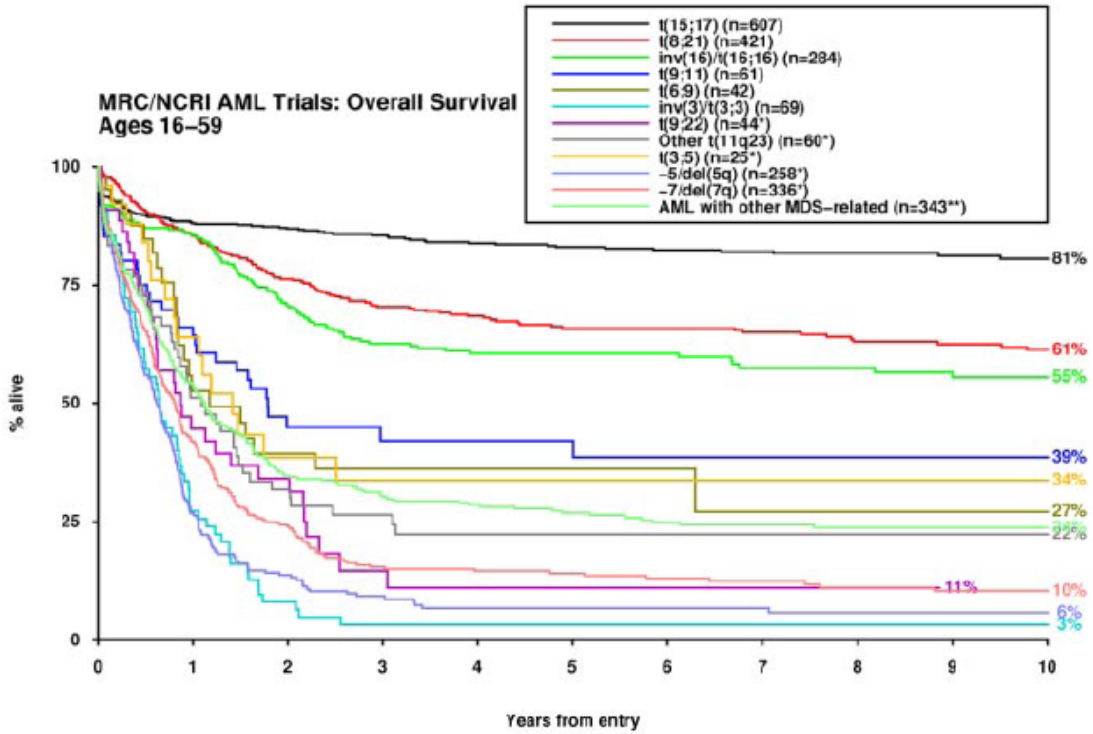
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Risk category†	Genetic abnormality
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]

.†Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.
‡Concurrent KIT and/or FLT3 gene mutation does not alter risk categorization.
§AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.
kOnly in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.
¶The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse risk gene mutations.
#Excluding KMT2A partial tandem duplication (PTD).
**Complex karyotype: $3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
††Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
‡‡For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
aTP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

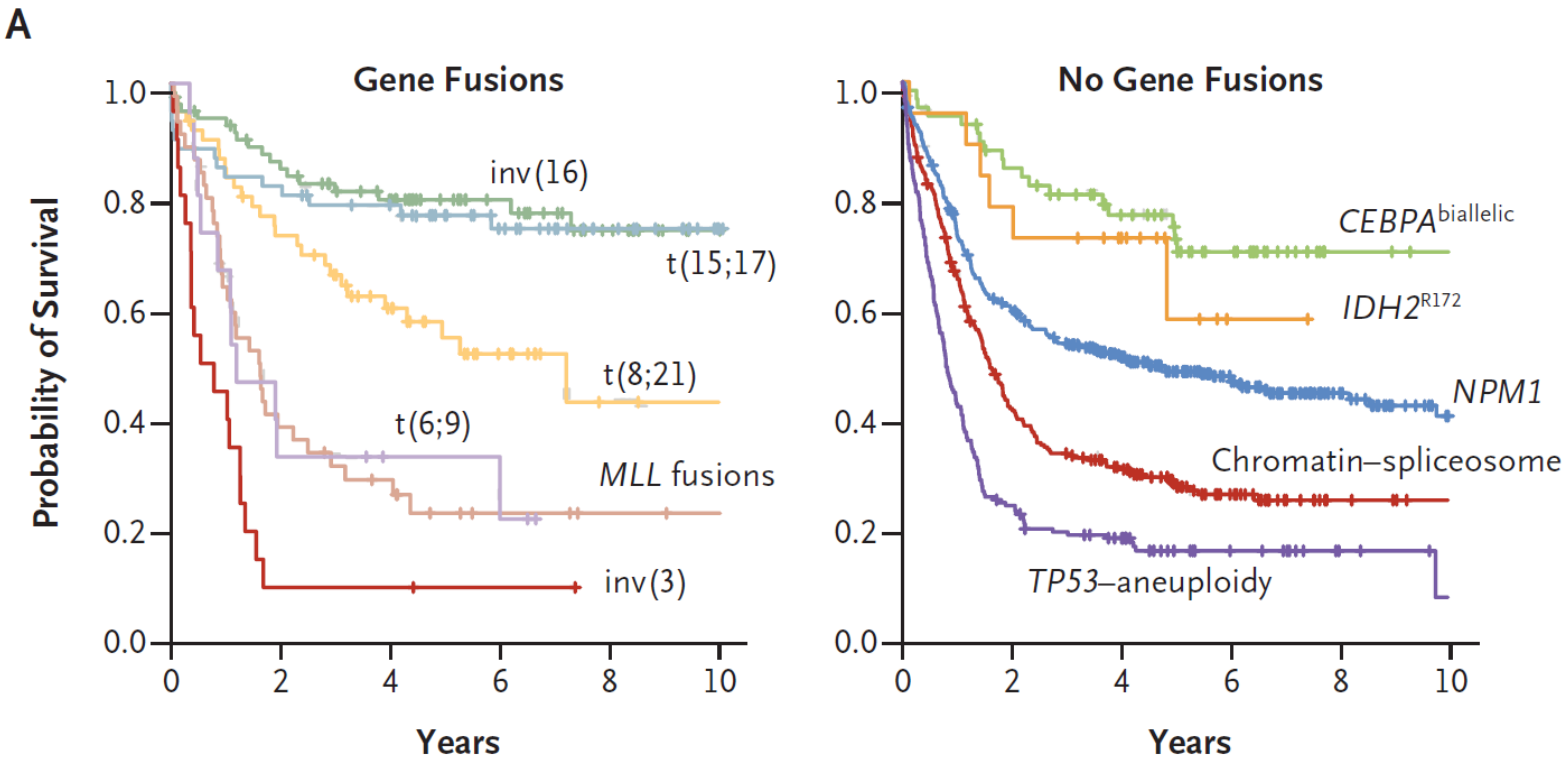
Döhner et a., 2022. Blood

Prognóstico – Importância Citogenética



Grimwade D et al, Blood 2010

Prognostico de LMA por alteração genética



Papaemmanuil E et al, N Engl J Med 2016

High-risk AML

- Highly unmet need
- HSCT may not be the answer – maintenance post-HSCT?
- High-dose decitabine [*N Engl J Med*. 2016;375:2023-2036]
- APR-246 (eprenetapopt) [*J Clin Oncol*. 2021;39:1584-1594]
- Magrolimab (anti-CD47) “do not eat me” signal [*J Clin Oncol*. 2023 Sep 13]

Global Leukemia Academy

Panel discussion

APTITUDE HEALTH®

Interactive discussion

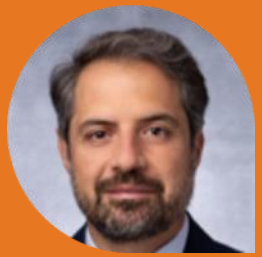
1. How do we address the gaps in donor availability within the region . . . or has the advent of haploidentical transplant made this no longer a concern?
2. What genomic testing should be considered a bare minimum in locations that are less resource-rich than the United States?
3. How do we best deliver transplant and acute leukemia services to those in regional and remote communities?

We encourage our audience to ask questions using the Q&A box.

Global Leukemia Academy

Session close

Elias Jabbour



APTITUDE HEALTH

Question 3 [REPEATED]

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

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

Question 4 [REPEATED]

Which of the following is NOT true for treating ALL?

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

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

C. MRD– CR does not correlate strongly with outcome

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

Question 5 [REPEATED]

Which of the following factors are important in assessing AML patients at diagnosis? Select all that apply.

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

Day 2: Virtual Plenary Sessions

Friday, Oct 20, 2023
5.00 PM – 8.00 PM UTC -5 (Houston time)
7.00 PM – 10.00 PM UTC -3 (Brasilia/Buenos Aires)

Time	Title	Speaker
7.00 PM – 7.10 PM	Welcome to Day 2	Naval Daver
7.10 PM – 7.30 PM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
7.30 PM – 7.50 PM	Current treatment options for relapsed AML in adult and elderly patients	Naval Daver
7.50 PM – 8.20 PM	AML case-based panel discussion • Case AML: young high-risk (10 min) • Case AML: elderly (10 min) – fellow (TBD) • Discussion (10 min) – panelists: all senior faculty	Roberta Demichelis and Sergio Rodriguez Diver All faculty
8.20 PM – 8.30 PM	Break	
8.30 PM – 8.50 PM	Long-term safety considerations for leukemias (focus on ALL)	Josep-Maria Ribera
8.50 PM – 9.10 PM	Current and future role of transplantation in acute leukemias in Latin America	Wellington Silva
9.10 PM – 9.50 PM	Panel discussion: How treatment in first line influences further therapy approaches in ALL and AML • Will CAR T and bispecifics change the treatment landscape? • Role of HSCT – is it still necessary? • What does the future look like? Adoption of therapies and evolving standards of care in LATAM	Elias Jabbour, Naval Daver, and all faculty
9.50 PM – 10.00 PM	Session close	Elias Jabbour

Thank you!

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

THANK YOU!

Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

SEE YOU TOMORROW!

October 19–20, 2023 – Latin America

Meeting sponsors AMGEN astellas

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Please join the next meeting in our regional series

Coming soon online