Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

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

10 –11 September 2023 – Japan and Asia-Pacific Region

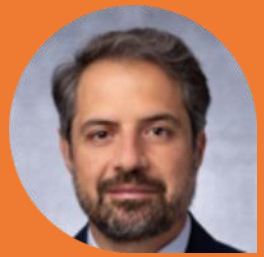
Meeting sponsors AMGEN astellas

APTITUDE HEALTH

Global Leukemia Academy

Welcome and meeting overview

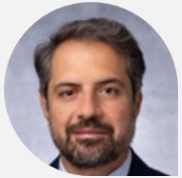
Elias Jabbour



APTITUDE HEALTH

Meet the Faculty

CHAIR



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

CO-CHAIR

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

FACULTY

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

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Boston MA, USA

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

Objectives of the program

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

Day 1: Virtual Plenary Sessions

Time (UTC+8)	Title	Speaker
8.00 AM – 8.10 AM	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
8.10 AM – 8.25 AM	Review of prognostic value of MRD in ALL and AML	Jae Park
8.25 AM – 8.40 AM	Latest achievements and developments in ALL and AML	Elias Jabbour
8.40 AM – 8.55 AM	Genetic characterization and risk stratification of AML	Daniel DeAngelo
8.55 AM – 9.25 AM	ALL case-based panel discussion • Case ALL – Michael Ashby • Case AYA ALL – Koichi Takahashi • Discussion	Elias Jabbour and all faculty
9.25 AM – 9.35 AM	Break	
9.35 AM – 9.50 AM	Therapeutic approaches in high-risk and frail AML patients	Naval Daver
9.50 AM – 10.05 AM	Current approach to maintenance strategies in ALL and AML	Jae Park
10.05 AM – 10.20 AM	Long-term safety considerations in AML	Shaun Fleming
10.20 AM – 10.50 AM	Panel discussion: Open questions in ALL and AML – Dr Fleming and Dr Yuda will discuss regionally specific topics	Naval Daver and all faculty
10.50 AM – 11.00 AM	Session close	Elias Jabbour and Naval Daver

Day 2: Virtual Plenary Sessions

Time (UTC+8)	Title	Speaker
8.00 AM – 8.10 AM	Welcome to Day 2	Elias Jabbour
8.10 AM – 8.30 AM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
8.30 AM – 8.50 AM	Current treatment options for relapsed AML in adult and elderly patients	Junichiro Yuda
8.50 AM – 9.20 AM	Case-based panel discussion • Case AML – Rithin Nedumannil • Case ALL, elderly – Huai-Hsuan Huang • Discussion	Naval Daver and all faculty
9.20 AM – 9.30 AM	Break	
9.30 AM – 9.50 AM	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	Daniel DeAngelo
9.50 AM – 10.20 AM	Current and future role of transplantation in acute leukemias • Jae Park (in general) • Shaun Fleming (in the JAPAC region) • Discussion	Jae Park/Shaun Fleming
10.20 AM – 10.50 AM	Panel discussion: How treatment in first line influences further approaches in ALL and AML • Will CAR T and bispecifics change the landscape? • Role of HSCT – is it still confirmed? • What does the future look like?	Elias Jabbour and all faculty
10.50 AM – 11.00 AM	Session close	Elias Jabbour and Naval Daver

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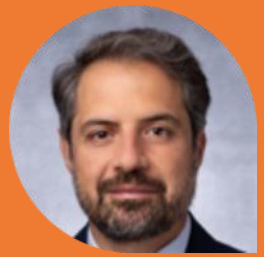
Introduction to the voting system

Elias Jabbour



APTITUDE HEALTH

Question 1

In which country do you currently practice?

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

Question 2

Which leukemias do you primarily treat?

A. AML

B. ALL

C. Both

Question 3

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

A. After induction/consolidation

B. Prior to allogeneic hematopoietic cell transplant

C. After transplant

D. All of the above

Question 4

Which of the following is NOT true for treating ALL?

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

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

C. MRD– CR does not correlate strongly with outcome

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

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Review of prognostic value of MRD in ALL and AML

Jae Park

APTITUDE HEALTH

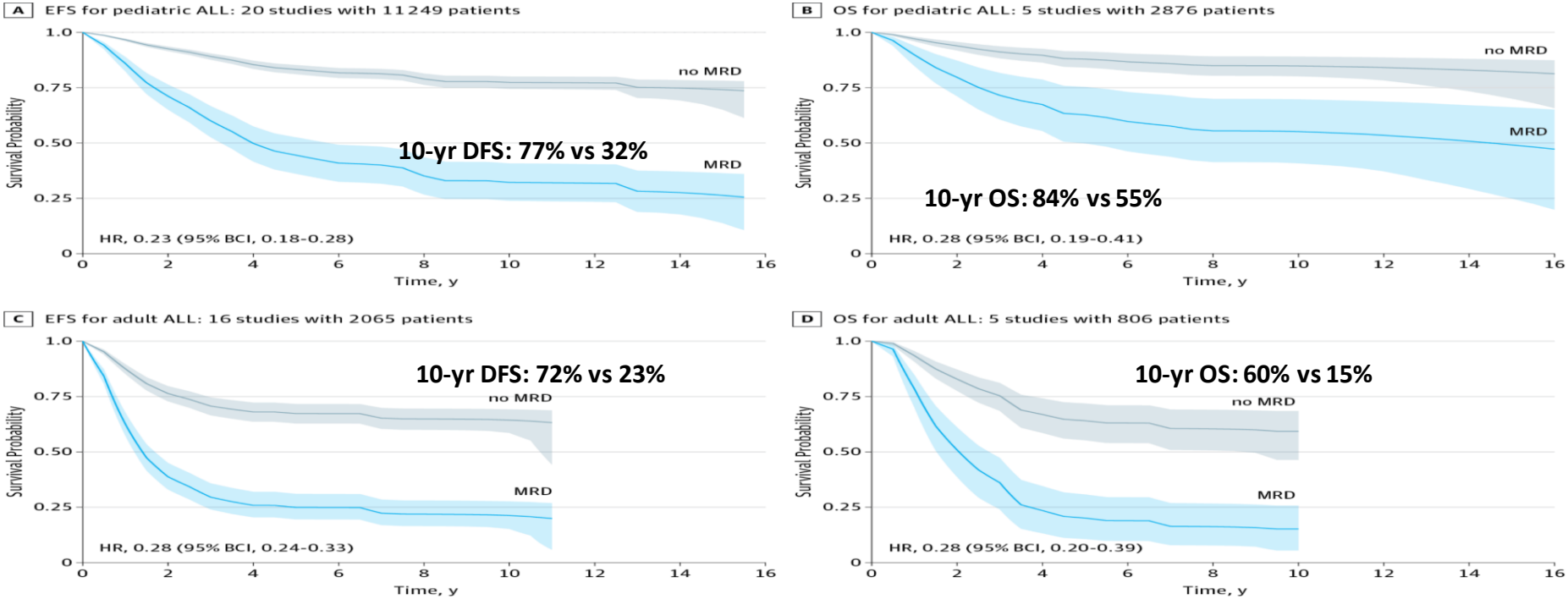
Measurable/Minimal Residual Disease (MRD) in ALL

- The single most predictive marker for outcome in childhood ALL
  - Identifies patients who will have an unfavorable outcome
  - Identifies patients who may benefit from more-intensive/alternative therapies
- Defined as the detection of at least 1 leukemia cell in 10,000 normal cells
  - 0.01% (10^{-4})
  - Used to evaluate post-induction therapeutic response
- Pediatric groups for ALL have been using MRD for risk stratification and therapeutic decision-making for years
  - MRD assessments are incorporated into treatment algorithms

Van Dongen JJ, et al. *Lancet*. 1998;352:1731-1738; Borowitz MJ, et al. *Blood*. 2008;111:5477-5485.

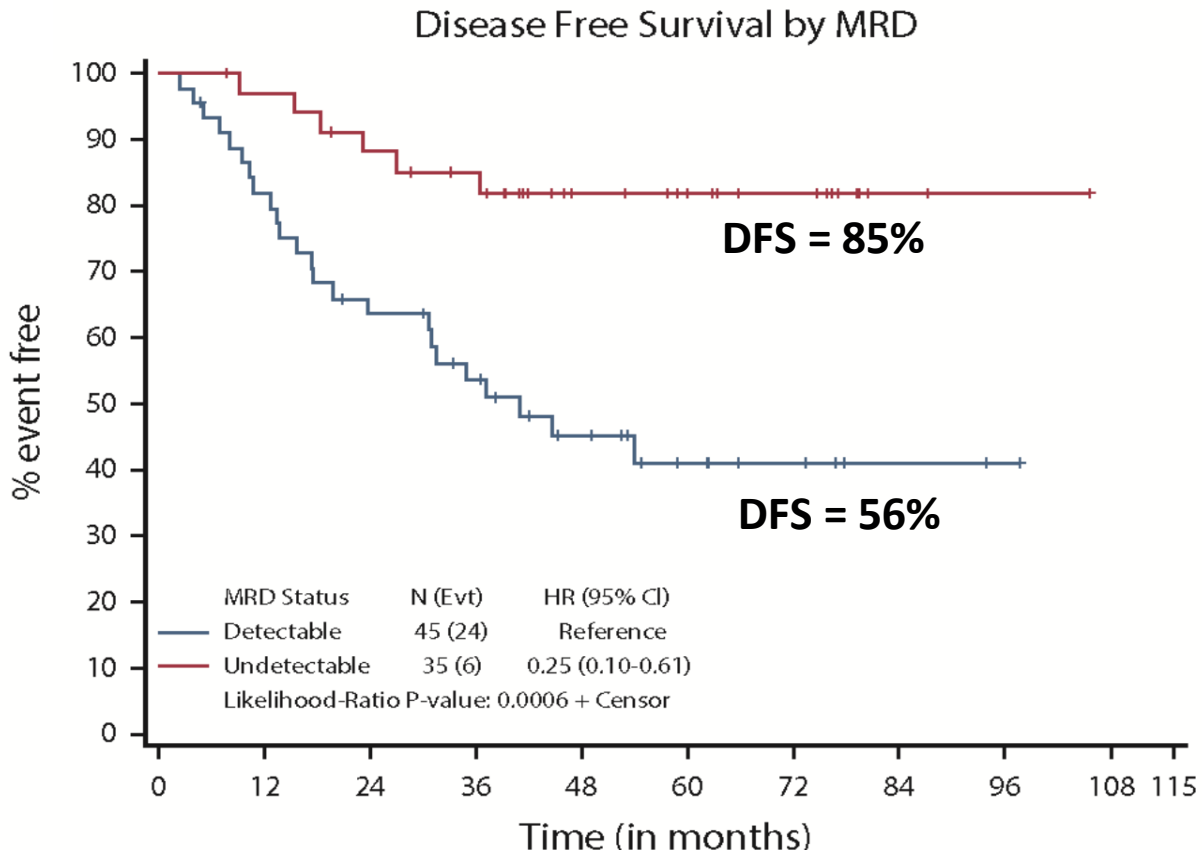
Meta-Analysis Evaluating MRD in ALL

- Meta-analysis of 39 studies (pediatric and adult), 13,637 patients with ALL
- Prognostic significance of MRD clearance was demonstrated for all therapies, MRD method (PCR vs Flow), timing, and MRD cutpoints



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

CALGB 10403 (AYA): Outcome by MRD Status



- Of patients in CR1 at EOI, only 43% had undetectable MRD

Stock W, et al. *Blood.* 2019;133:1548-1599.

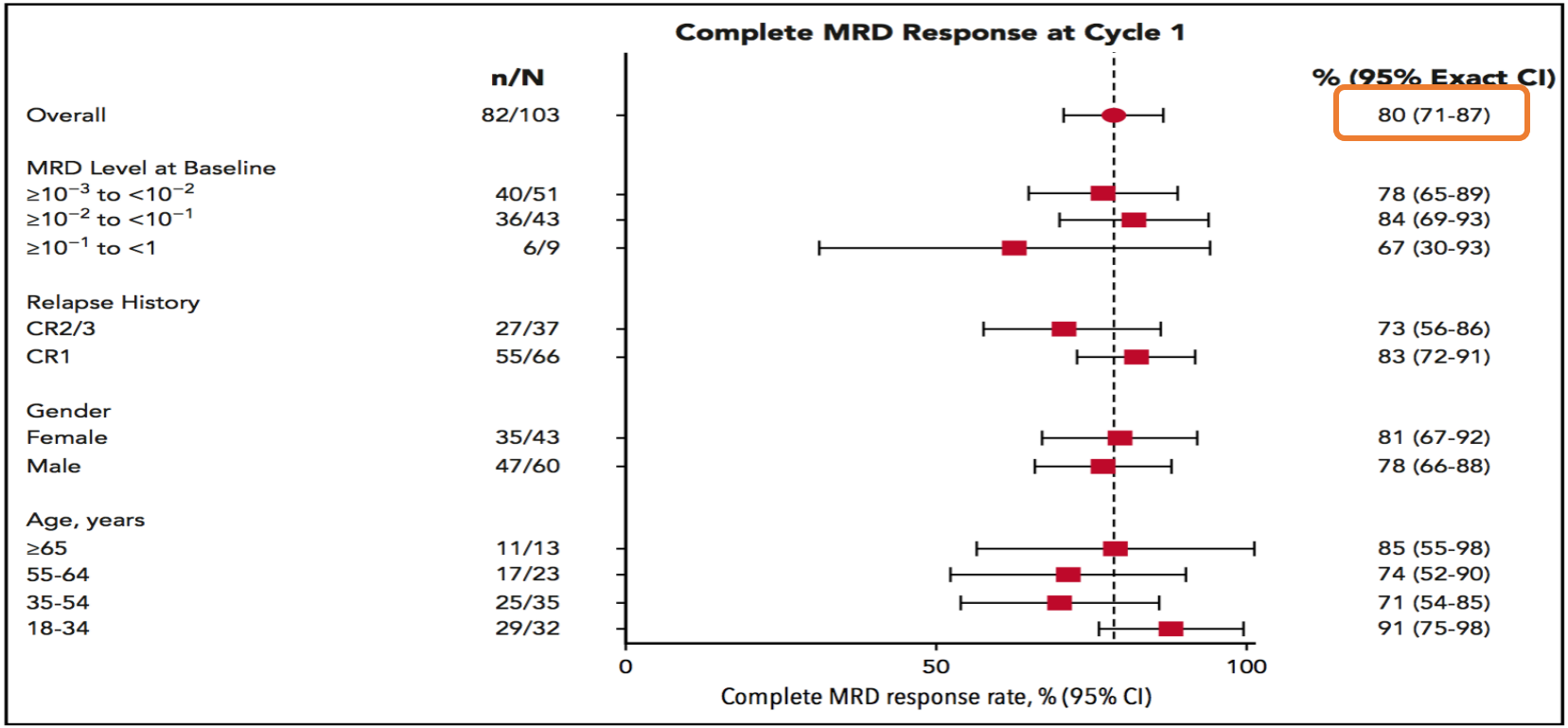
Blinatumomab in MRD+ B-ALL

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

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

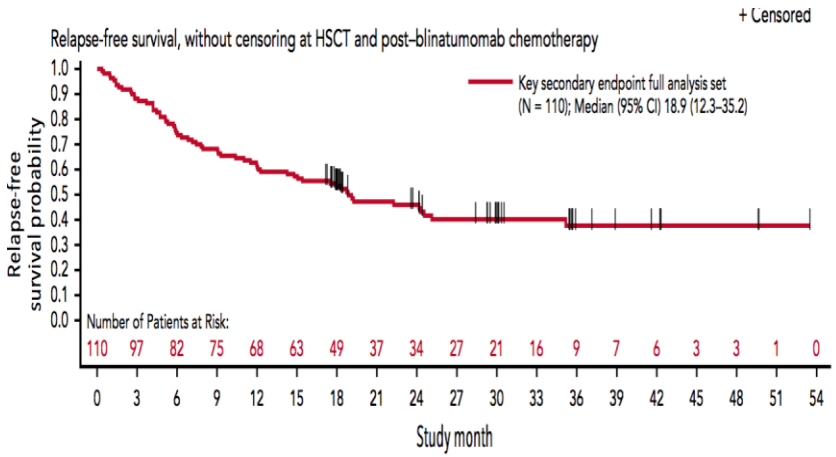
Gökbuget N, et al. *Blood.* 2018;131:1522-1531.

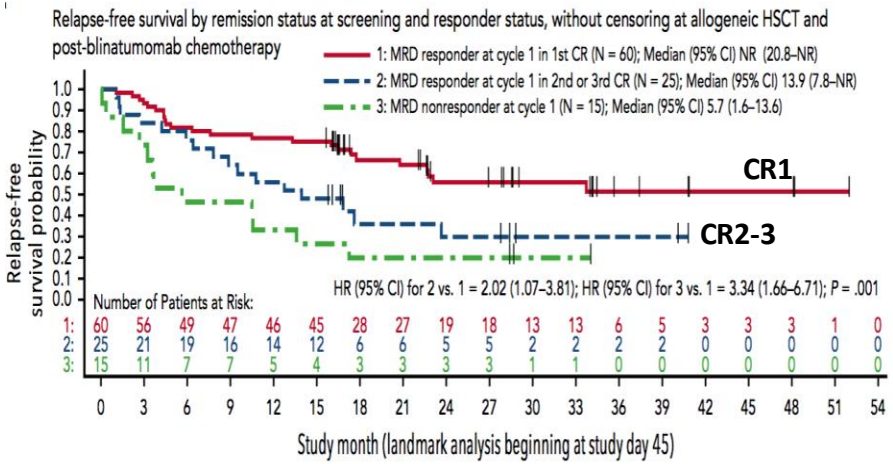
CR Rates by Subgroups in MRD+ B-ALL



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

RFS of MRD+ ALL Patients After Blinatumomab





70% of patients proceed to allo-HSCT

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

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

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

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

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

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

Current Challenges With MRD

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

Comparison of MRD Assays

MRD Method	Sensitivity	Advantages	Disadvantages
Multiparameter flow cytometry (FCM)	10^{-4} (0.01%)	• Fast • Cost effective • Widely available platform • Clinically proven platform	• Subjective interpretation • Immunophenotype may change during treatment • Inadequate standardization • Immunotherapy treatment can complicate interpretation
RQ-PCR for IgH/TCR gene rearrangements	10^{-4} to 10^{-5} (0.01% to 0.001%)	• Well standardized • More sensitive than FCM	• Technically labor intensive • Requires technical expertise • Expensive
RQ-PCR for gene fusions	10^{-4} to 10^{-5} (0.01% to 0.001%)	• More sensitive than FCM • Technically simpler	• Need for baseline specimen • Limited standardization • Not all ALL cases have a gene rearrangement – immature T-ALL
NGS	10^{-6} (0.0001%)	• Very sensitive • Relatively fast	• Not standardized yet • Requires bioinformatics • Limited clinical validation • Expensive

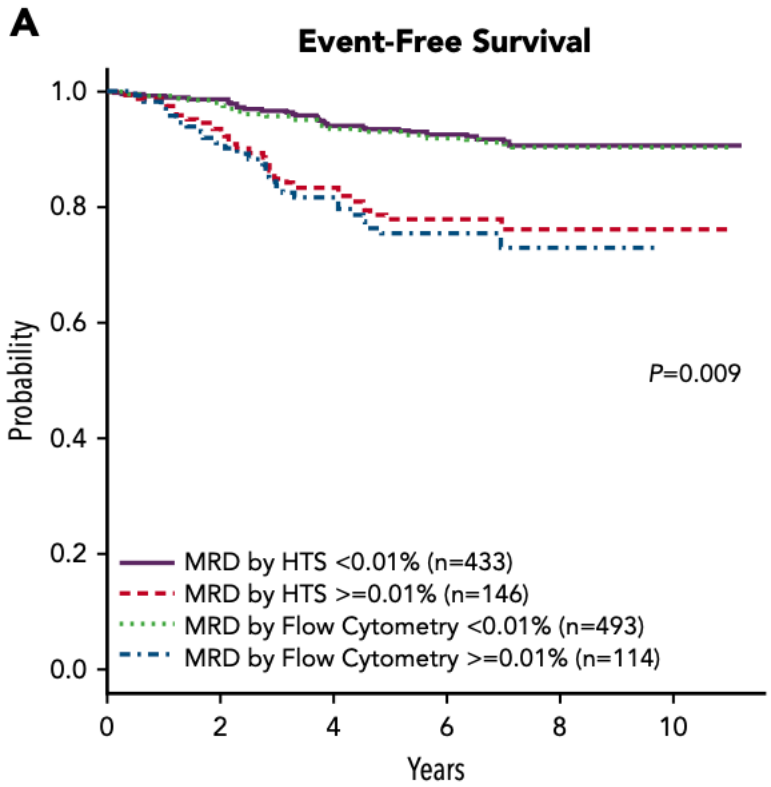
Chen X, Wood BL. *Blood Rev*. 2017;31:63-75; Short NJ, Jabbour E. *Curr Oncol Rep.* 2017;19:6.

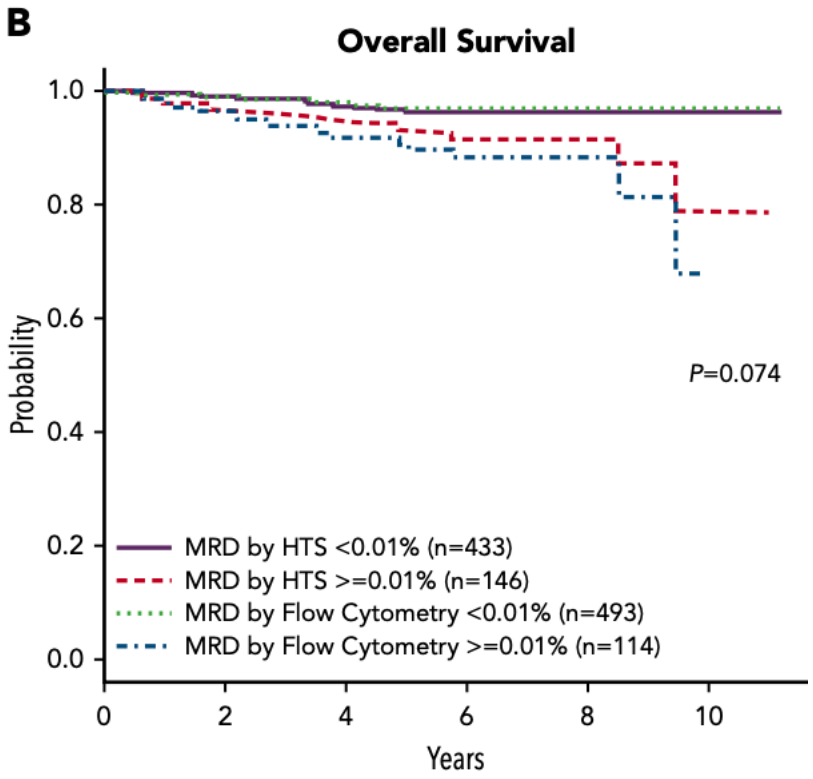
Children's Oncology Group
Comparison of MRD by FCM and NGS

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

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

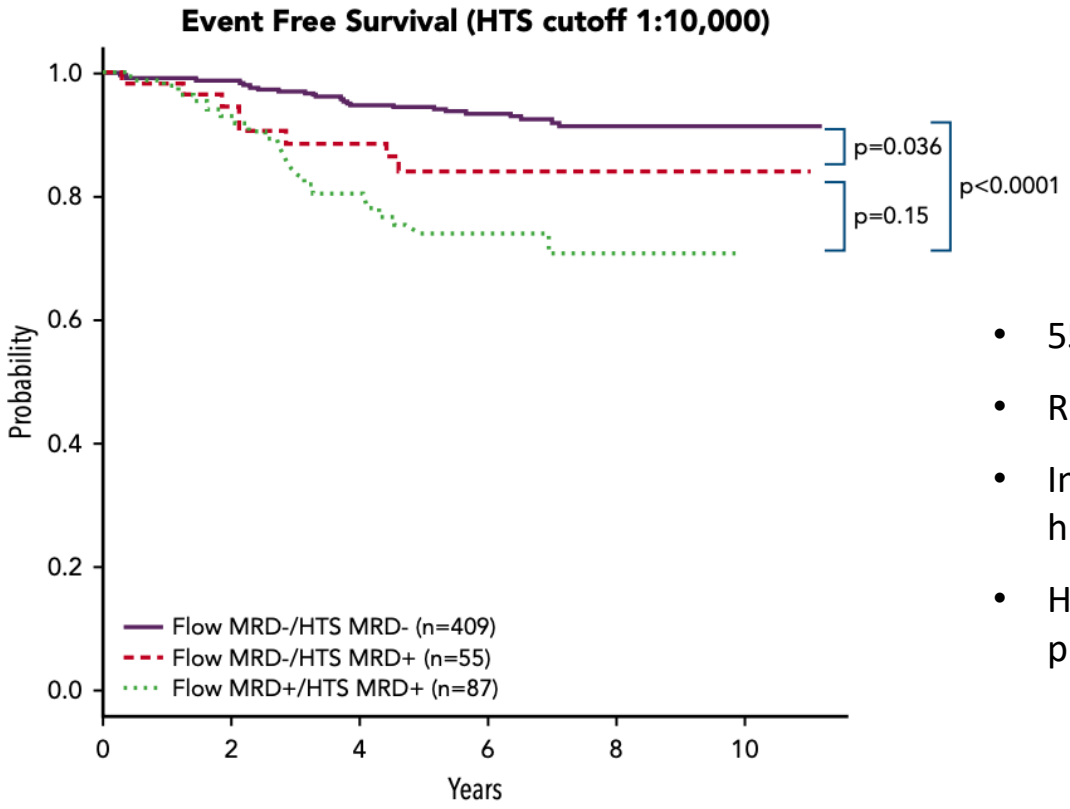
Strong Correlation Between MRD by HTS or FCM (0.01%)





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

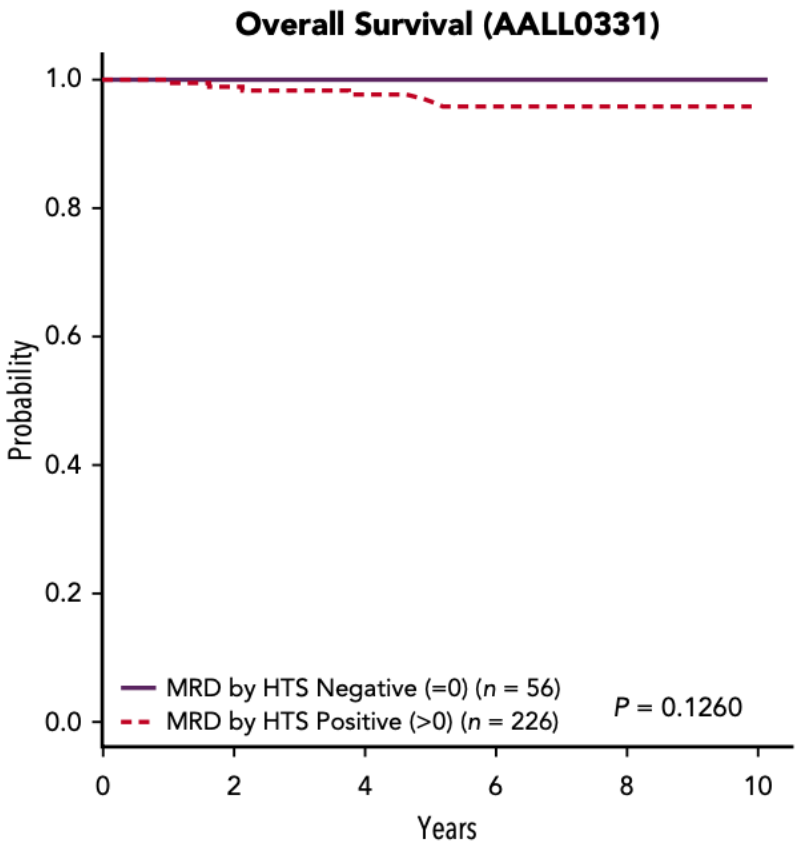
Discordant MRD by HTS or FCM Has Intermediate Prognosis



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

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

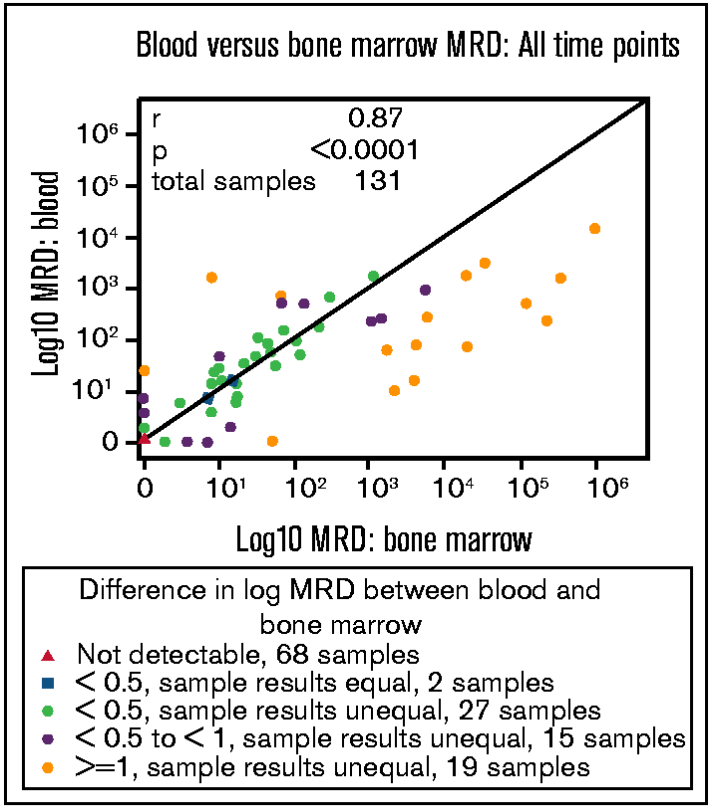
HTS Can Identify Patients With Excellent Outcomes



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

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

Concordance of BM and PB MRD Assessment



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

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

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

Conclusions

- MRD monitoring throughout therapy is needed *and* critical to guide prognosis and risk-directed treatments
- MRD monitoring should include early assessment of response to therapy (EOI) and post-treatment monitoring for early relapse detection and to guide therapeutic intervention prior to overt relapse, ie, continued assessment vs 1-time assessment
- NGS/HTS is a robust clinical platform for MRD determination
- Possible strategy for monitoring may include different MRD platforms at different time points during therapy in ALL
  - PB MRD monitoring by NGS may substitute for post-treatment monitoring (more suitable for later time points at present)

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Q&A

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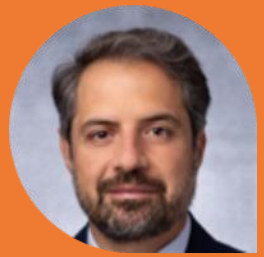
Latest achievements and developments in ALL and AML

Elias Jabbour



APTITUDE HEALTH

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

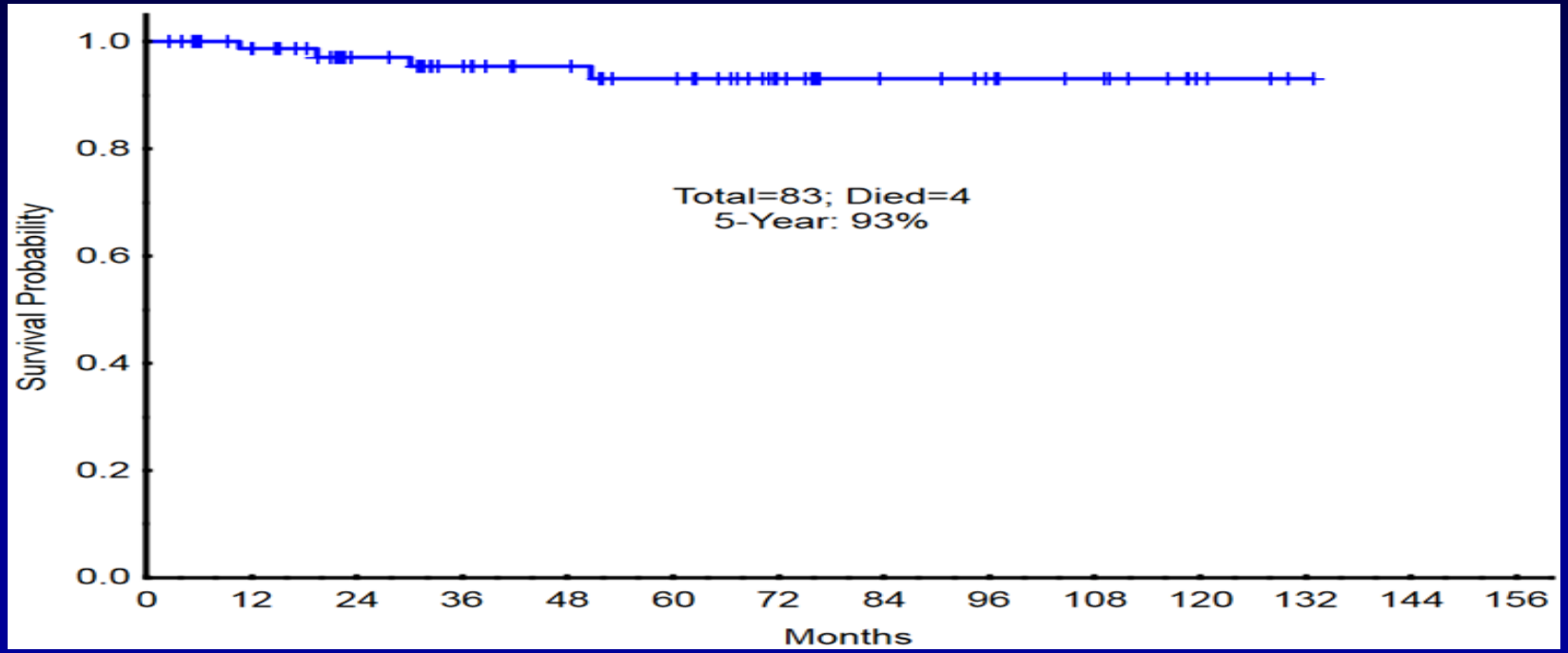
Disease	Therapies	% cure/10-yr survival
Hairy cell leukemia	CDA + rituximab	90
APL	ATRA + arsenic	80–90
CBF AML	FLAG-GO/IDA	80–90
AML – younger	FLAG-IDA-VEN and CLIA-VEN + FLT3i/IDHi; MoAbs	60+
AML – older	Triple-nucleoside + venetoclax low intensity Rx, FLT3i/IDHi, MoAbs,	20 → 50+?
ALL	ChemoRx + CD19/CD22/CD20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



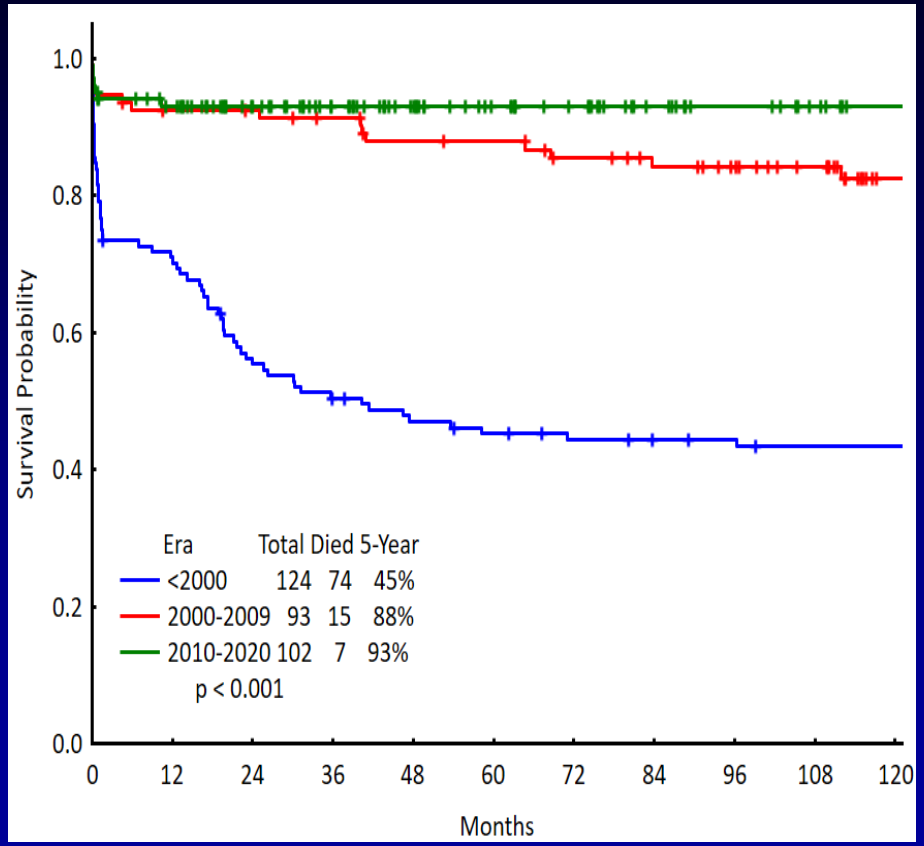
Chihara. BJH. March 2016.

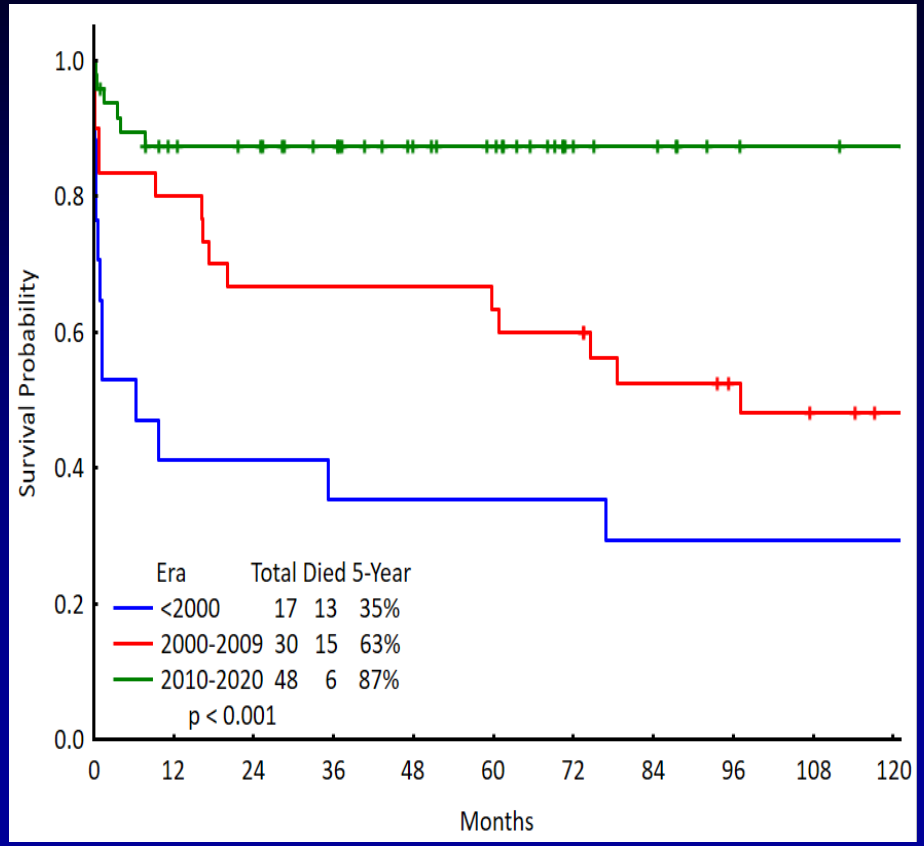
ATRA + As_2O_3 Without Chemotherapy in APL: MD Anderson Experience

- **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.

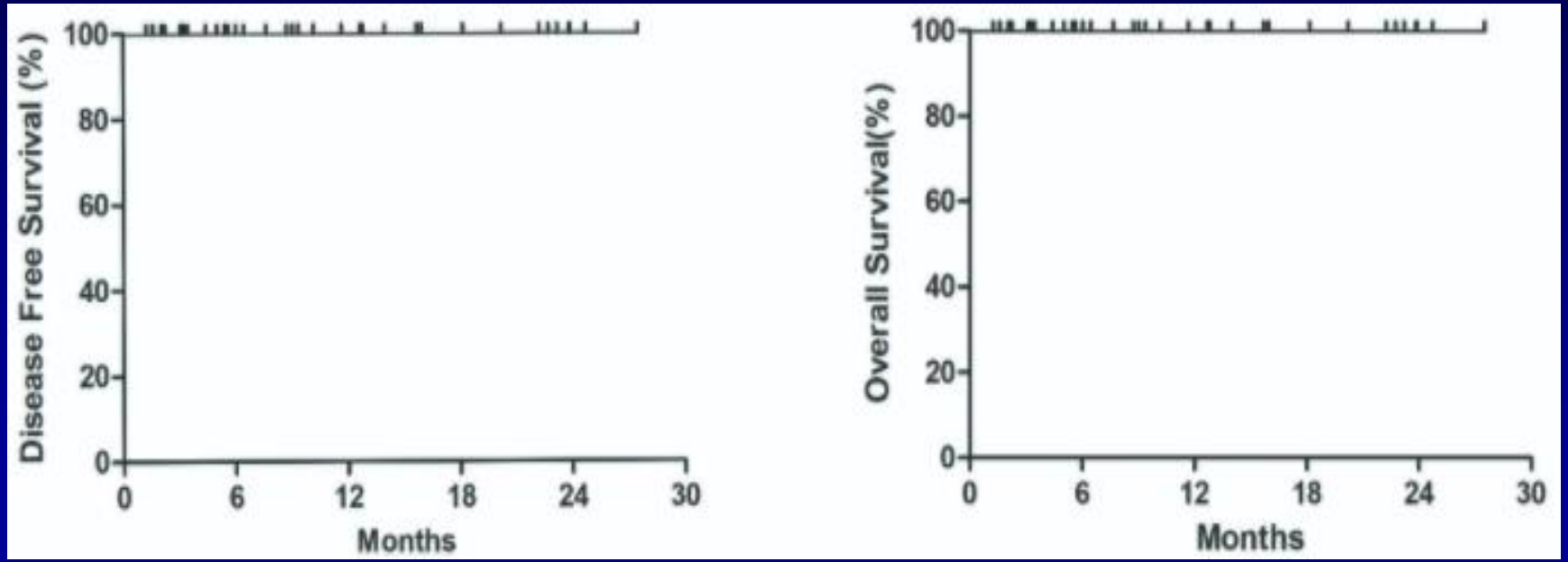
MDACC: FLAG-GO in CBF-AML

- 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.

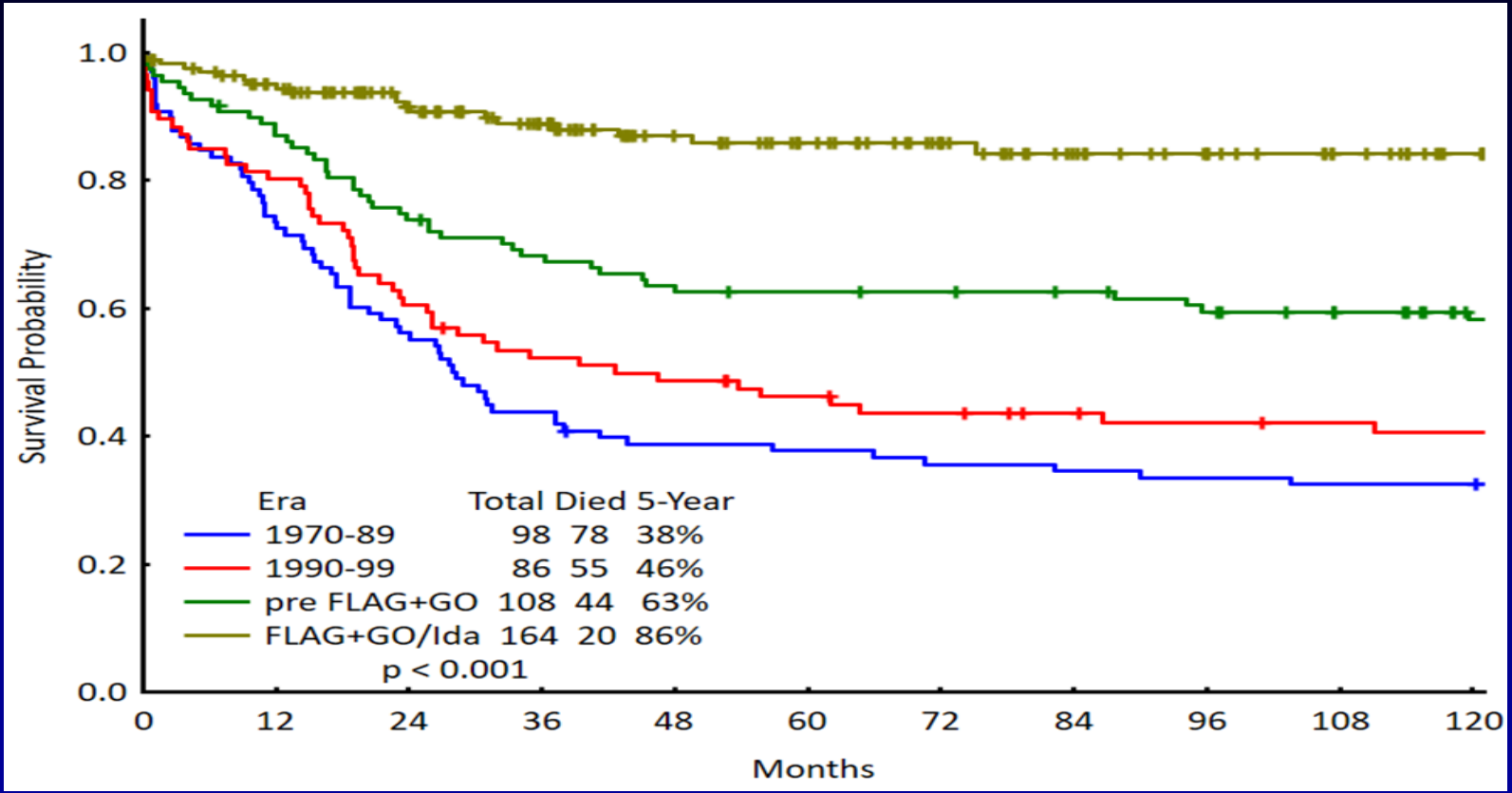
ATRA + Realgar Indigo (oral arsenic) in APL

- 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

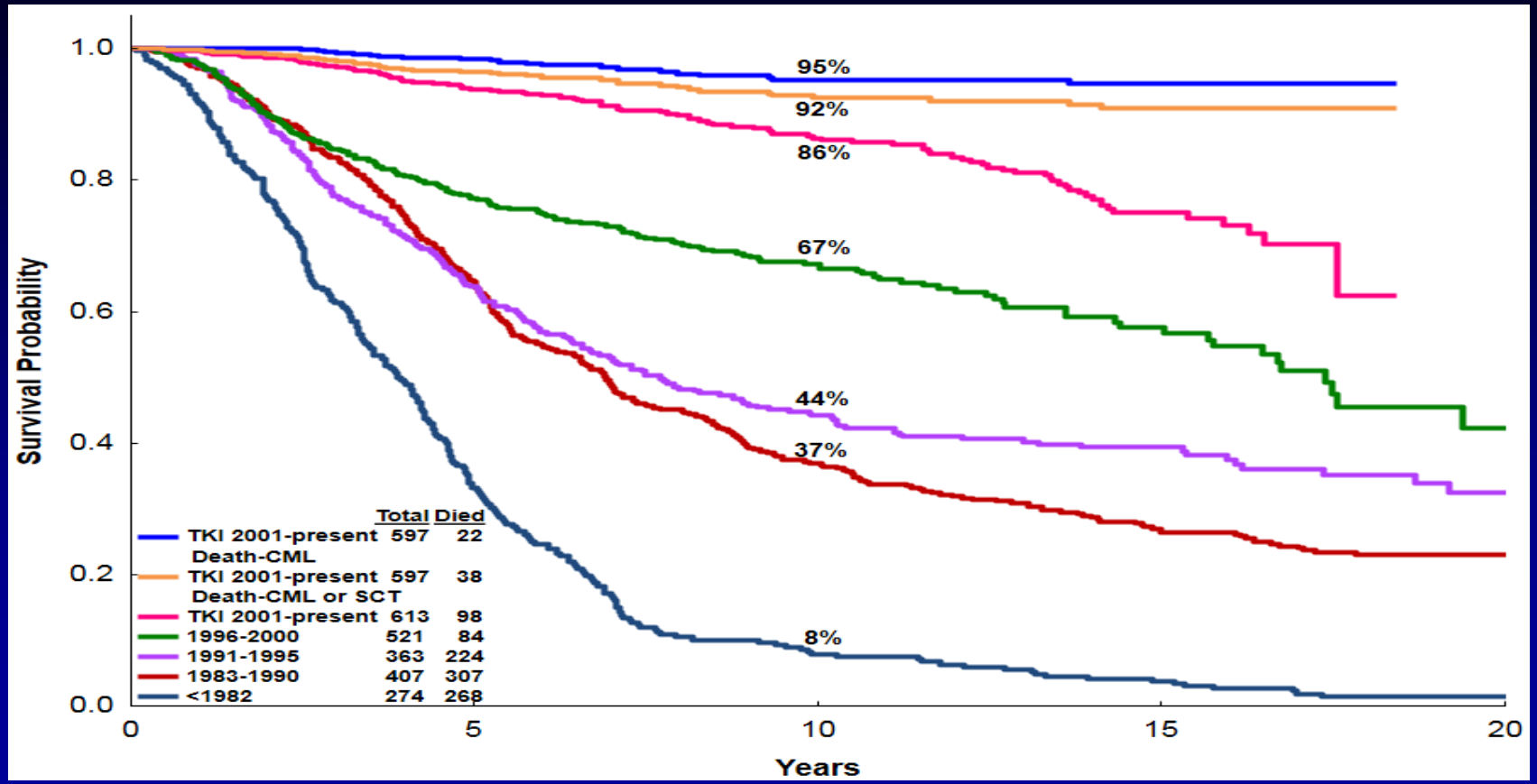


Courtesy of Dr Kantarjian.

Therapy of CML in 2023

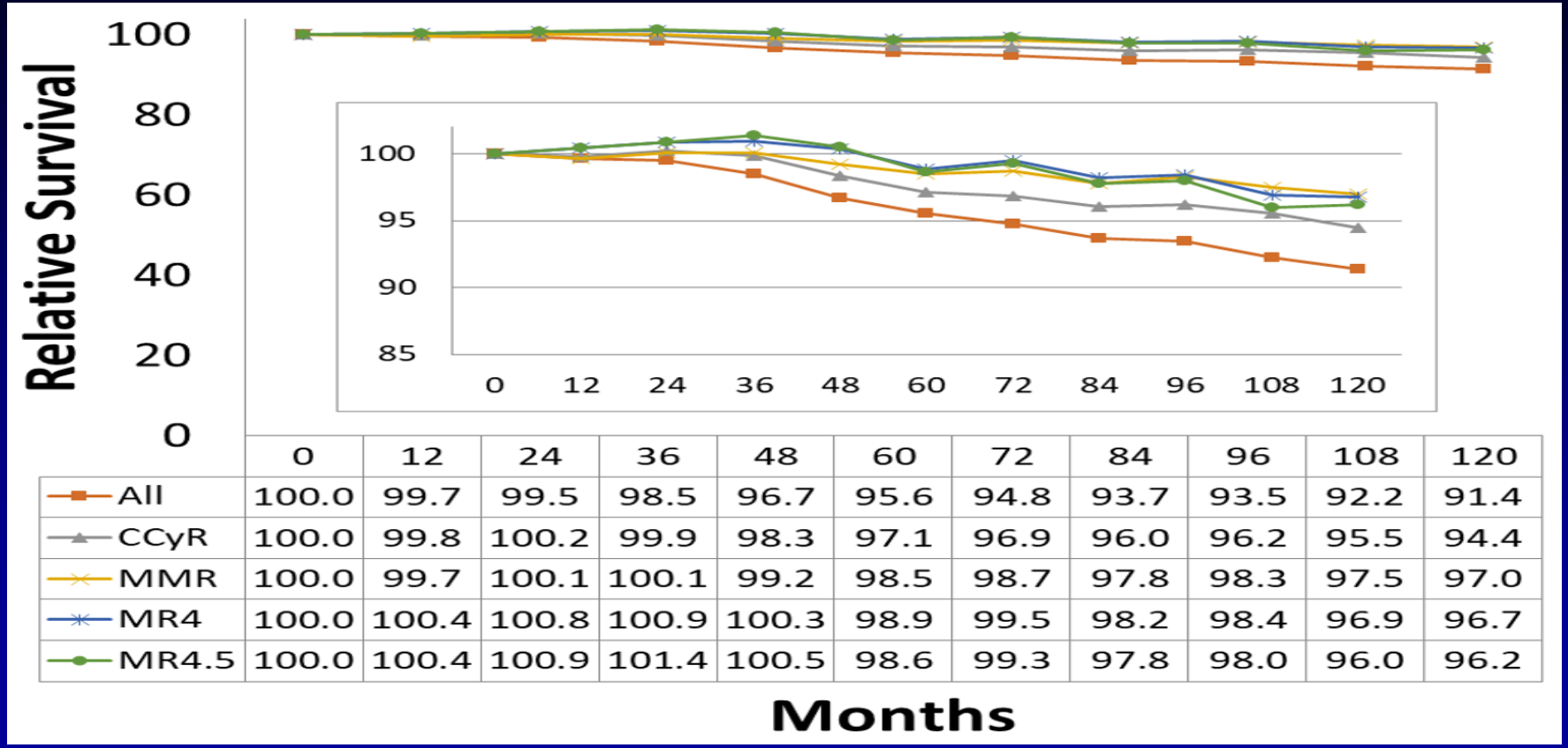
- Frontline
  - Imatinib 400 mg daily
  - Dasatinib 100 mg daily (50 mg at MD Anderson)
  - Nilotinib 300 mg BID
  - Bosutinib 400 mg daily
- Second/third line
  - Nilotinib, dasatinib, bosutinib, ponatinib, asciminib, omacetaxine
  - Allogeneic SCT
- Other
  - Decitabine, peg IFN, omacetaxine (only 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



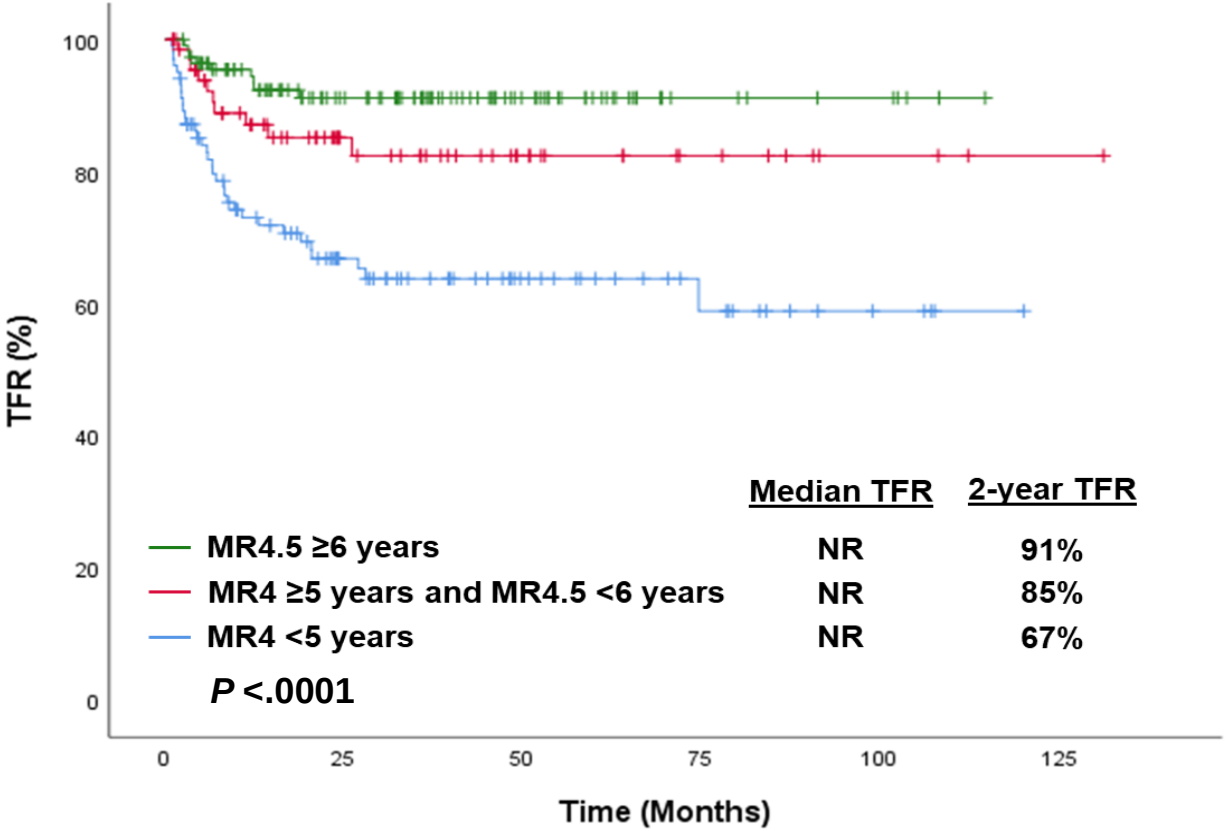
	0	12	24	36	48	60	72	84	96	108	120
All	100.0	99.7	99.5	98.5	96.7	95.6	94.8	93.7	93.5	92.2	91.4
CCyR	100.0	99.8	100.2	99.9	98.3	97.1	96.9	96.0	96.2	95.5	94.4
MMR	100.0	99.7	100.1	100.1	99.2	98.5	98.7	97.8	98.3	97.5	97.0
MR4	100.0	100.4	100.8	100.9	100.3	98.9	99.5	98.2	98.4	96.9	96.7
MR4.5	100.0	100.4	100.9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



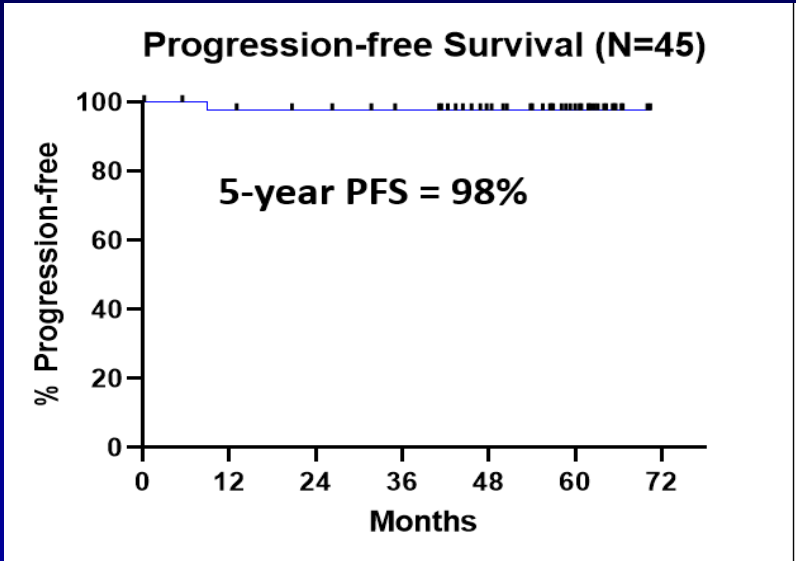
Haddad. *Blood*. 2021;138:abstract 1480.

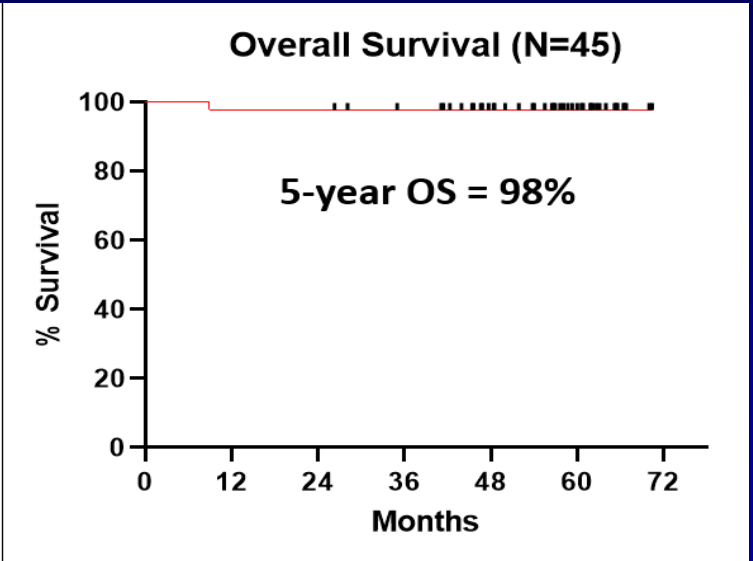
Frontline CML Therapy in 2023+

- 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

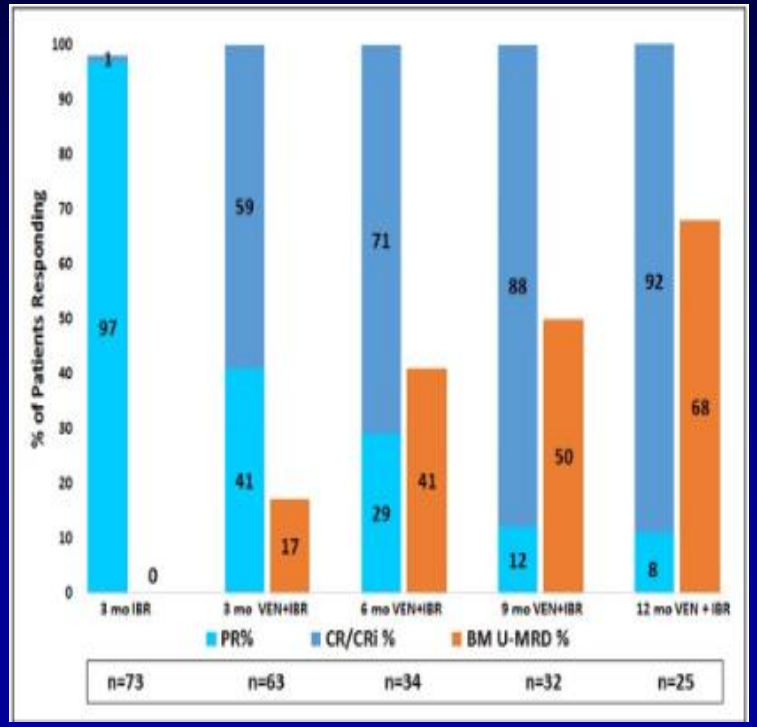
Cure of CLL – Couplets vs Triplets

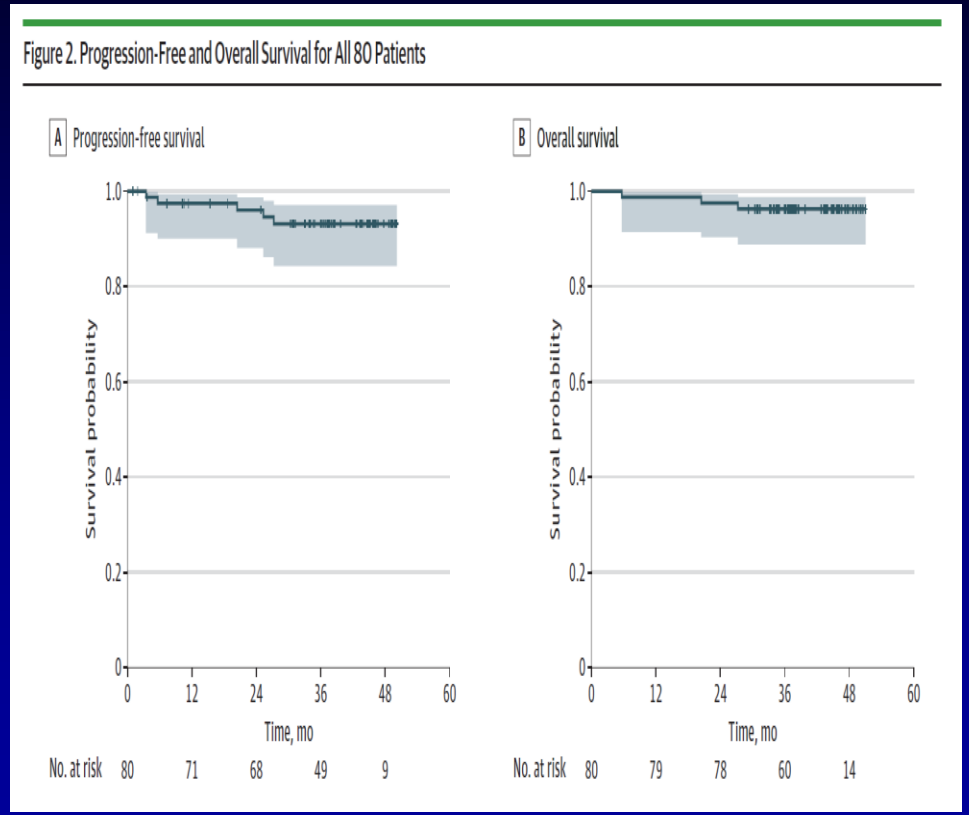
- Ibrutinib-venetoclax finite Rx duration = cure
- Questions: duration (2 vs more years); couplets vs triplets

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. *JAM A 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

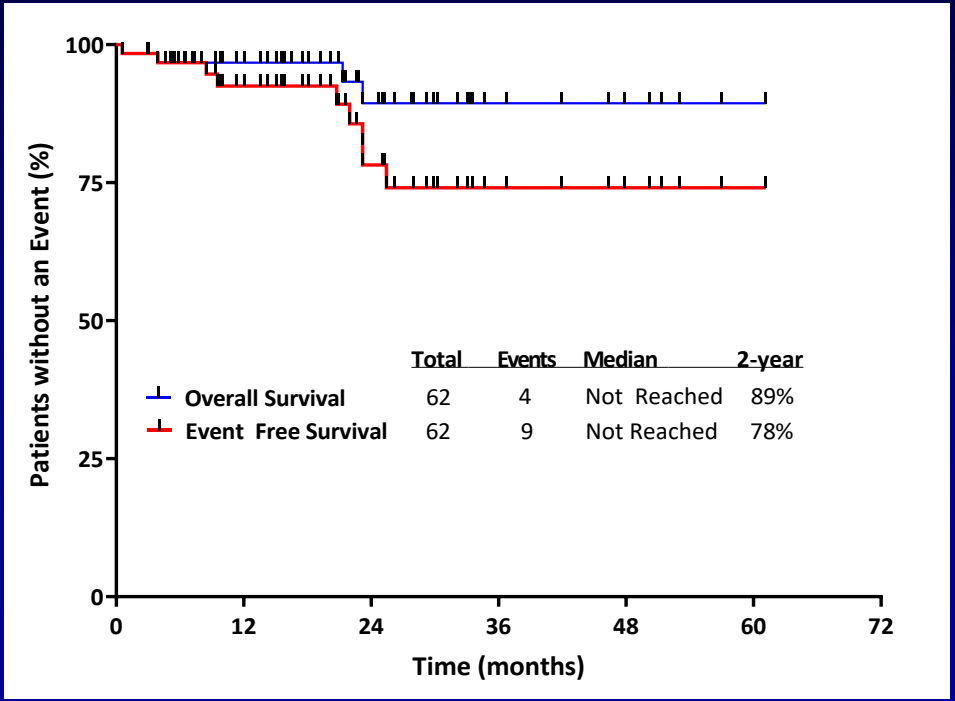
Reasons for Recent Success in Adult ALL

- 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

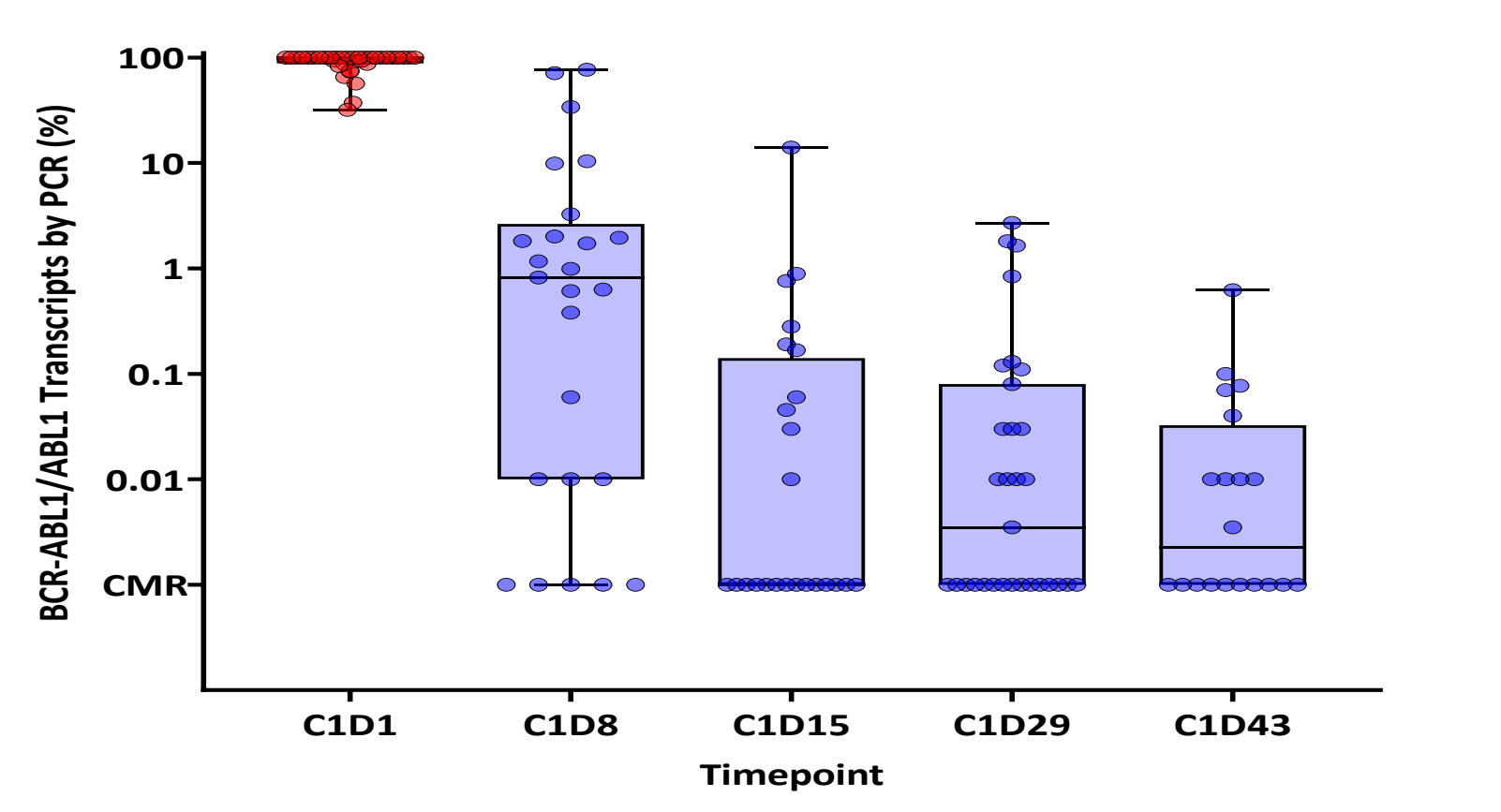
- 62 pts Rx with simultaneous ponatinib 30–15 mg/D and blinatumomab ×5 courses. 12–15 ITs
- Only 1 pt had SCT(2%)
- Median F/U 19 months. 2-yr EFS 78%, OS 89%
- 6 relapses (all p190): 3 CNS, 1 CRLF2+ (Ph–), 2 systemic

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



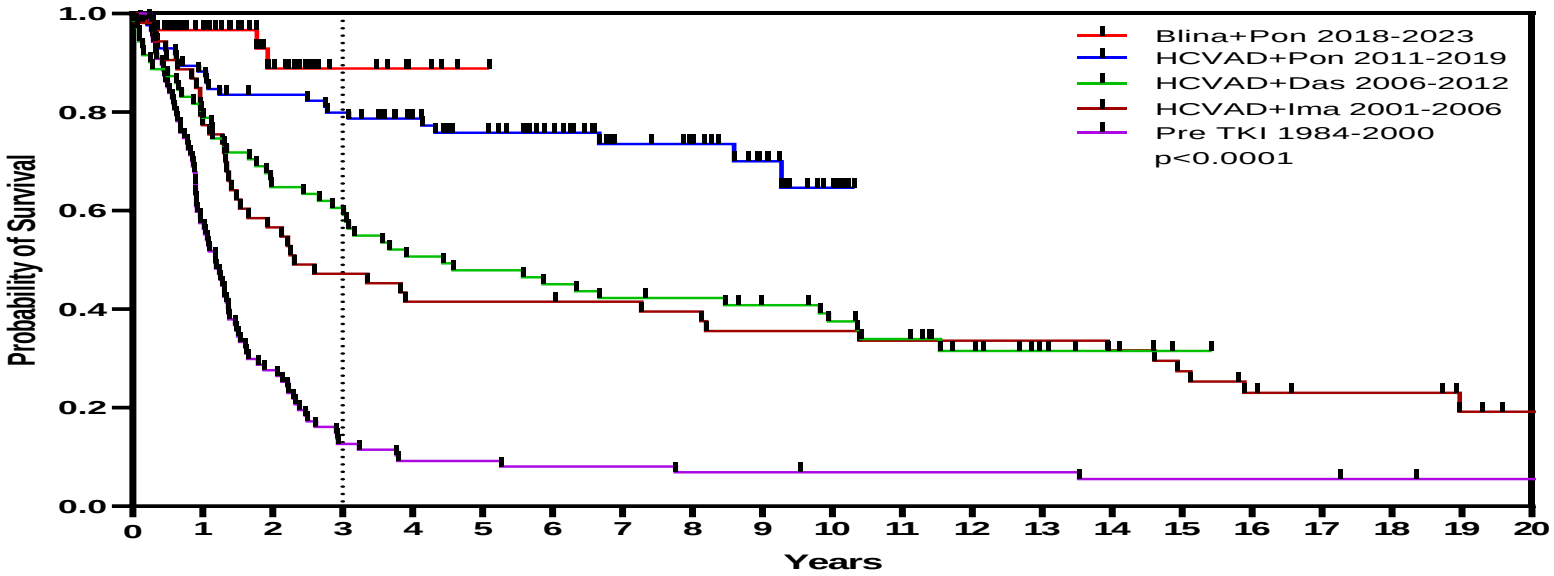
Short. *HemaSphere.* 2023;7:abstract S118 (updated August 2023).

Ponatinib + Blinatumomab in Ph+ ALL: Early MRD Responses



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

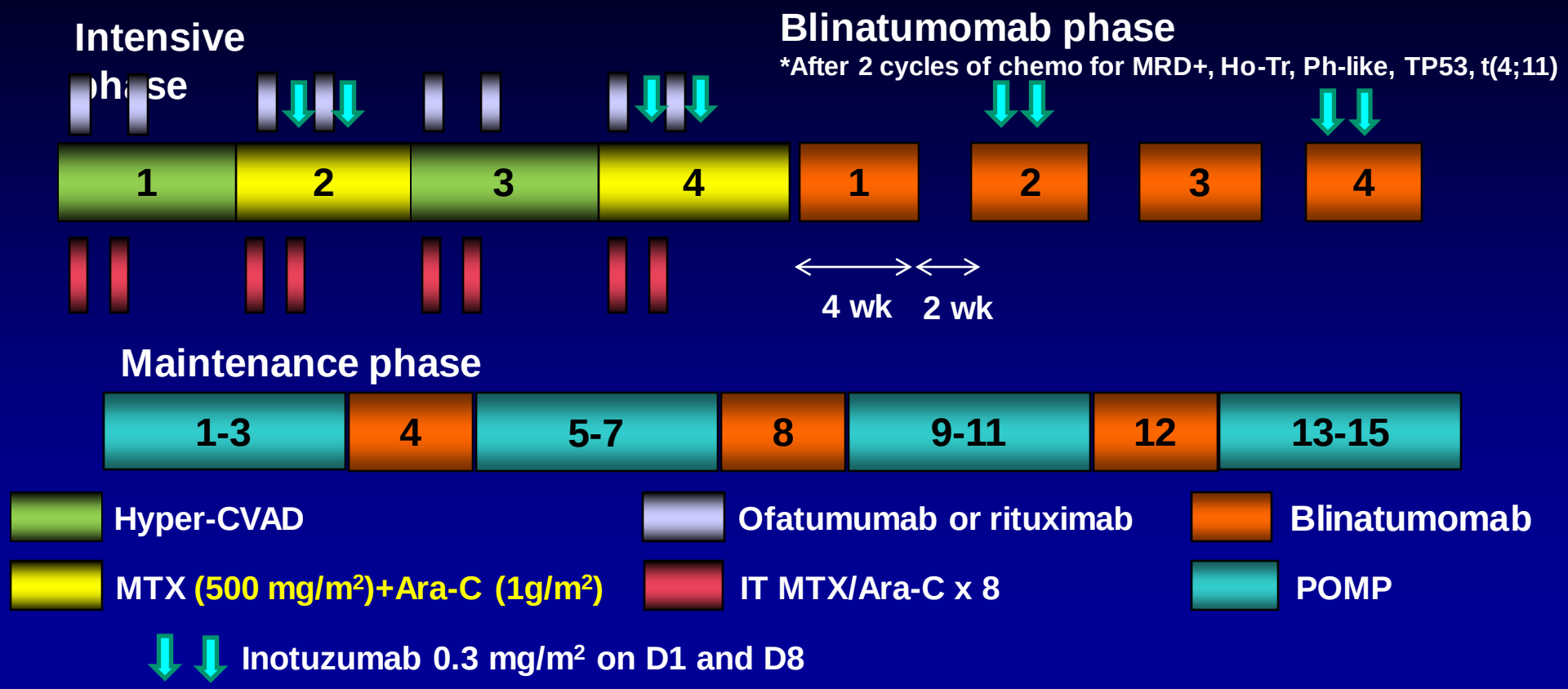
Ph+ ALL: Survival by Decade (MDACC 1984–2023)



	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

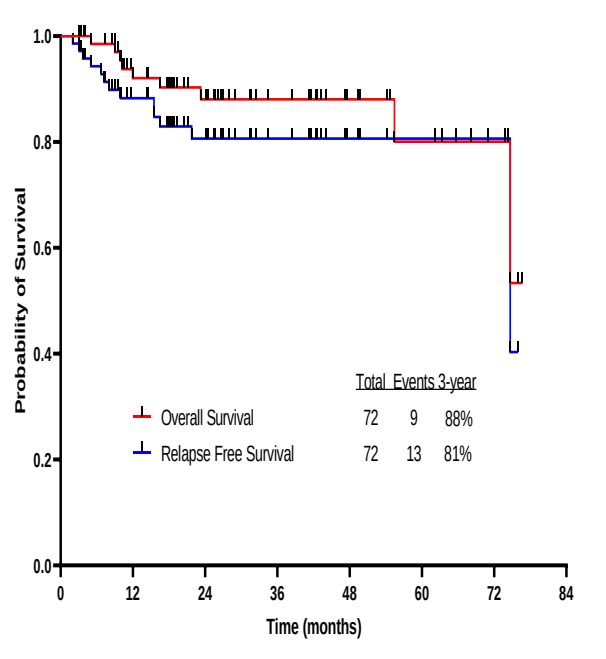
Hyper-CVAD + Blina + InO in B-ALL: Regimen

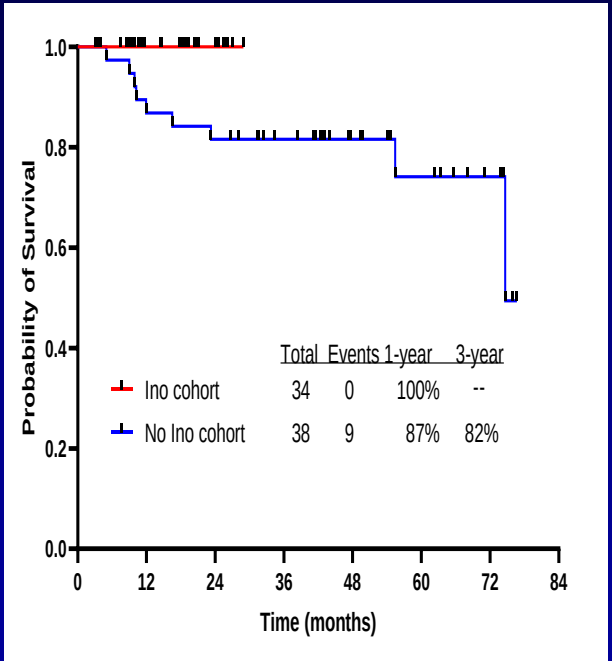


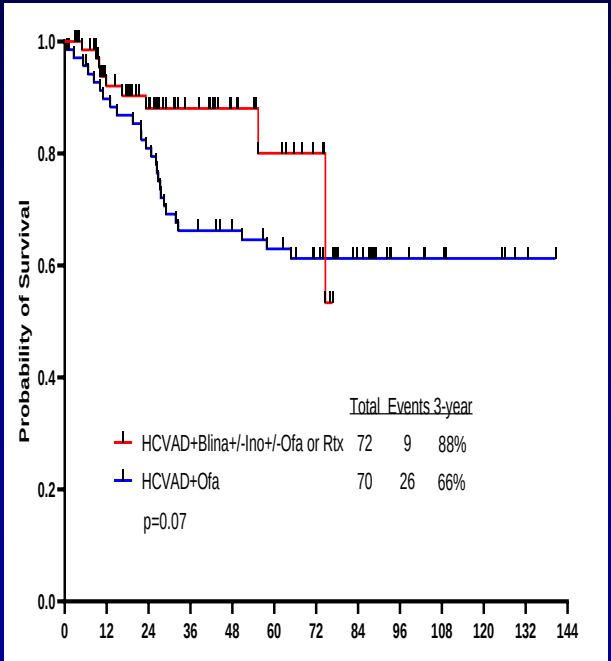
Short. *HemaSphere*. 2023;7:abstract P358.

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/m^2 D1 & 8; C2, 4, 6, 8 (2.4 mg/m^2)
- CR rate 100%; MRD negative 95% (69% at CR); NGS-MRD negative 74%; 60-day mortality 0%; 21 (32%) allo-SCT



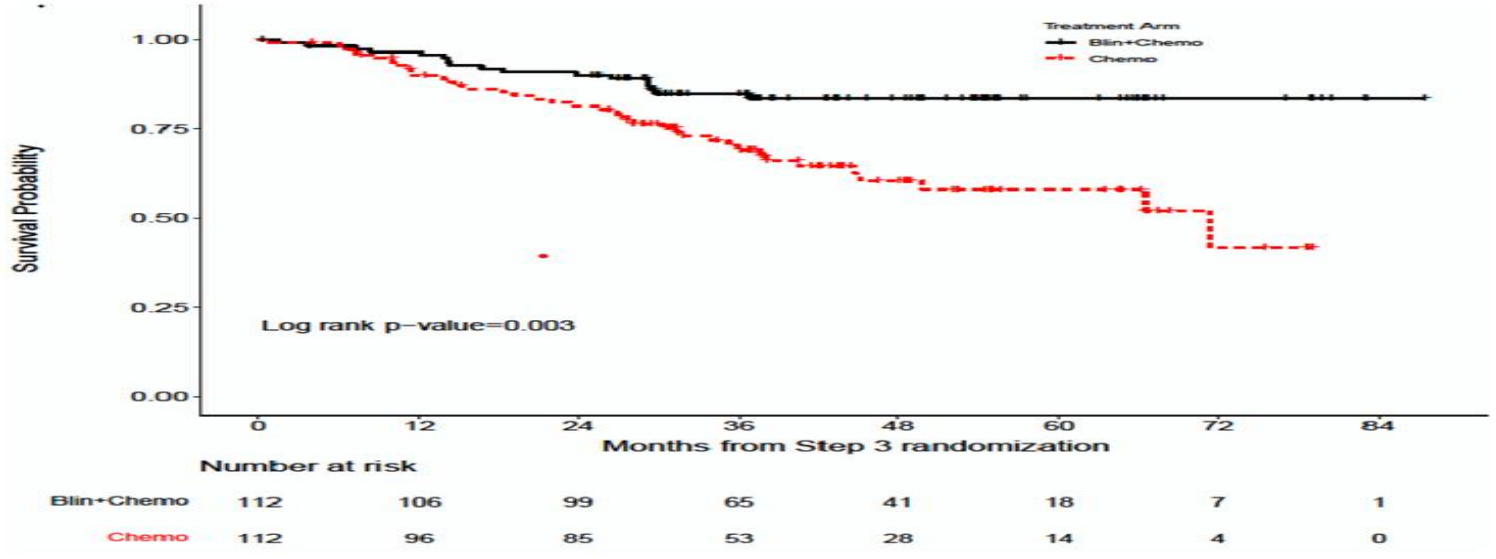




Short. *HemaSphere*. 2023;7:abstract P358.

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)



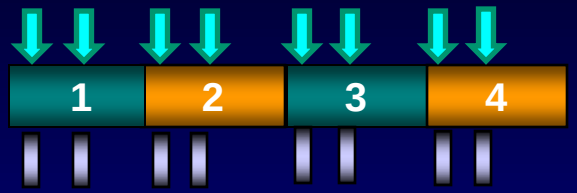
Litzow MR, et al. *Blood*. 2022;140(suppl 2): abstract LBA-1.

The “Intermediate” Leukemias

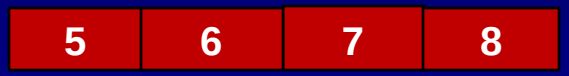
- Older ALL
- Younger AML

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

Intensive phase



Consolidation phase



Maintenance phase

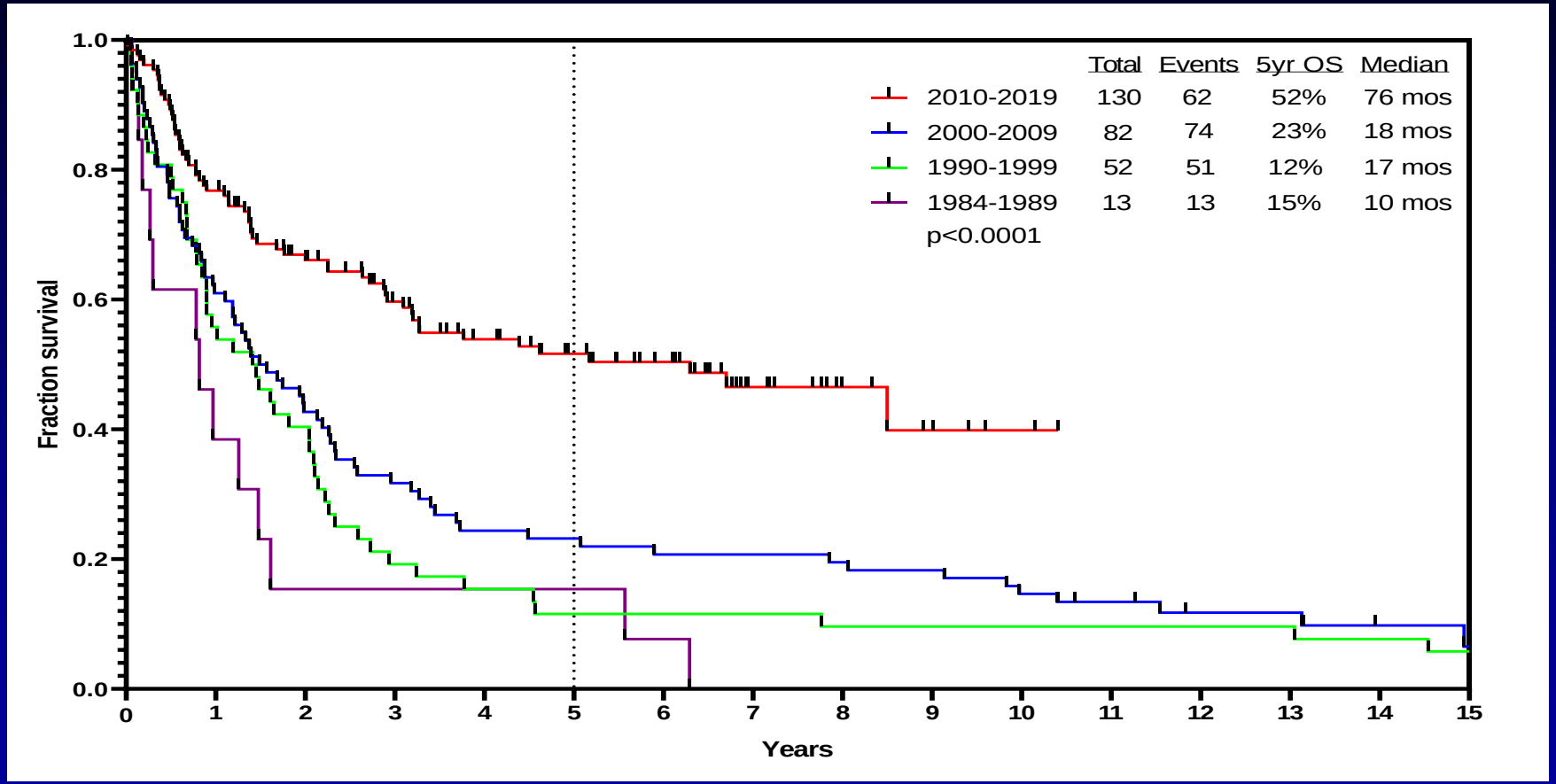
- Mini-HCVD
- Mini-MTX + cytarabine
- Blinatumomab
- IT MTX + Ara-C
- POMP

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

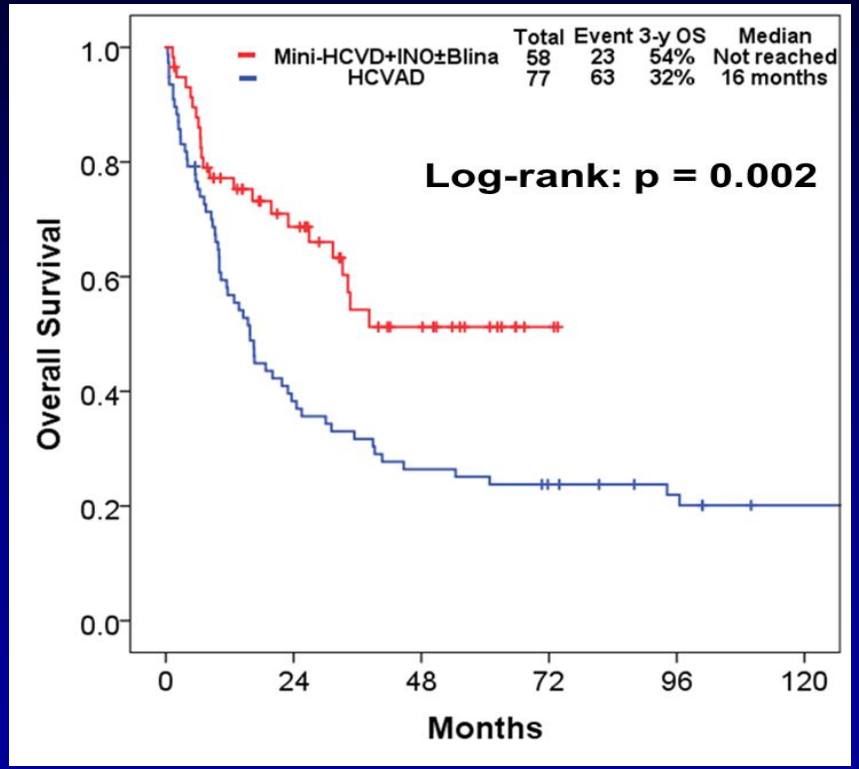
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Short et al. *Blood*. 2018;132:abstract 36.

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

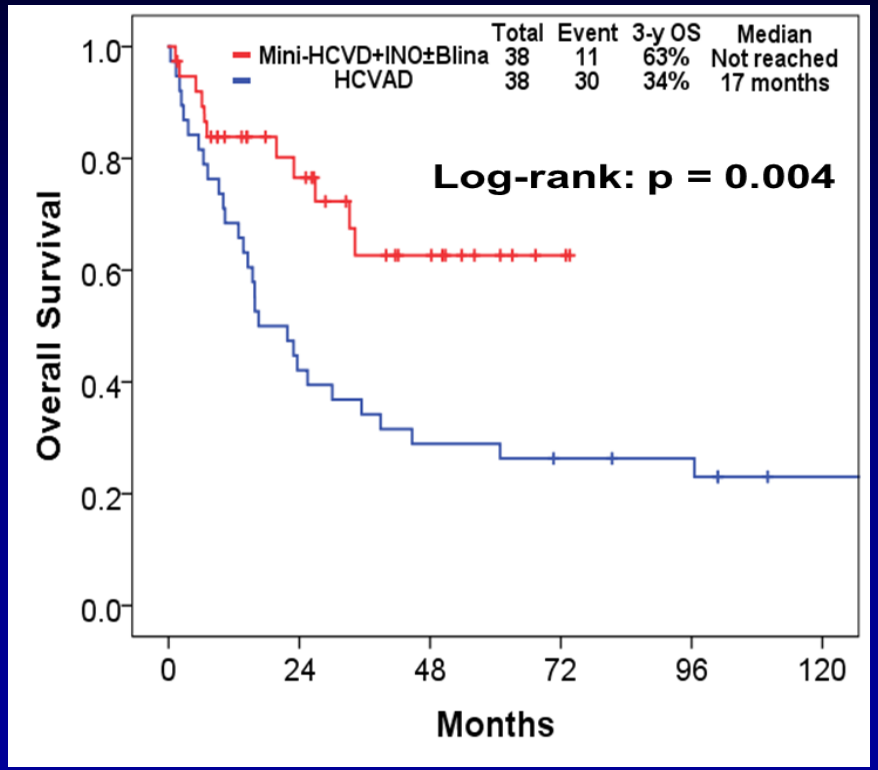


Mini-HCVD + INO ± Blina vs HCVAD in Older ALL: Overall Survival

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)

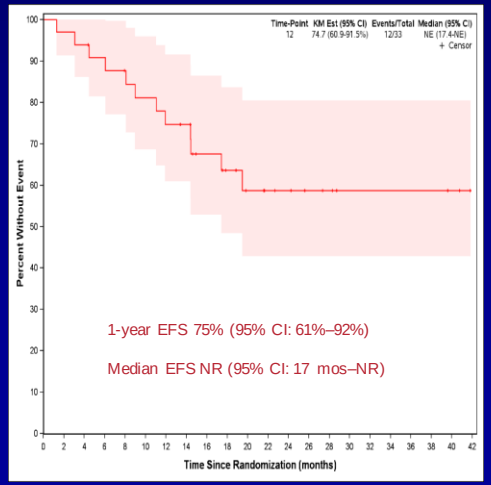
- 33 pts; median age 71 yrs (60–84). Median CD22 92%. F/U 22 months
- Induction: INO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 & 15 (1.8 mg/m^2)
- Maintenance: If CR-CRi INO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) ×2 then BLINA ×2
- If no CR-CRi—BLINA 28 mcg/D ×21 then ×28 ×3
- IT ×8
- CR 85% post INO ×3; cumulative CR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

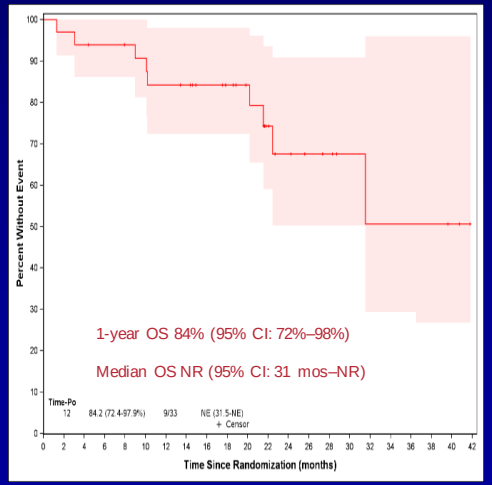
*CR+CRh+CRi

* 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+

FAI/CLIA + venetoclax ± FLT3/IDHi induction; consolidation × 1–2

CR

Age, PS, comorbidities, CG, molecular, MRD, donor

Low risk of relapse
High risk of SCT

High risk of relapse
Low risk of SCT

FAI-CLIA + VEN ± FLT3/IDHi × 6

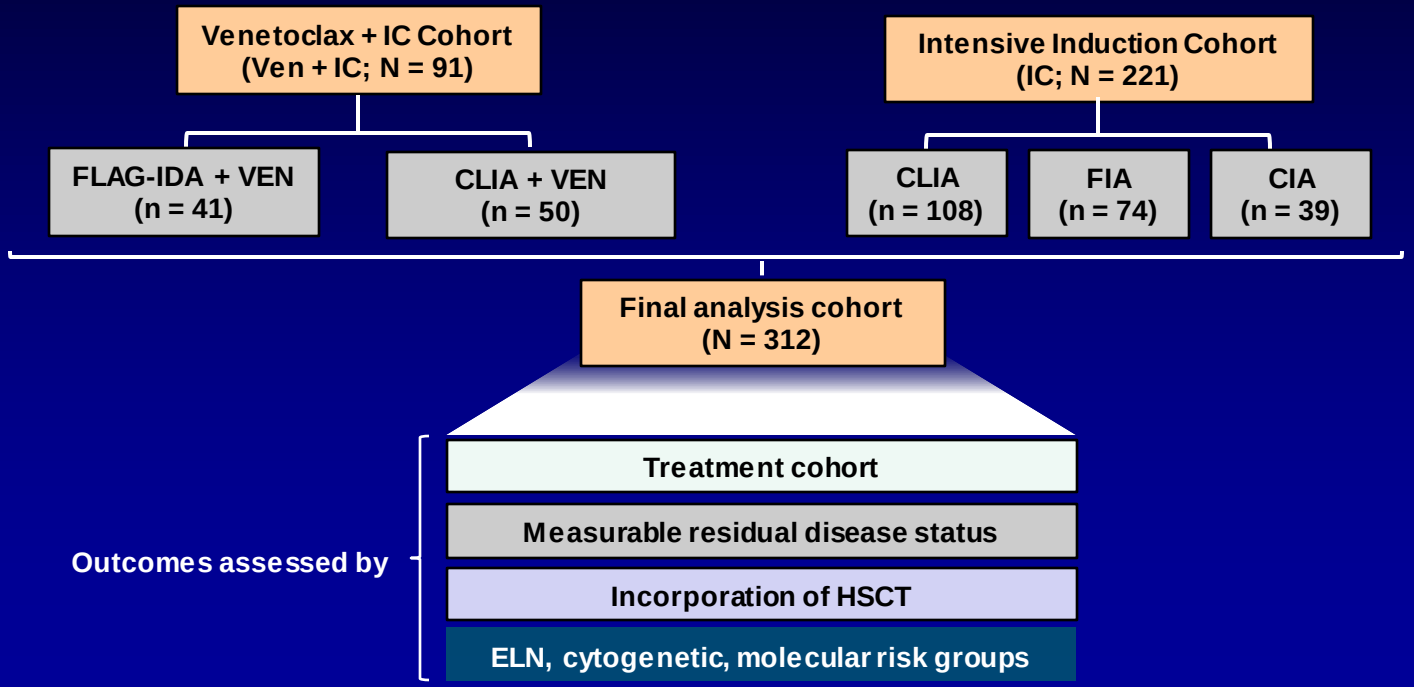
Allo-SCT

Maintenance AZA + VEN ± FLT3 × 2 yr

Personal communication from Dr Kantarjian.

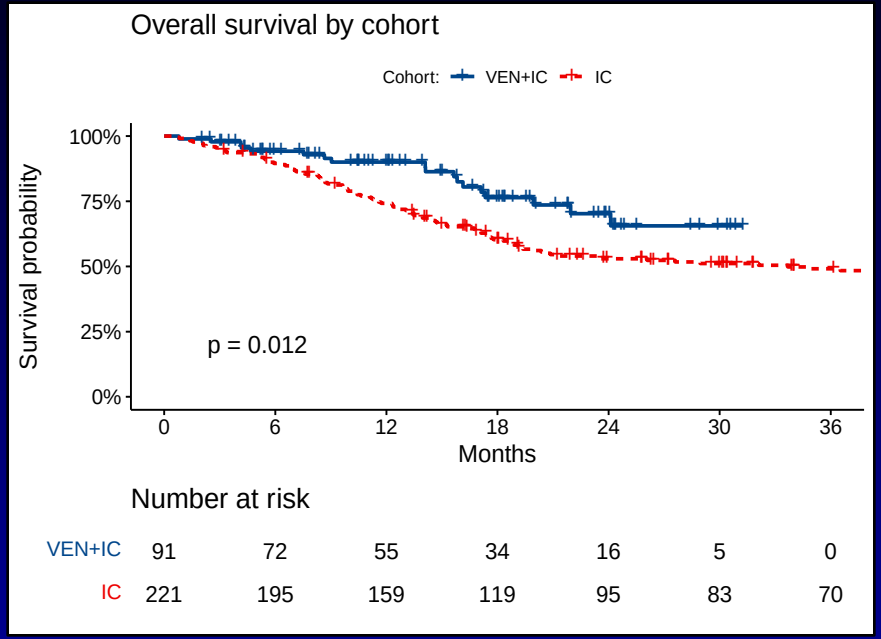
VEN + IC in AML – Study Design

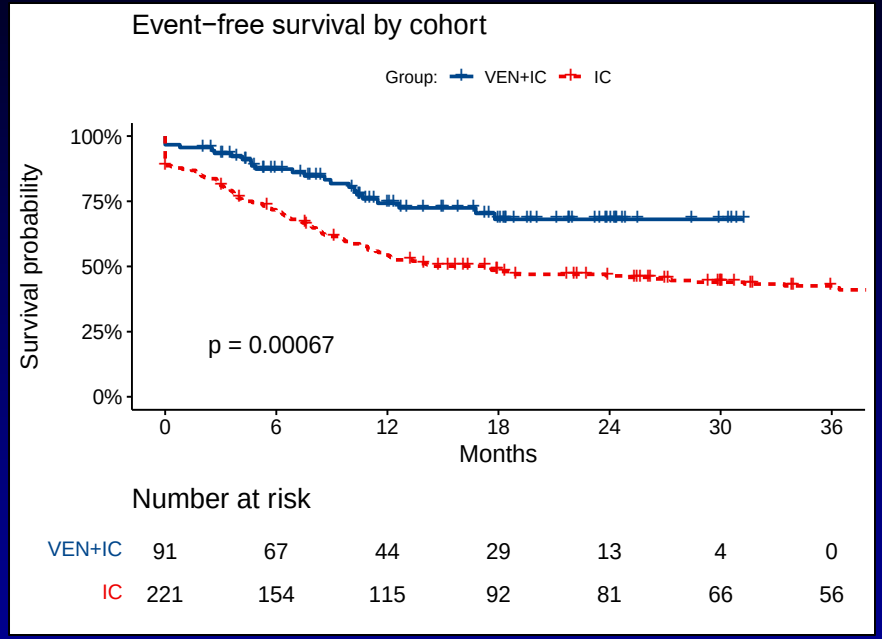
Patients with ND-AML (de novo, sAML, tAML, stAML) treated with intensive chemotherapy (IC) at MDACC on prospective clinical trial protocols



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

AML – Outcome With Intensive ChemoRx ± Venetoclax





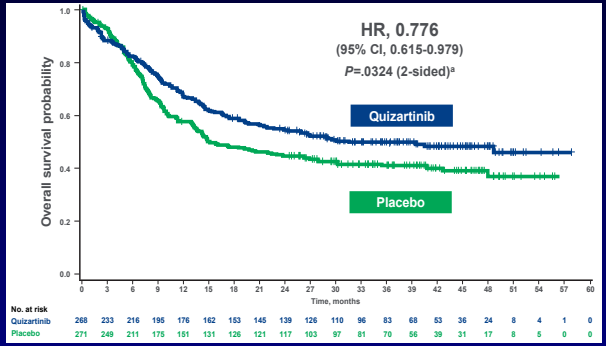
Demographic Median (95% CI) or %(SE)	Ven + IC	IC
Median OS, months	**NR (–)**	**34 (20–NR)**
12-Month OS	90 (3)	74 (3)
24-Month OS	70 (6)	52 (4)

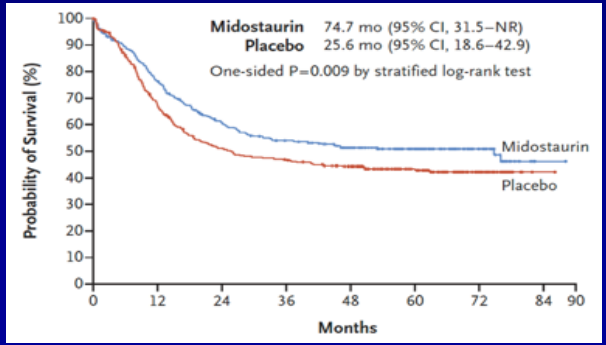
Demographic Median (95% CI) or %(SE)	Ven + IC	IC
Median EFS, months	**NR (-)**	**17 (11-34)**
12-Month EFS	74 (5)	54 (3)
24-Month EFS	68 (6)	46 (3)

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

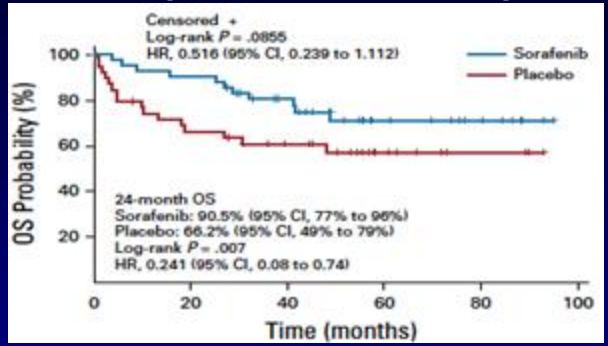
FLT3 Inhibitors Improve OS in AML

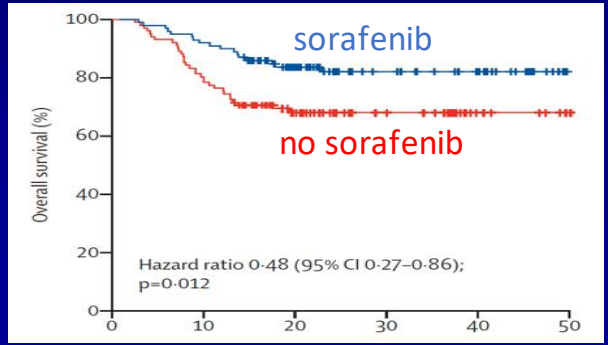
New Dx AML
intensive chemoRx + TKI/placebo



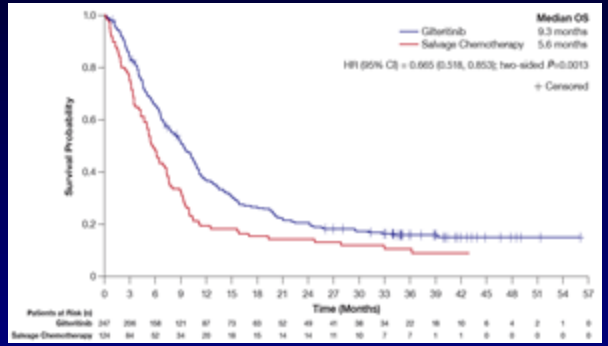


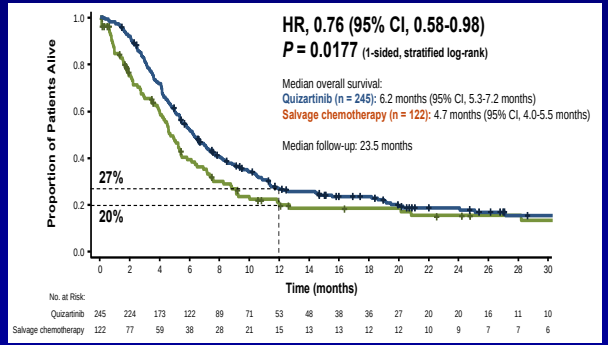
TKI post allo SCT
(sorafenib 2 studies)





R/R AML
TKI vs chemoRx



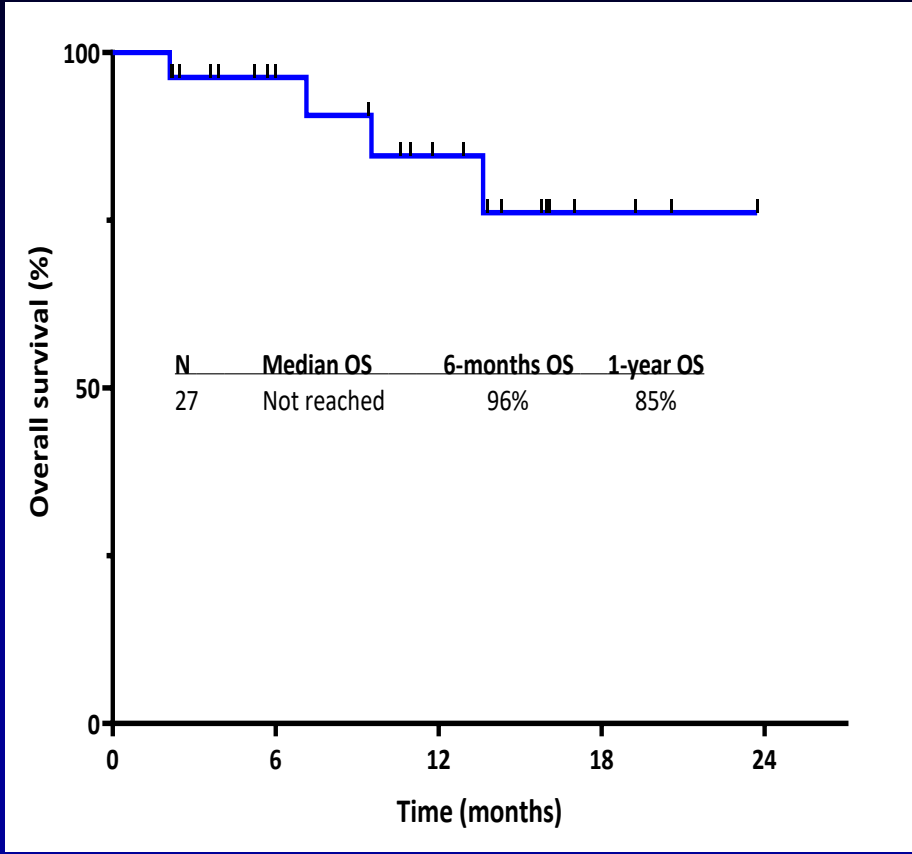


Erba HP, et al. EHA 2022. Abstract S100; Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464; Burchert A, et al. *J Clin Oncol.* 2020;38(26):2993-3002; Xuan Y, et al. *Lancet Oncol.* 2020;21(9):1201-1212; Perl AE, et al. Blood. 2022;139(23):3366-3375; Cortes JE, et al. *Lancet Oncol.* 2019;20(7):984-997.

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

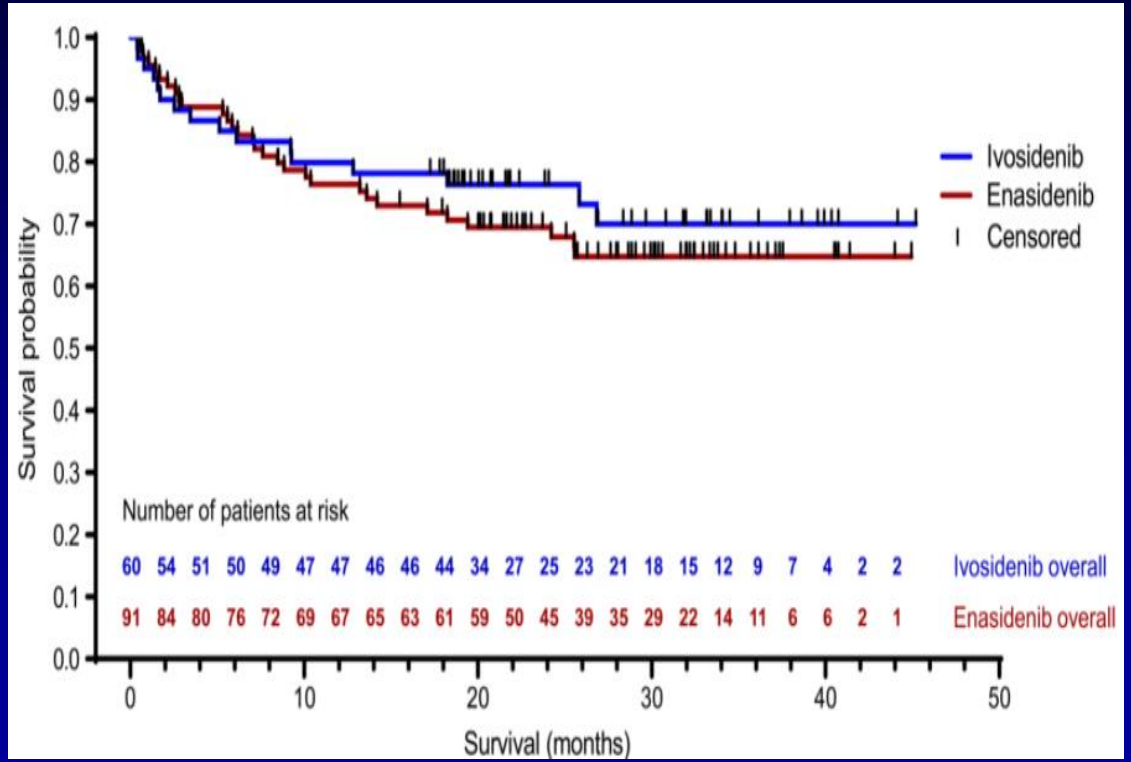


Short. Blood. 2022;140:abstract 831.

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

Randomization 2:1
N = 433

Venetoclax + Azacitidine
(N = 286)
Venetoclax 400 mg PO, daily, days 1–28
+ Azacitidine 75 mg/m^2 SC /IV days 1–7

Placebo + Azacitidine
(N = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m^2 SC /IV days 1–7

Endpoints

Primary
- Overall survival

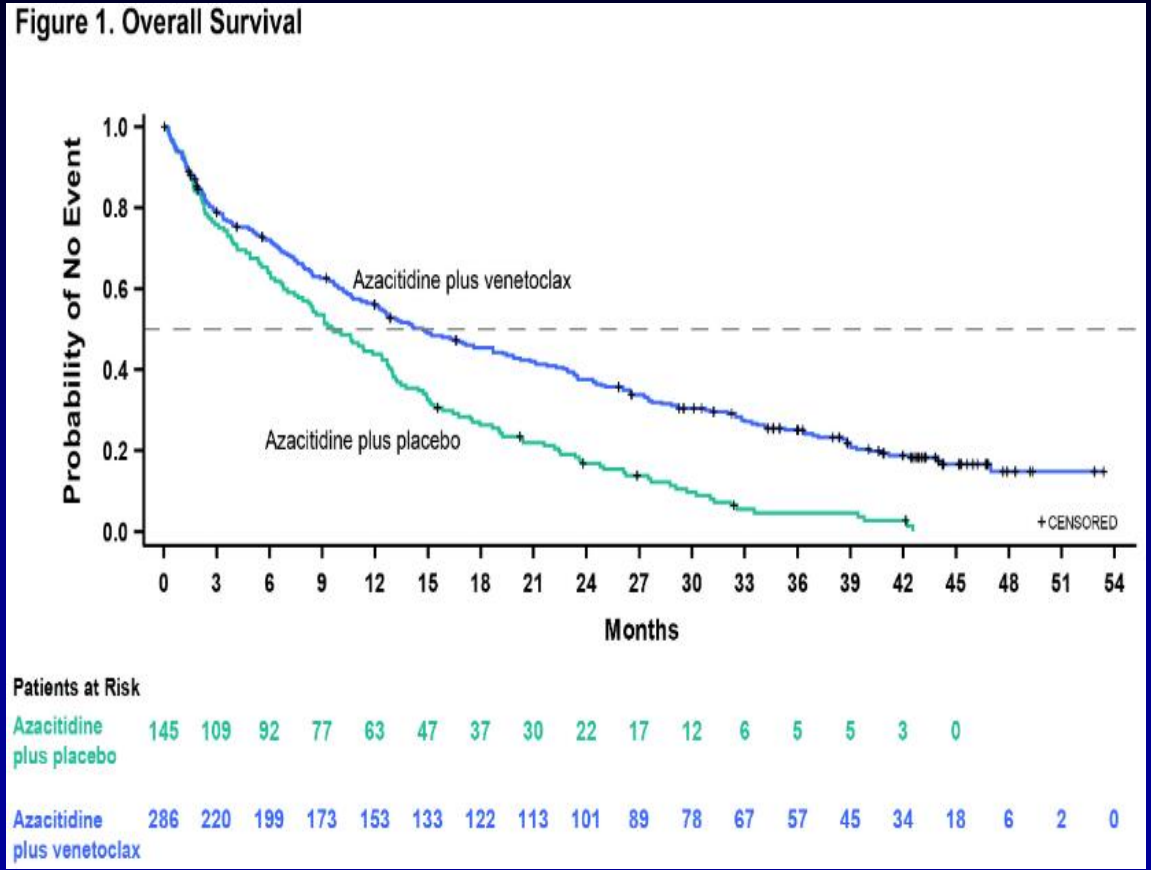
Secondary
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

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

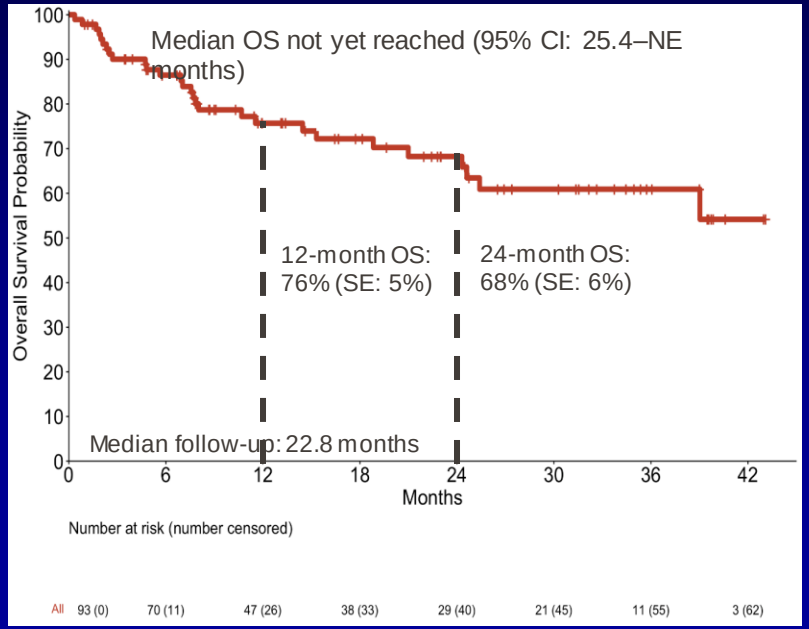
- 431 pts older, unfit with newly Dx AML randomized 2:1 to AZA-VEN (n = 286) or AZA (n = 145)
- 3-yr OS ≈7% with AZA; ≈25% with AZA-VEN
- Interpretation – HMA + VEN suboptimal

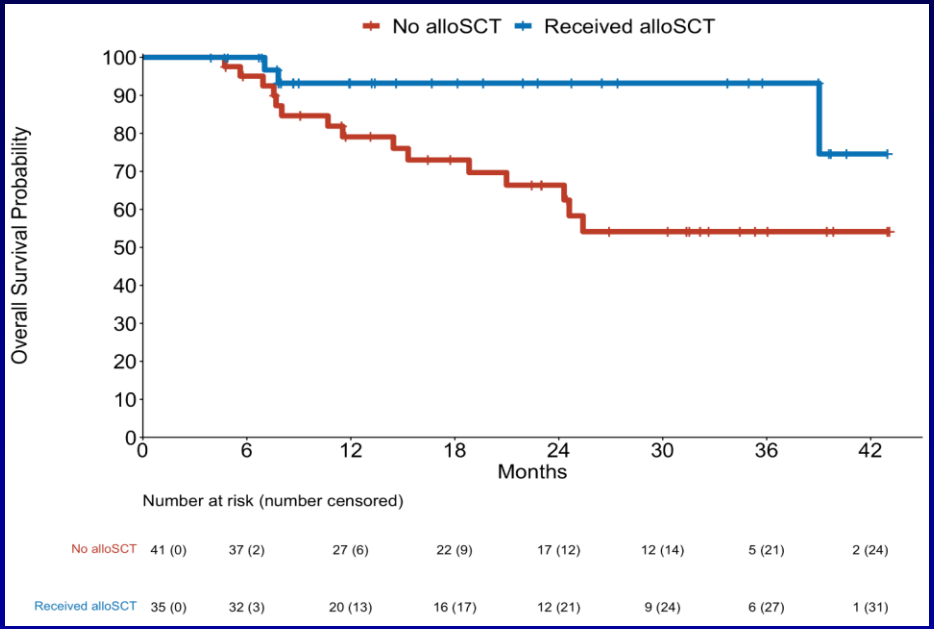


Pratz KW, et al. ASH 2022. Abstract 219.

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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- Office: 713-792-4764

Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

Genetic characterization and risk stratification of AML

Daniel DeAngelo

APTITUDE HEALTH

Disclosure Information

The following relationships exist related to this presentation

- I serve as a consultant for Amgen, Autolus, Blueprint, Gilead, Incyte, Jazz, Kite, Novartis, Pfizer, Servier, and Takeda
- I receive research funding from AbbVie, GlycoMimetics, Novartis, and Blueprint Medicines
- I am on the DSMB for Daiichi-Sankyo, FibroGen, and Mount Sinai Myeloproliferative Neoplasms Consortium
- I am the co-chair of the NCI (CTEP) Leukemia Steering Committee

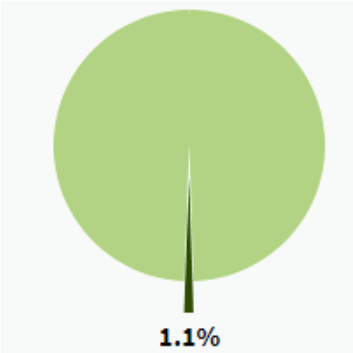
Off-Label/Investigational Discussion

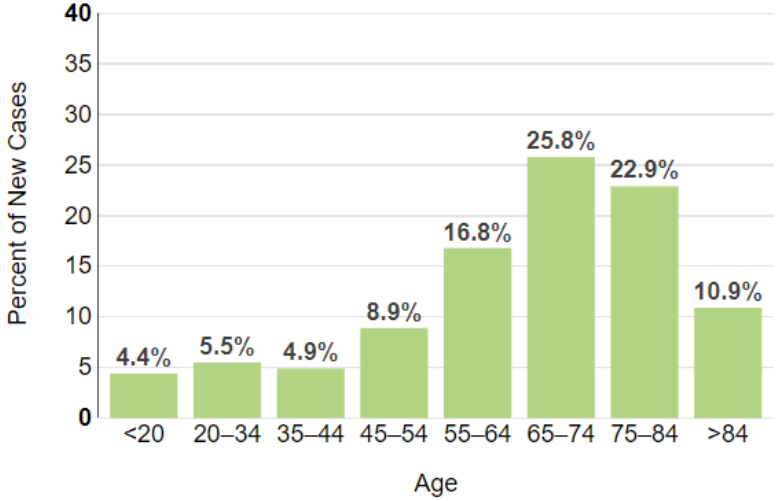
In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations. None

AML: Epidemiology and Demographics

At a Glance

Estimated New Cases in 2021	20,240
% of All New Cancer Cases	1.1%





5-Year Relative Survival

29.5%

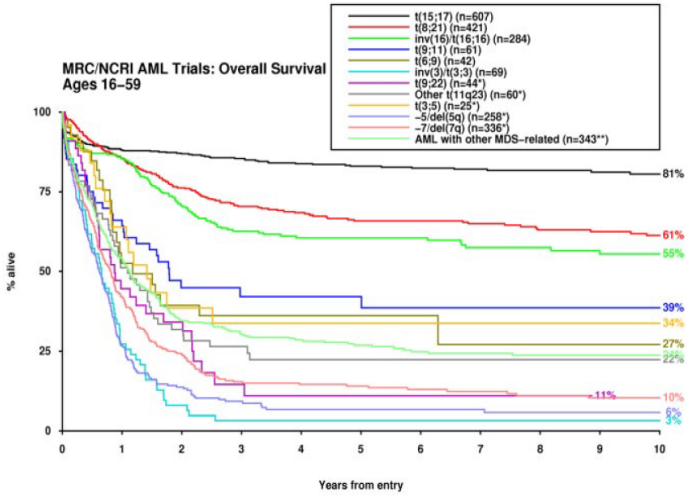
2011–2017

Risk factors: age, exposure to radiation/chemotherapy, antecedent chronic myeloid bone marrow disease, bone marrow failure disorders (aplastic anemia, etc)

National Cancer Institute. Cancer Stat Facts: Leukemia — Acute Myeloid Leukemia (AML). Surveillance, Epidemiology, and End Results Program. Accessed Sep 5, 2023. https://seer.cancer.gov/statfacts/html/amyl.html

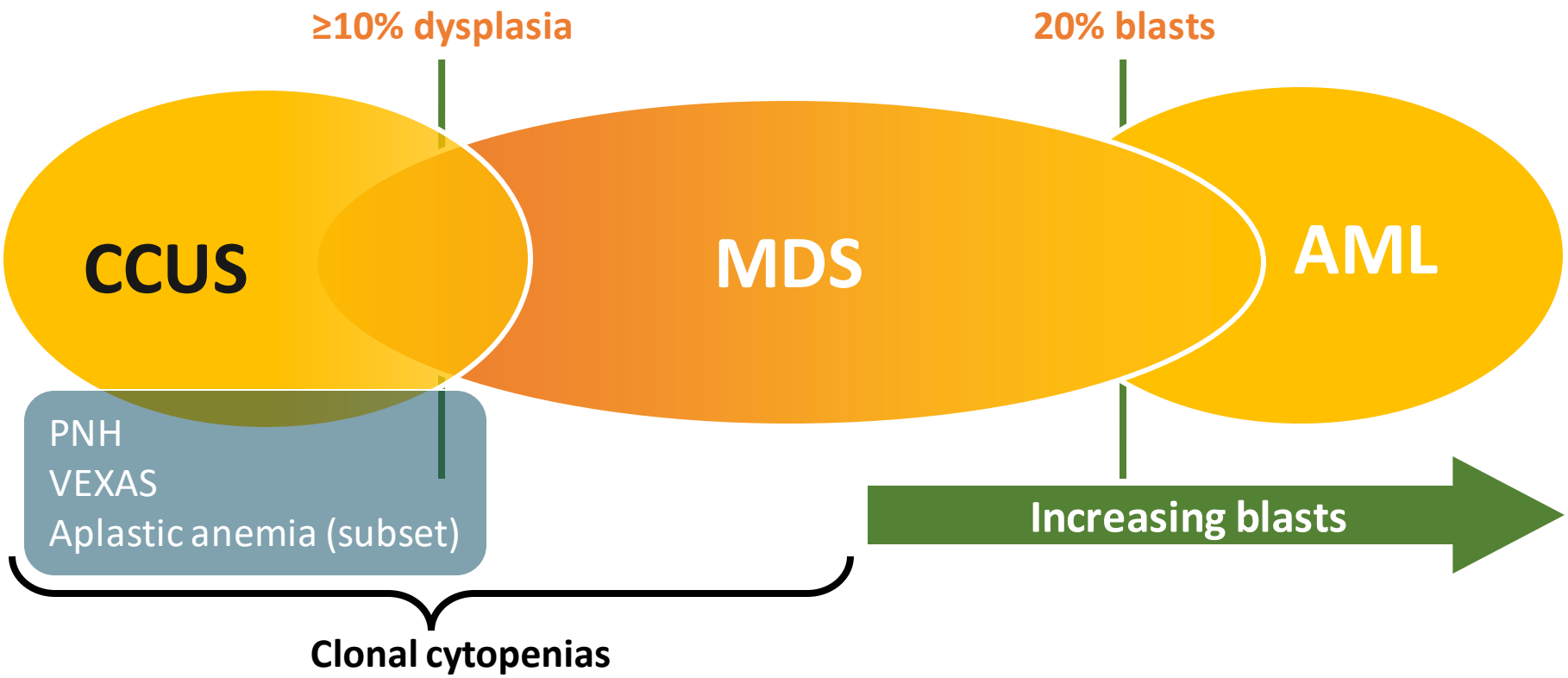
AML: Prognostic Features

- **Age:** inferior outcomes in older adults
- **Disease "context"**
  - Favorable: de novo
  - Unfavorable
    - "Therapy-related" AML (prior chemotherapy/XRT)
    - "Secondary" AML (prior myelodysplastic syndrome [MDS]/myeloproliferative neoplasms [MPN])
- **Genetics (chromosomes and gene-level mutations)**
  - Favorable
    - APL [t(15;17)] if survive initial presentation
    - "Core binding factor" AML: t(8;21); inversion 16
    - Molecular: *NPM1* mutant without *FLT3*-ITD abnormality (with normal karyotype)
  - Unfavorable
    - Complex karyotype (≥3 abnormalities), chromosome 5 and 7 abnormality, etc
    - *TP53* mutation



Grimwade D, et al. *Blood.* 2010;116:354-365; Döhner H, et al. *Blood.* 2017;129:424-447.

The Historical Border of MDS/AML



AML, acute myeloid leukemia; CCUS, clonal cytopenia of undetermined significance; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (syndrome).

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Traditional ICUS

MDS by WHO 2008

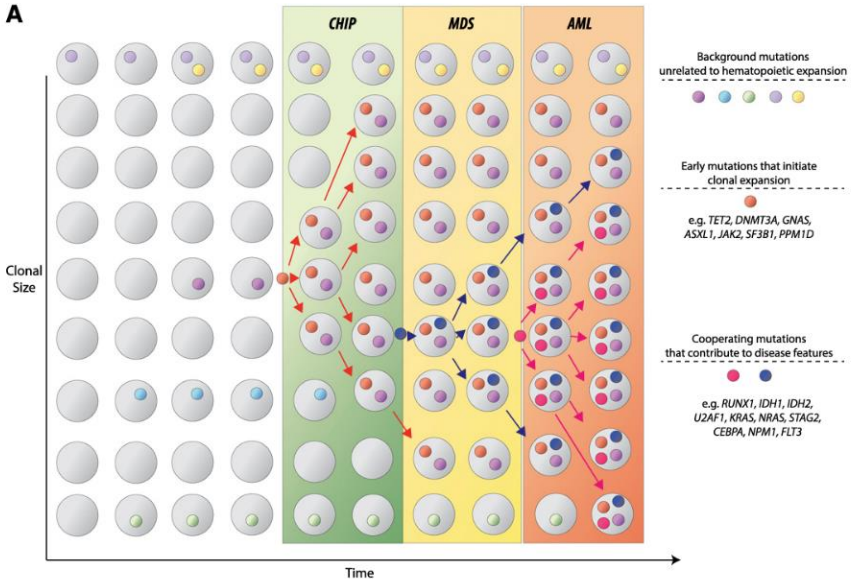
	'Non-clonal' ICUS	CHIP	CCUS	Lower Risk MDS	Higher Risk MDS
Clonality	–	+	+	+	+
Dysplasia	–	–	–	+	+
Cytopenias	+	–	+	+	+
BM Blast %	< 5%	< 5%	< 5%	< 5%	< 19%
Overall Risk	Very Low	Very Low	Low (?)	Low	High
Treatments	Obs/BSC	Observation	Obs/BSC/GF	Obs/BSC/GF IMiD/IST	HMA/HCST

Clonal Cytopenias

BM, bone marrow; BSC, best supportive care; GF, growth factors; HCST, hematopoietic stem cell transplantation; HMA, hypomethylating agent; ICUS, idiopathic cytopenia of unknown significance; IMiD, immunomodulatory drug; IST, immunosuppressive therapy; MDS, myelodysplastic syndrome; Obs, observation; WHO, World Health Organization.

Steensma DP, et al. *Blood.* 2015;126:9-16.

Assessing Risk of Developing MDS: Myeloid Precursor Conditions (CHIP and CCUS)



Prevalence in the population → Risk for transformation into MDS/AML

	CH	ICUS	CCUS (low risk)	CCUS (high risk)	MDS
Clonality	YES	NO	YES	YES	YES
Cytopenia	NO	YES	YES	YES	YES
Dysplasia	NO	NO	NO	NO	YES
High risk features*	NO	NO	NO	YES	YES/NO
↑ Blasts	NO	NO	NO	NO	YES/NO
Risk of progression	~ 0.5-1%/year	~ 1%/year	~ 10%/year	~ 20%/year	

* High risk features:
1. DTA mutation (*DNMT3A*, *TET2*, *ASXL-1*) + 1 other myeloid mutation
2. Spliceosome mutation (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*)

*High-risk features include DTA mutation (*ONMT3A, TET2, ASXL1*) + 1 other myeloid mutation; spliceosome mutation (*SF3B1, SRSF2, U2AF1, ZRSR2*).
CH, clonal hematopoiesis.

Steensma DP, et al. *Blood.* 2015;126:9-16; Bewersdorf JP, et al. ASCO 2021. Abstract 7045

Risk of Developing Myeloid Malignancy for CH Patients

High Risk Mutations
Absent

single DNMT3A
Absent

Maximum VAF
< 0.2 (20%)

Number of Variants
1

CHIP or CCUS
CHIP

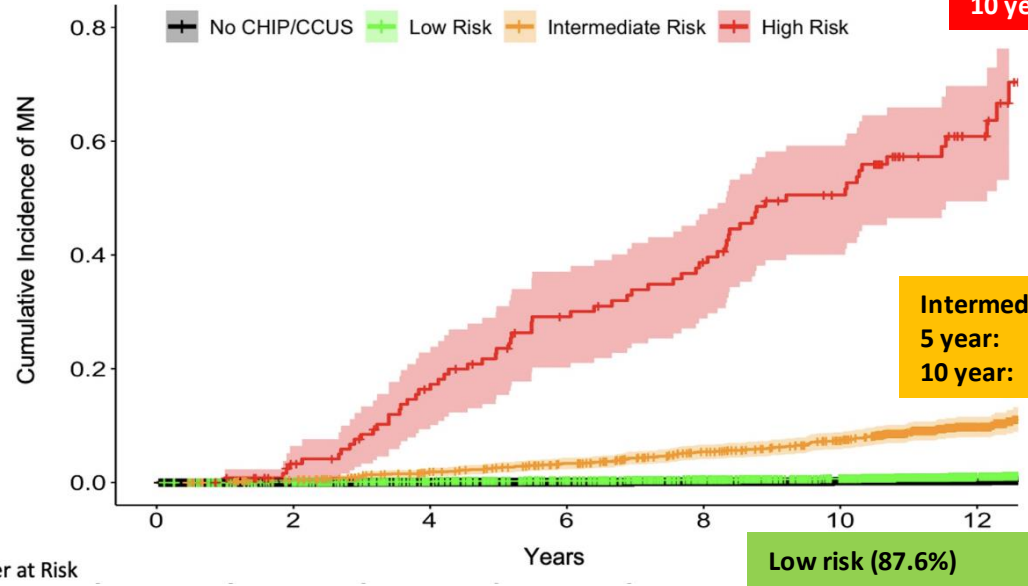
Mean corpuscular volume
< 100 fl

Red cell distribution width
< 15%

Age
< 65 years

High-risk mutations
SF3B1, SRSF2, ZRSR2,
JAK2,
TP53,
RUNX1, FLT3, IDH1, and *IDH2*

- UK Biobank: 193,743 healthy volunteers
- 11,337 (5.85%) had pathogenic variants



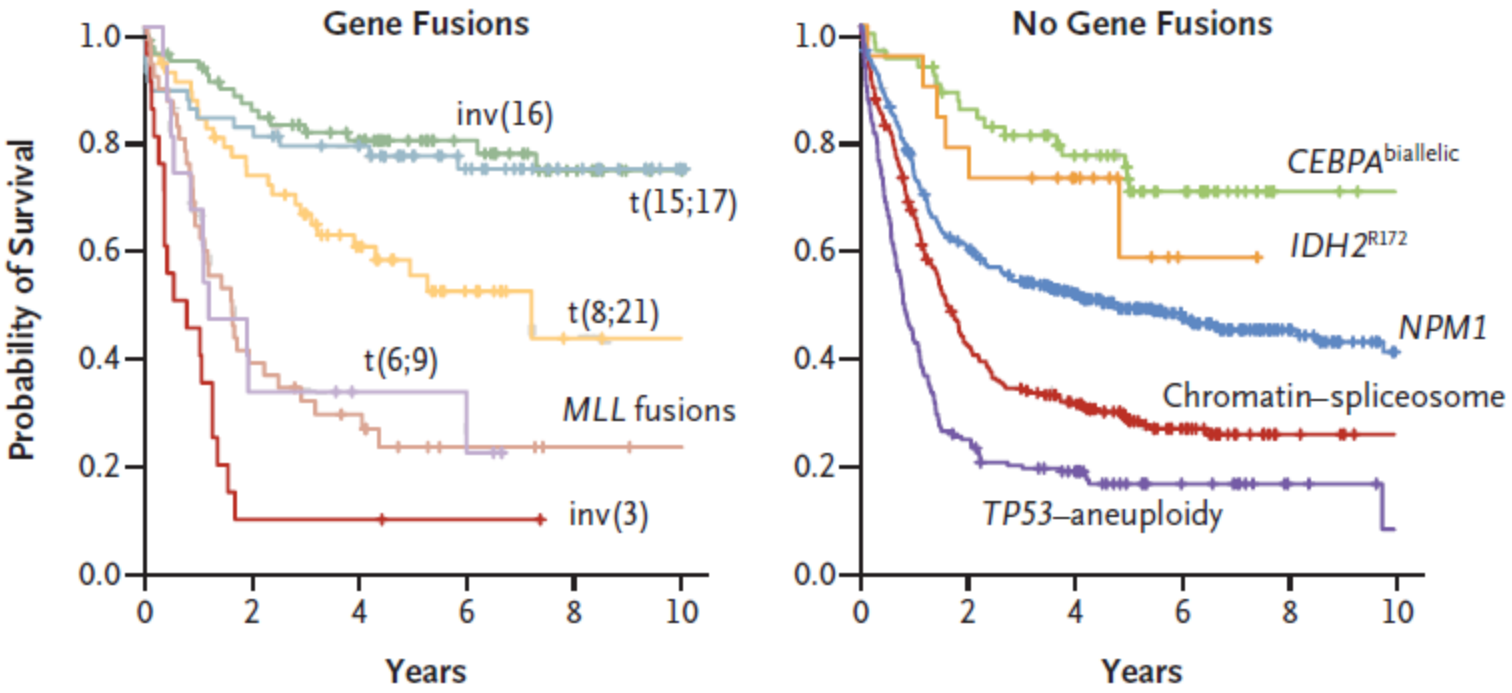
High risk (1.13%)
5 year: 24.4 ± 4.12%
10 year: 52.2 ± 4.96%

Intermediate risk (11.3%)
5 year: 2.76 ± 0.482%
10 year: 7.83 ± 0.807%

Low risk (87.6%)
5 year: 0.232 ± 0.0484%
10 year: 0.669 ± 0.0827%

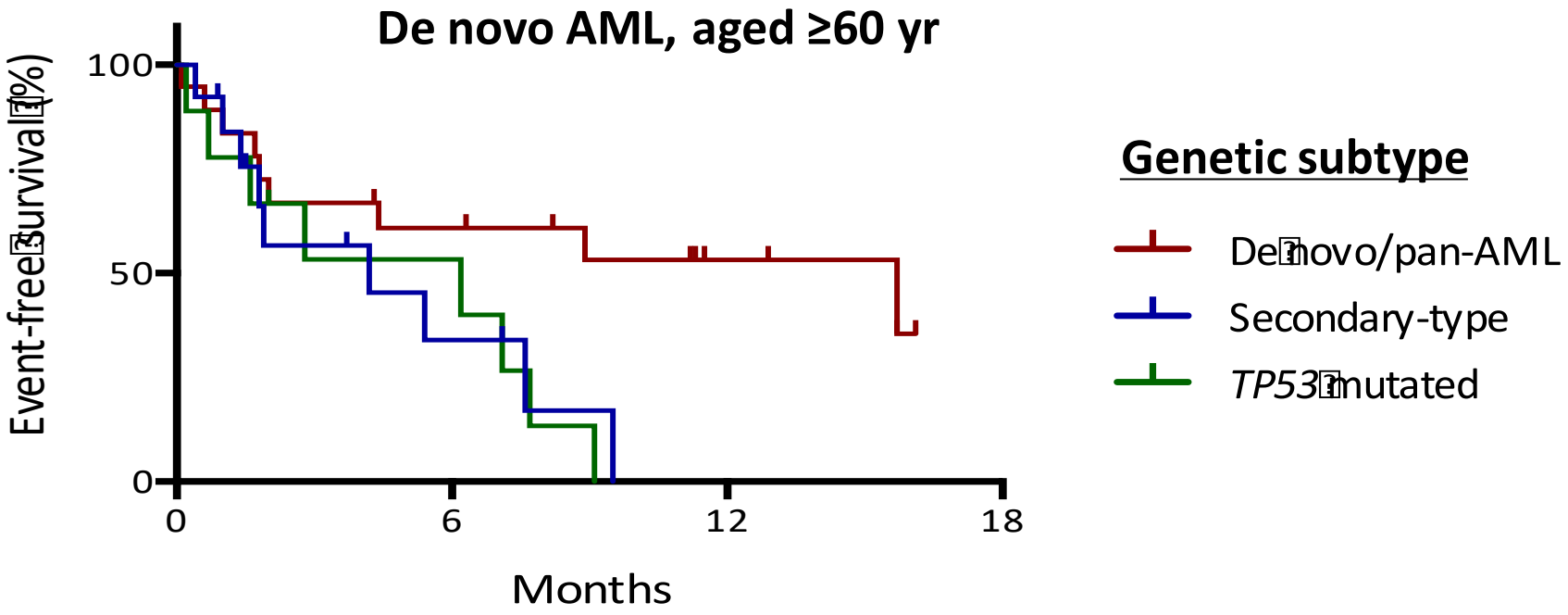
Weeks LD, et al. *NEJM Evid.* 2023;2:10.1056/evidoa2200310.

Genomic Classification and Prognosis in AML



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

In Elderly De Novo AML, Secondary-Type Mutations Are Associated With Adverse Outcomes



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

2 New Classification Systems

- **<u>WHO 2022</u>**
  - Keeps ≥20% as AML
  - Adds a number of new subgroups
    - Low blasts with *SF3B1*
    - Low blasts with isolated del5Q
    - *TP53*

- **<u>International Consensus Classification (ICC)</u>** of Myeloid Neoplasms
  - Redefines MDS/AML as ≥10% blasts

Khoury JD, et al. *Leukemia*. 2022;36:1703-1719.

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

Change in Blast Percentages: (require ≥10% blasts in PB or BM)

- **APL with t(15;17)(q24.1;q21.2)/*PML::RARA***
- **AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1***
- **AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11***
- AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*
- AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
- AML with other rare recurring translocations
- AML with mutated *NPM1*
- AML with in-frame bZIP-mutated *CEBPA*

Bold = AML regardless of blast count.

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

AML and MDS: New Thoughts on Diagnosis

- **Will there be a lot more AML and fewer MDS patients?**
- **WHO: ≥20% blasts is AML[1]**
- **ICC: ≥10% blasts is AML[2]**

- To acknowledge the biologic continuum between MDS and AML, the name of the previous category of MDS-EB2 in adults with ≥10% blasts is changed to MDS/AML, defined as a cytopenic myeloid neoplasm and 10%–19% blasts in the blood or BM
- Patients with MDS/AML should be eligible for both MDS and AML trials, which will facilitate optimizing the management of such patients. In the future, genetic features rather than an arbitrary blast cutoff may drive treatment decisions in this group[3]

1. Khoury JD, et al. *Leukemia.* 2022;36:1703-1719; 2. Arber DA, et al. *Blood*. 2022;140:1200-1228; 3. Estey E, et al. *Blood*. 2022;139:323-332.

MDS vs AML: A New Category “MDS/AML” Has Been Created for Patients With 10%–19% Blasts (MDS-EB2)

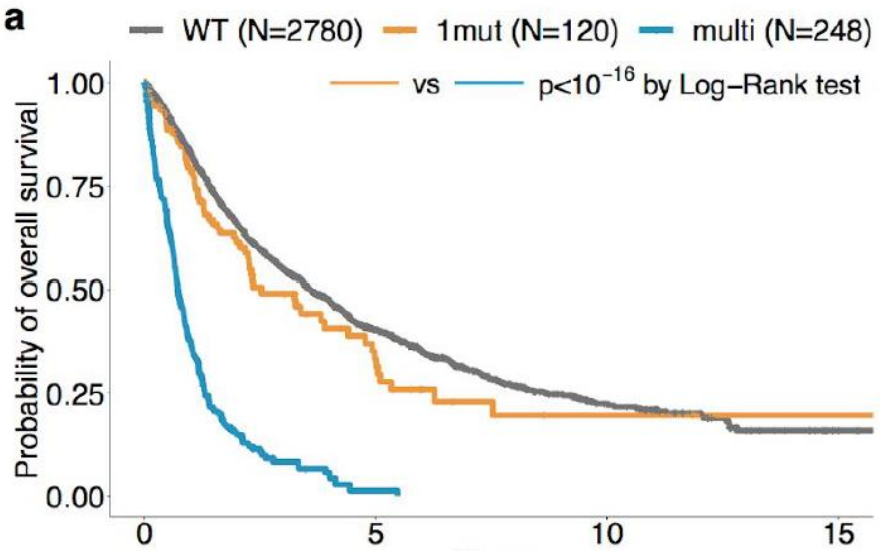
- There is a biologic continuum between MDS and AML, arbitrariness of the 20% threshold, and some imprecision in counting blast
  - Only applicable to adult patients (aged ≥18 years); pediatric cases with 10%–19% blasts will continue as MDS with excess blasts
- Treatment approaches to AML and MDS are becoming increasingly blurred; further study is needed to determine which factors should drive treatment choice
- MDS/AML entity is essentially equivalent to the WHO 2022 entity MDS-IB2

A New Entity "MDS With Mutated *TP53*" Has Been Created

- Cytopenic patients with multi-hit *TP53* mutation (VAF ≥10%), multi-hit status determined by VAF >50%, >1 distinct mutation, *TP53* locus LOH, and/or complex karyotype
- Supersedes all other MDS subtypes, with or without excess blasts
- Encompasses patients with 0%–19% blasts
  - Single *TP53* mutation for MDS/AML with 10%–19% blasts
- Therapy-relatedness and underlying germline predisposition conditions are applied as qualifiers to the diagnosis
  - *TP53*-mutated MDS has similarly poor outcome whether presenting de novo or secondary to cytotoxic therapy

Allelic State Influences Outcome in *TP53*-Mutated MDS

- "Multi-hit" cases enriched in t-MDS, excess blasts, and very poor IPSS-R risk
- Effect of multi-hit seen in patients treated with HMA, lenalidomide, and SCT, and independent of karyotype risk and other prognostic variables

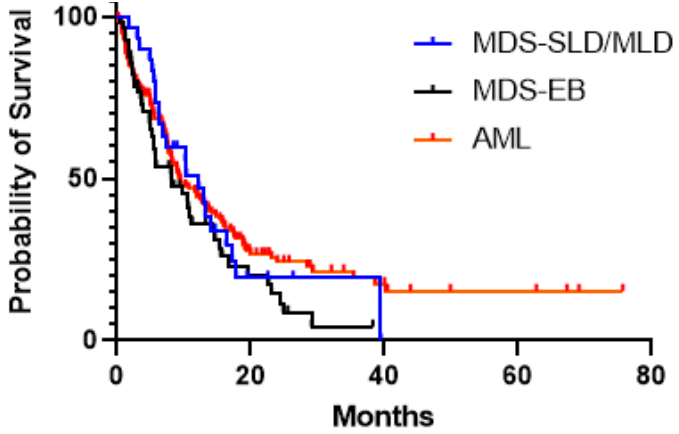


Bernard E, et al. *Nat Med.* 2020;26:1549-1556.

TP53-Mutated AML and MDS Appear to Represent a Single Entity With Shared Biology and Prognosis

- No independent influence of therapy-relatedness, monosomal karyotype, MDS vs AML, blood counts
- *TP53* VAF does not significantly impact OS, but other studies have shown an effect of *TP53* VAF and functional annotation of mutation pathogenicity
- *TP53* immunohistochemistry is a useful predictor of mutated *TP53* in MDS and AML
- "*TP53*-mutated myeloid neoplasms" group in ICC
  - MDS with mutated *TP53:* multi-hit VAF ≥10%, <10% blasts
  - MDS/AML with mutated *TP53*: any VAF ≥10%, 10%–19% blasts
  - AML with mutated *TP53*: any VAF ≥10%, ≥20% blasts
  - Therapy-relatedness applied as a qualifier to diagnosis

Patients with *TP53*-mutated MDS and AML (n = 247)



Weinberg OK, et al. *Blood Adv.* 2022;6:2847-2853; Yabe M, et al. *Cancers.* 2021;13:5502; Kanagal-Shamanna R, et al. *Blood Cancer J.* 2021;11:52; Sallman DA , et al. *Leukemia.* 2016;30:666-673; Grob T, et al. *Blood.* 2022;139:2347-2354.

European Leukemia Net (ELN) 2022 Guidelines

Genetic Risk Group	Frequency	Survival	Subset
Favorable	15%	**65%**	• t(8;21)(q22;q22); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3* ITD • in-frame bZIP-mutated *CEBPA* (normal karyotype)
Intermediate	55%	**50%**	• Mutated *NPM1* with mutated *FLT3*-ITD • Wild-type *NPM1* without *FLT3*-ITD • t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* • Other cytogenetic abnormalities not classified as favorable or adverse
Poor	30%	**20%**	• 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*

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

Genetic Classification: Conclusions

- <u>AML</u>
  - Mutations matter!
    - Clonal hematopoietic disorder vs MDS vs AML
    - Risk stratification for developing myeloid malignancy in CCUS
      - Weeks LD, et al. *NEJM Evid.* 2023;2:10.1056/evidoa2200310.
  - Prognosis: genetic mutations, comorbid disease, performance status
    - Beware of *TP53* mutations
  - 2 new classification for AML/MDS!
    - WHO 2022 still using 20% blast cutoff
    - ICC 2022 decreases blast cutoff to 10% in most cases

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Theresa Nguyen, NP
Mary Gerard, PA
Kelly Ling, PA
Ryan Osborn, PA
Ellen Toomey-Mathews, RN

Special Thanks

Patients and their families!!!

The End: Questions?

Questions or need help?

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Global Leukemia Academy

Q&A

APTITUDE HEALTH

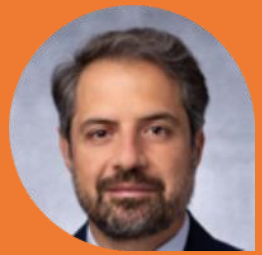
Global Leukemia Academy

ALL case-based panel discussion

Case 1: Michael Ashby

Case 2: Koichi Takahashi

Moderator: Elias Jabbour



APTITUDE HEALTH

Global Leukemia Academy

Case 1: Adult ALL

Michael Ashby
Alfred Hospital, Melbourne, VIC, Australia

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Clinical information

- 48-year-old man
- Newly diagnosed Ph-negative precursor B-ALL
- Presented with B symptoms and circulating blasts
- Referred from external hospital for evaluation

Past medical history

- Ex-smoker, 20-pack-year history
- Anxiety
- Married with 2 children

Risk stratification

- High white cell count at diagnosis: 50×10^9/L
  High LDH: 500
  No CNS involvement
- Complex cytogenetics
  Genomic sequencing not undertaken
- CD20 negative

Treatment options: MCQ

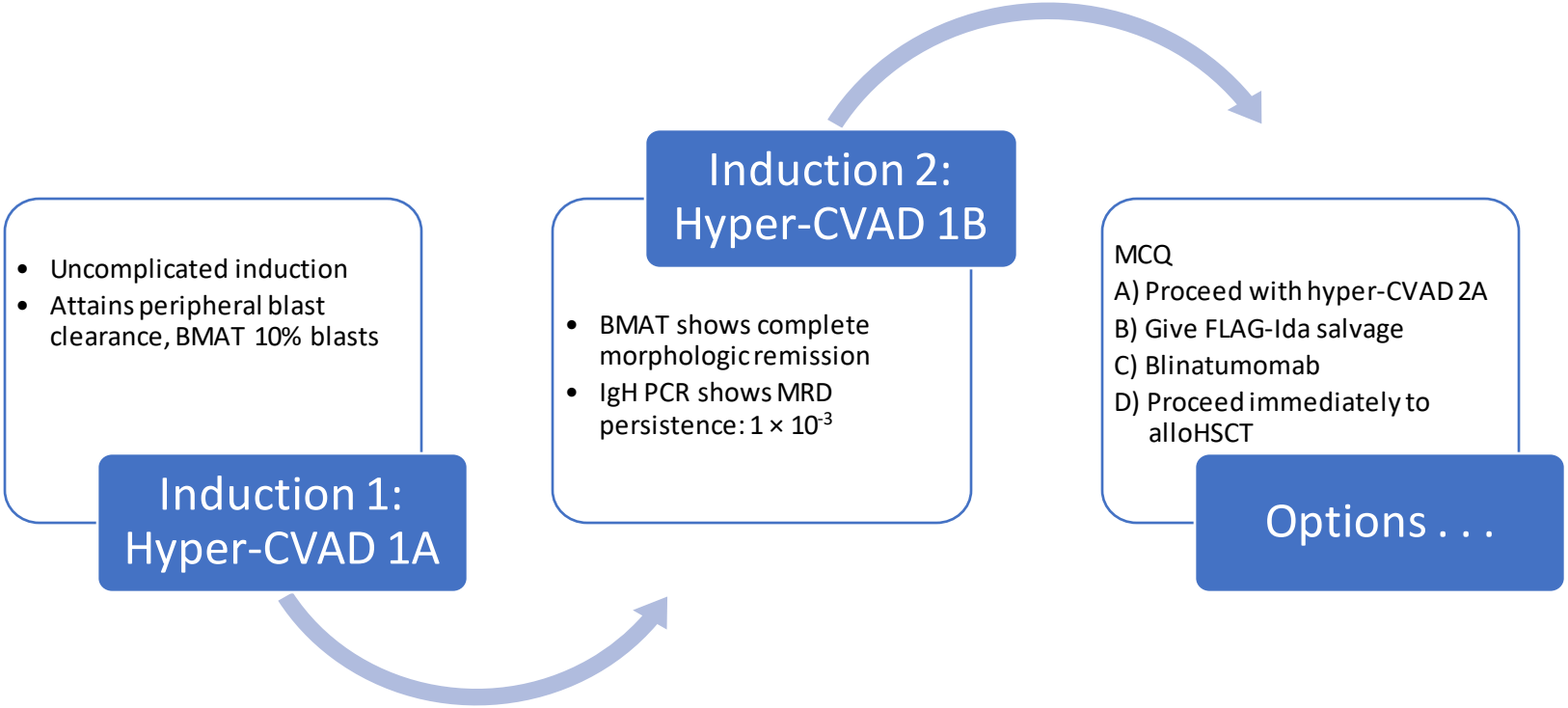
a. Hyper-CVAD

b. Modified BFM induction (pediatric-inspired regimen)

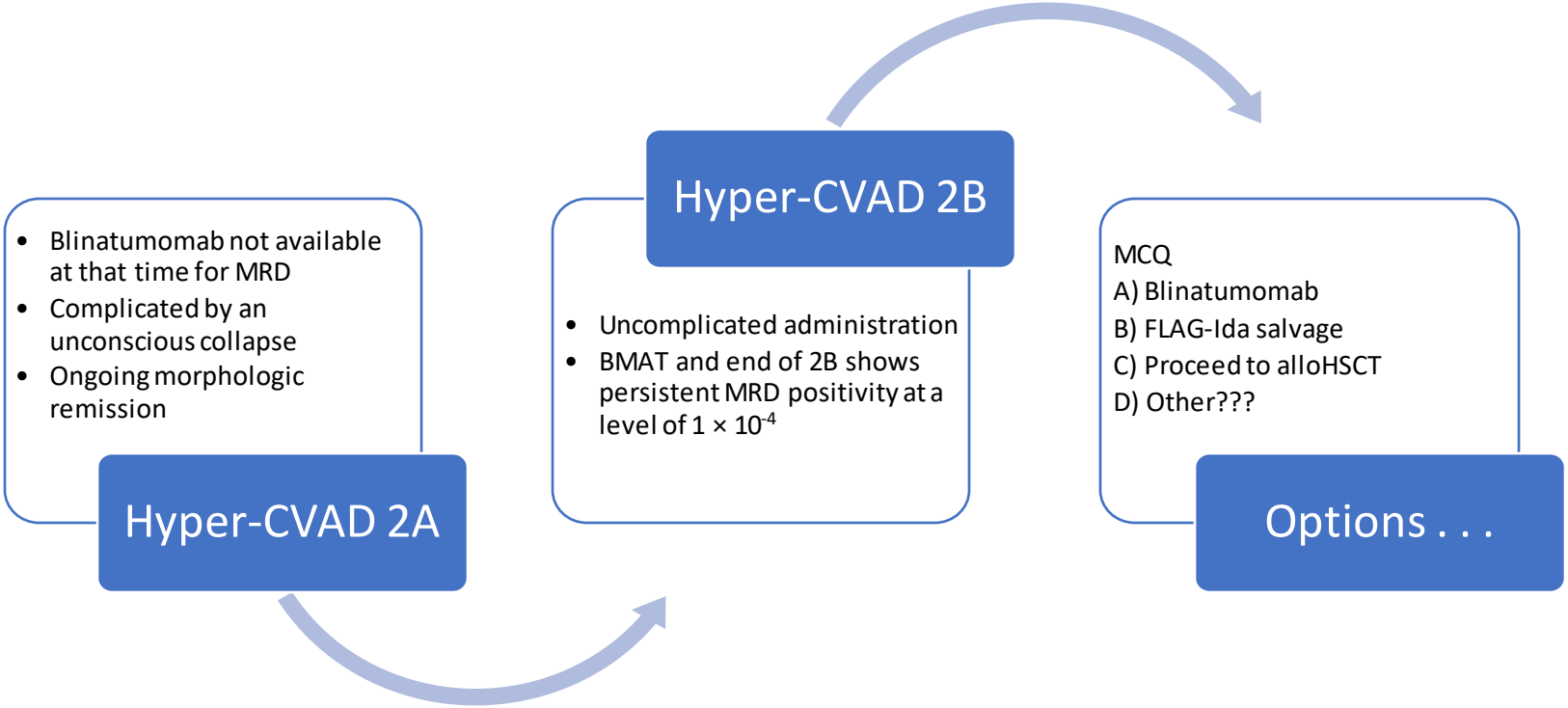
c. LALA-94 (adult regimen)

d. Immediate allogeneic stem cell transplant

Clinical progress



Progress continues . . .



Proceeded to alloHSCT

- Received a myeloablative (Cy-TBI) conditioned alloHSCT from sibling donor
- D+30 BMAT: MRD-negative remission
- D+90 BMAT: ongoing MRD-negative remission

- **So, a happy ending, right?**

All good things must come to an end

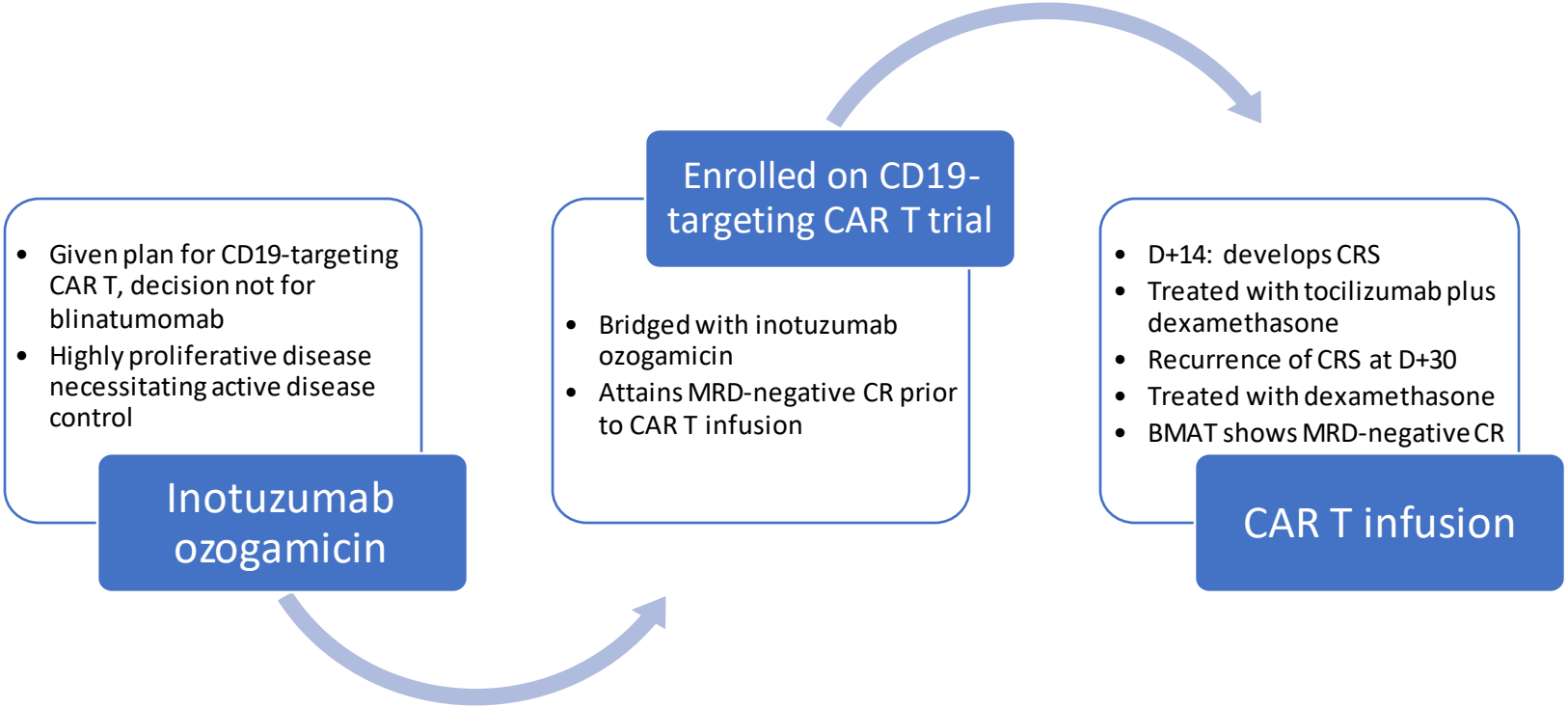
Admitted 12 months posttransplant	Initial therapy
• High white cell count • Recurrence of B symptoms • Bone marrow aspirate confirms relapsed B-ALL	• Admitted to hospital • Received dexamethasone and vincristine to control peripheral blasts

Question 1

Therapeutic options?

A) Blinatumomab
B) Inotuzumab ozogamicin
C) FLAG-Ida
D) Venetoclax-navitoclax
E) CAR T

Therapy continues . . .



6-months post-CAR T . . .

Presents for routine follow-up	Frank discussions with patient
• Blasts in peripheral blood • Bone marrow biopsy confirms relapsed B-ALL • Flow shows persistent CD19+ expression	• Outcome likely to be poor • Any therapy at this stage is almost certainly palliative • He is keen to have whatever therapy he can

Question 2

Treatment?
A) Second allograft B) Blinatumomab C) Inotuzumab ozogamicin D) FLAG-Ida salvage E) Venetoclax-navitoclax F) Others???

Commenced on blinatumomab plus DLI

- Commences first cycle of blinatumomab
  - Attains a morphologic complete remission
  - MRD positive 1×10^{-4}
- Given first cycle of sequential DLI – no GVHD
- Second cycle of blinatumomab
  - MRD negative
- Given second cycle of sequential DLI – develops cutaneous GVHD
- Completes 5 cycles of blinatumomab

Outcome . . . so far

- Now 4 years post-completion of blinatumomab-DLI
  - Monitoring for 2 years with 3-monthly bone marrow biopsies plus MRD testing → remained MRD negative throughout
  - Last review 3 weeks ago
    - Well
    - Back at work
    - Normal blood counts
    - No cGVHD

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Case 2: AYA ALL

Koichi Takahashi

MD Anderson Cancer Center, Houston, TX, USA

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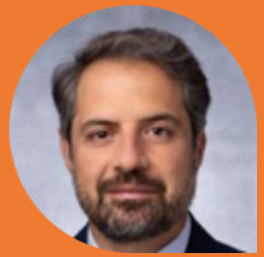
ALL case-based panel discussion

Moderator: Elias Jabbour



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BREAK

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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

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Therapeutic approaches in high-risk and frail AML patients

Naval Daver

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Q&A

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Global Leukemia Academy

Current approach to maintenance strategies in ALL and AML

Jae Park

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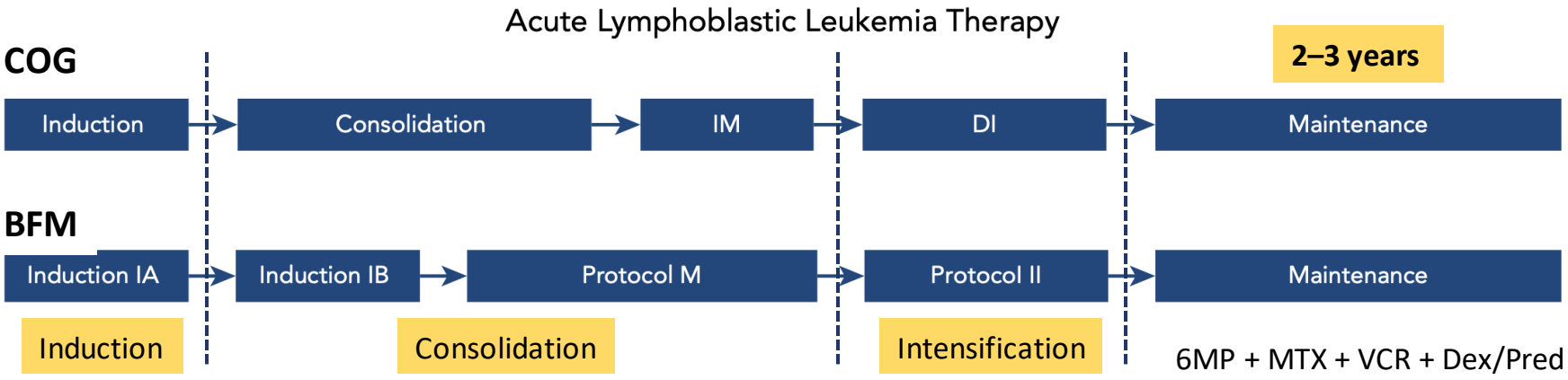
Current Approaches to Maintenance Strategies in ALL

Jae H. Park, MD
Associate Attending Physician
Director, Adult ALL Clinical Program
Chief, Cellular Therapy Service
Memorial Sloan Kettering Cancer Center

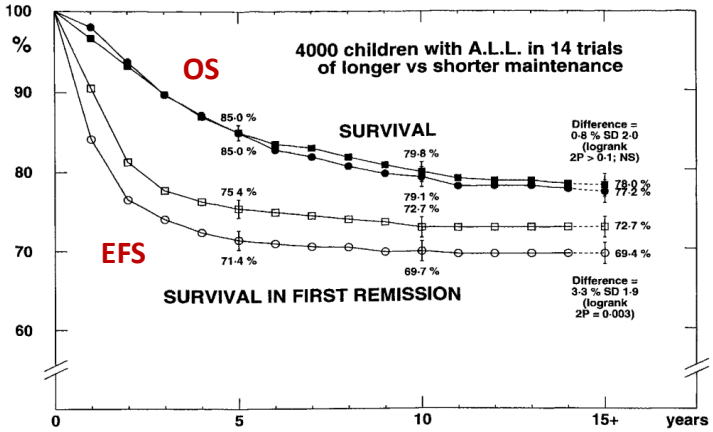
Memorial Sloan Kettering Cancer Center™

Overall Treatment Approach in ALL



Teachey D, et al. *Blood.* 2021;137:168-177.

Impact of Maintenance Duration on Clinical Outcome in Pediatric/AYA ALL



Deaths/person–years														
Longer	51/1521	52/1457	53/1377	41/1274	26/1113	15/913	5/719	8/548	5/407	4/326	3/285	1/252	0/218	1/177	1/456
Shorter	30/1550	66/1487	61/1395	38/1300	29/1139	24/922	8/717	8/520	5/395	2/321	4/278	0/249	0/216	1/180	2/449
Events/person–years															
Longer	144/1465	142/1315	54/1188	20/1105	12/967	5/794	4/630	3/479	2/359	3/285	0/248	0/219	0/187	0/153	0/401
Shorter	248/1431	115/1239	38/1142	25/1068	13/935	5/762	4/598	1/439	3/340	0/274	1/235	0/210	0/183	0/153	0/384

Longer duration a/w improved EFS but no OS benefit

Cooperative group and y	Length of therapy, y	Sex-based difference in therapy length	Outcome (5-y EFS)		
			Girls	Boys	Statistically significant difference
AIEOP-BFM 2000-2006[76],*	2 from diagnosis	No	59.1% ± 6.4% (HR)	43.5% ± 5.3% (HR)	Not reported
			80.7% ± 1.7% (IR)	74.9% ± 1.8% (IR)	
			92.3% ± 1.3% (SR)	92.3% ± 1.3% (SR)	
COG 2000-2005[1],†	2-3 from start IM	Yes	Hazard ratio (girls vs boys), 0.83 (95% CI, 0.77-0.90)		$P < .001$
DCOG 2004-2012[77],‡	2 from diagnosis	No	89.2% ± 1.7%	85.3% ± 1.7%	N/S in univariable analysis
DFCI 2005-2010[78],§	2 from EOI	No	87% (95% CI, 83%-91%)	86% (95% CI, 82%-89%)	N/S in multivariable analysis
MRC 2003-2011[79,80],‖	2-3 from start IM	Yes	Hazarc ratio (girls vs boys), 0.78 (95% CI, 0.54-1.13)		N/S in multivariable analysis
NOPHO 2008-2014[81],¶	2-2.5 from diagnosis	No	84% ± 1%	84% ± 2%	N/S in univariable analysis
SJCRH 2007-2017[82],#	2.5 from diagnosis	No	89.2% ± 4.9%	87.6% ± 4.3%	N/S in univariable analysis

- Historically, longer duration of maintenance for boys vs girls
  - But recent data confirm no survival benefit with longer maintenance in boys

Childhood ALL Collaborative Group. *Lancet*. 1996;347:1783-1788.

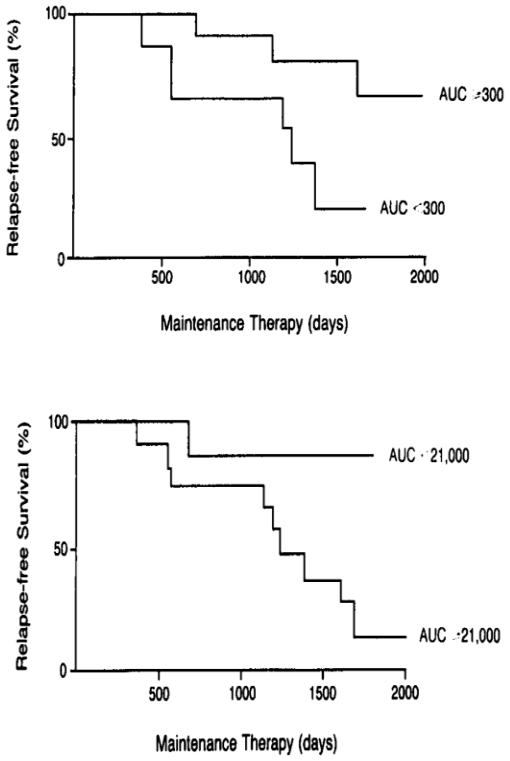
Teachey D, et al. *Blood.* 2021;137:168-177.

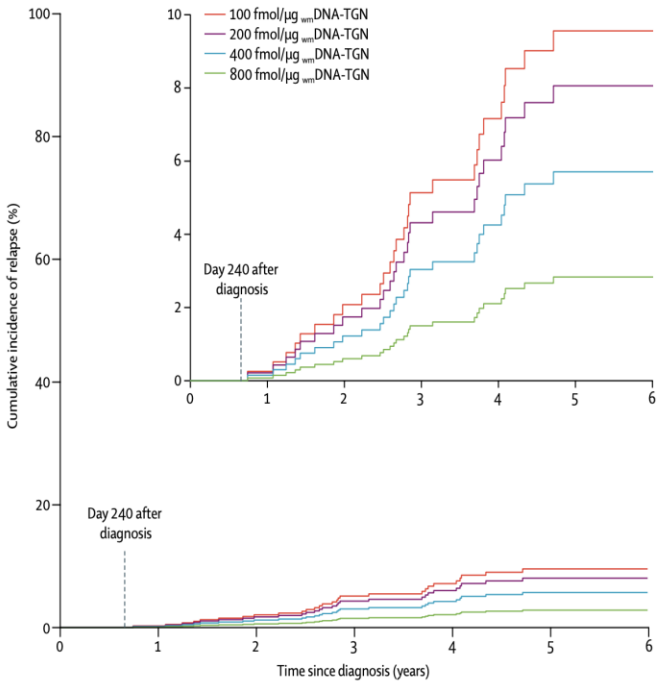
Equal Length of Maintenance Therapy for Boys and Girls in Updated Pediatric/AYA ALL Studies

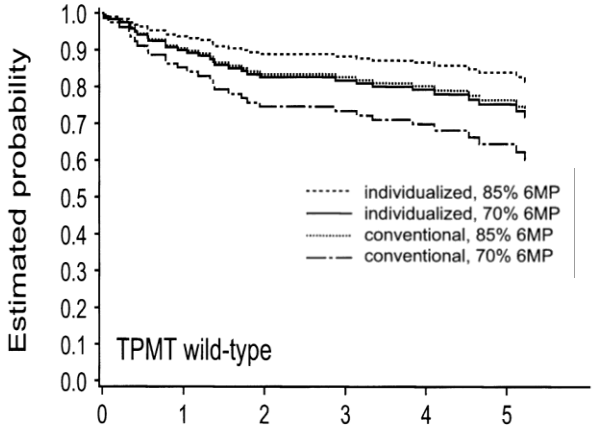
Cooperative group	Longer therapy for boys than girls in current generation of clinical trials	Last year that boys were treated longer than girls in clinical trials*	Total therapy duration in current generation of clinical trials, y
AIEOP†	No	Never	2 from diagnosis
BFM†	No	1999	2 from diagnosis
BSPHO/CLCG-EORTC‡	No	Never	2 from EOI
COG	No	2019	2 from start IM1
COALL‡	No	Never	2 from EOI
DCOG‡	No	Never	2 from EOI
DFCI	No	1991	2 from EOI
INS†	No	Never	2 from diagnosis
JCCLSG	No	Never	2 or 3 from diagnosis§
MRC‡	No	2020‖	2 from EOI‖
NOPHO‡	No	Never	2 from EOI
SFCE/FRALLE‡	No	Never	2-2.5 from diagnosis¶
SJCRH	No	2007	2.5 from diagnosis
TCCSG	No	Never	2 or 3 from diagnosis#
TPOG	Yes, SR and HR B-ALL only	Current	1.5 to ~3 from diagnosis**

Teachey D, et al. *Blood.* 2021;137:168-177.

Drug Exposure of 6MP and MTX Is Associated With Relapse Risk





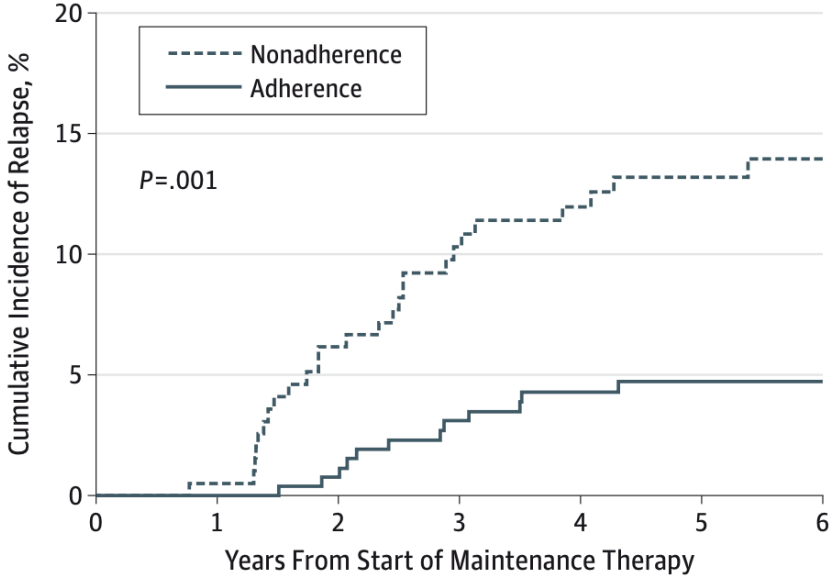


Koren G, et al. *N Engl J Med.* 1990;323:17-21.

Nielsen S, et al. *Lancet Oncol.* 2017;18:515-524.

Relling M, et al. *Blood.* 1999;93:2817-2823.

Adherence to Maintenance Therapy and Relapse Risk in Children With ALL



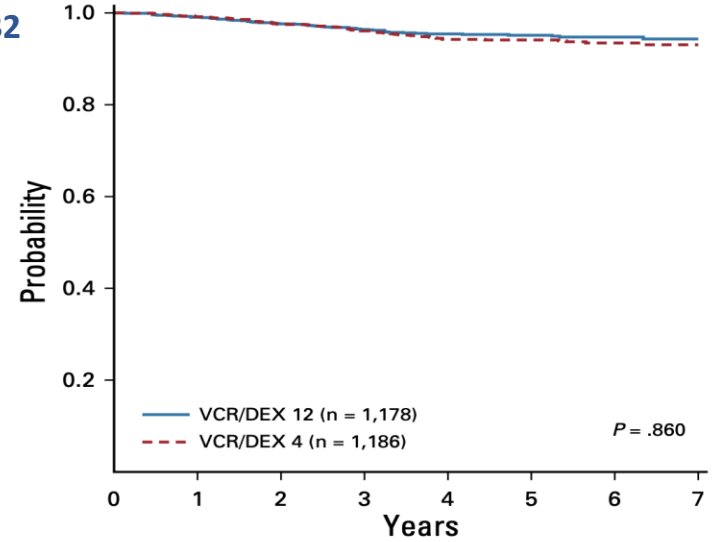
No. at risk at each year						
Adherence	272	267	259	244	222	203
Nonadherence	198	195	182	166	146	124

Adherence is defined as a 95% or greater adherence rate; nonadherence is an adherence rate lower than 95%.

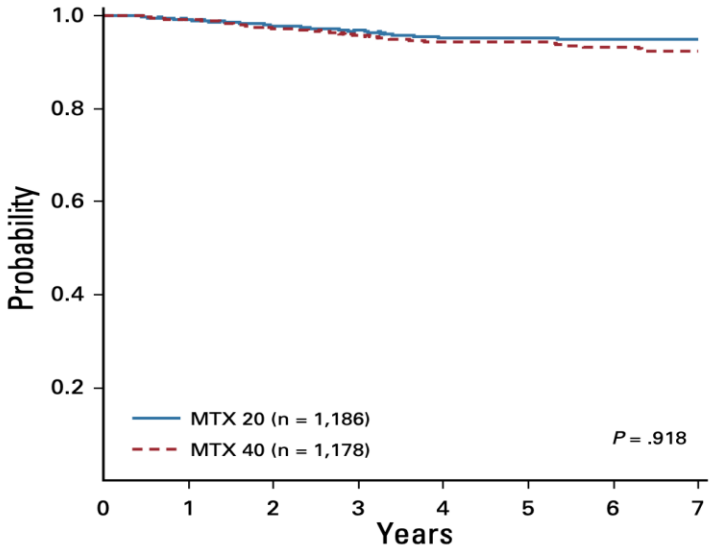
Bhatia S, et al. *JAMA Oncol.* 2015;1:287-295.

Reduction of VCR and DEX Dose Intensity in Maintenance Therapy for Pediatric/AYA ALL

AALL0932



VCR/DEX 4: At Risk	1,186	1,175	1,150	1,078	793	537	294	59
Events	0	10	19	17	18	1	3	1
VCR/DEX 12: At Risk	1,178	1,160	1,138	1,075	780	532	286	60
Events	0	11	17	14	10	2	2	1

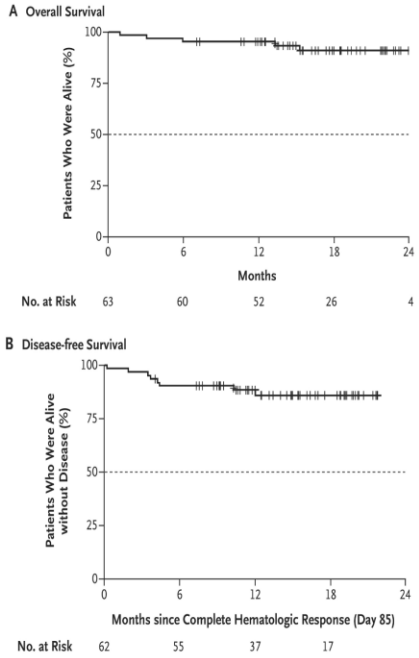


MTX 20: At Risk	1,186	1,170	1,151	1,076	792	546	306	63
Events	0	10	16	13	13	2	1	0
MTX 40: At Risk	1,178	1,165	1,137	1,077	781	523	274	56
Events	0	11	20	18	15	1	4	2

Angiolillo A, et al. *J Clin Oncol.* 2021;39:1437-1447.

Varying Maintenance Duration in Frontline Ph+ B-ALL

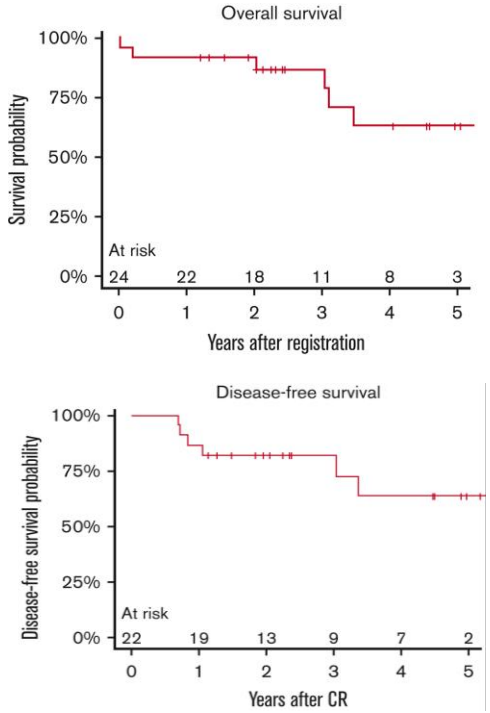
DAS + Blinatumomab (D-ALBA)



DAS 140 mg/d × 12 mo

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

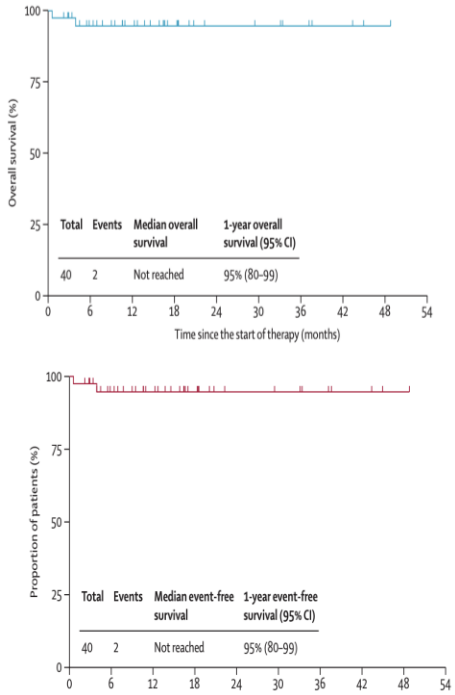
DAS + Blinatumomab (SWOG)



Pred 60 mg/m^2/d × 5d q4 wk × 18 + DAS 140 mg/d indefinitely

Advani A, et al. *Blood Adv*. 2023;7:1279-1285.

PON + Blinatumomab



PON 15 mg/d for at least 5 years

Jabbour E, et al. *Lancet Haematol.* 202310:e24-e34.

Summary

- Maintenance therapy remains an integral part of multiagent chemotherapy-based frontline therapy in ALL
  - Recent updated trials with intensified frontline regimens (risk-based dose intensification) include equal lengths of maintenance therapy for boys and girls, ~2 years
  - Adequate drug exposure and careful monitoring and adjustment of 6MP/MTX are important to maximize the potential benefit of maintenance therapy
  - Adherence to maintenance therapy is critical for long-term success of treatment
- Reduction of maintenance intensity appears feasible with preserved efficacy and less long-term toxicities in favorable-risk patients
- With incorporation of immunotherapy into front line (eg, blinatumomab, inotuzumab, and CD19 CAR T cells) and improved tools of identifying high-risk patients for relapse (NGS MRD), it is likely we can reduce the intensity and duration of maintenance therapy, but more studies are needed

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Q&A

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Long-term safety considerations in AML

Shaun Fleming

APTITUDE HEALTH

Disclosures

Consultancy/advisory board participation/honoraria

- Amgen
- Novartis
- Servier
- AbbVie
- Pfizer
- Gilead
- BMS

Research grants

- Amgen

The Risks Faced by Patients With AML Are Dynamic

Remission induction and consolidative therapy

- Acute treatment toxicity
- Infection
- Disease relapse

Allogeneic stem cell transplantation

- Treatment-related mortality
- Graft vs host disease
- Infection
- Graft failure

First 2–5 years

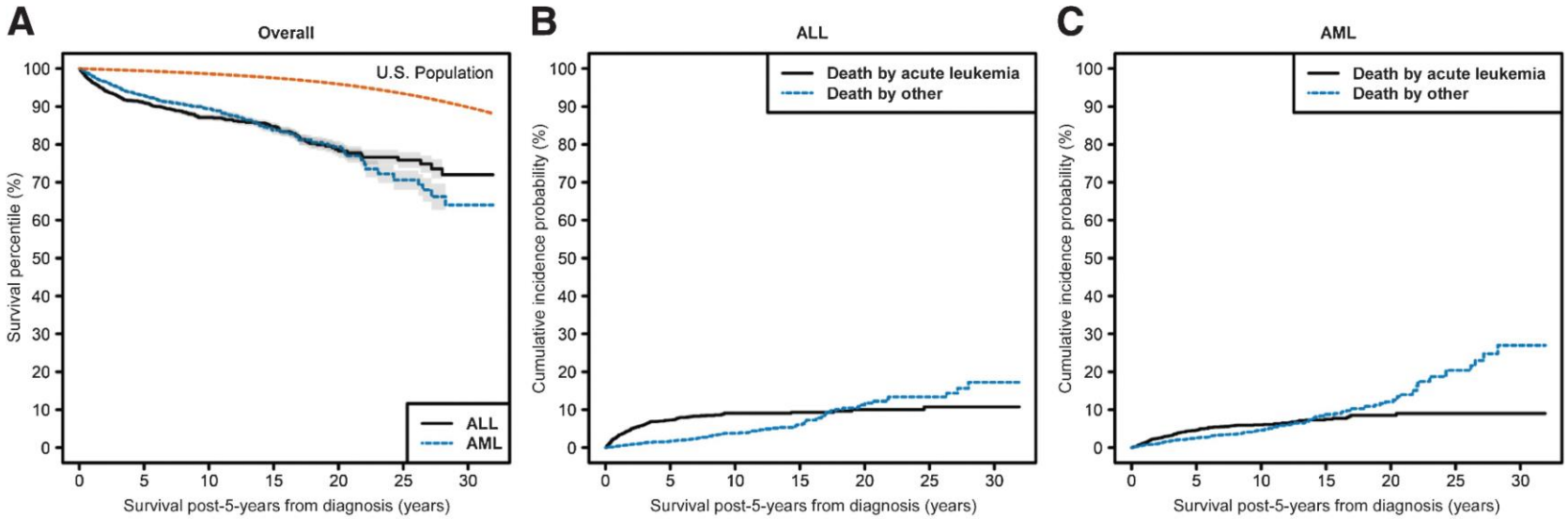
- Disease relapse
- Residual acute toxicity

Long term

- Late effects
- Effects of ageing
- Secondary malignancies

A Pretty Stark Reality

- Even in younger adults who are survivors of acute leukemia, as adolescents or young adults, survival is poorer than age-matched controls



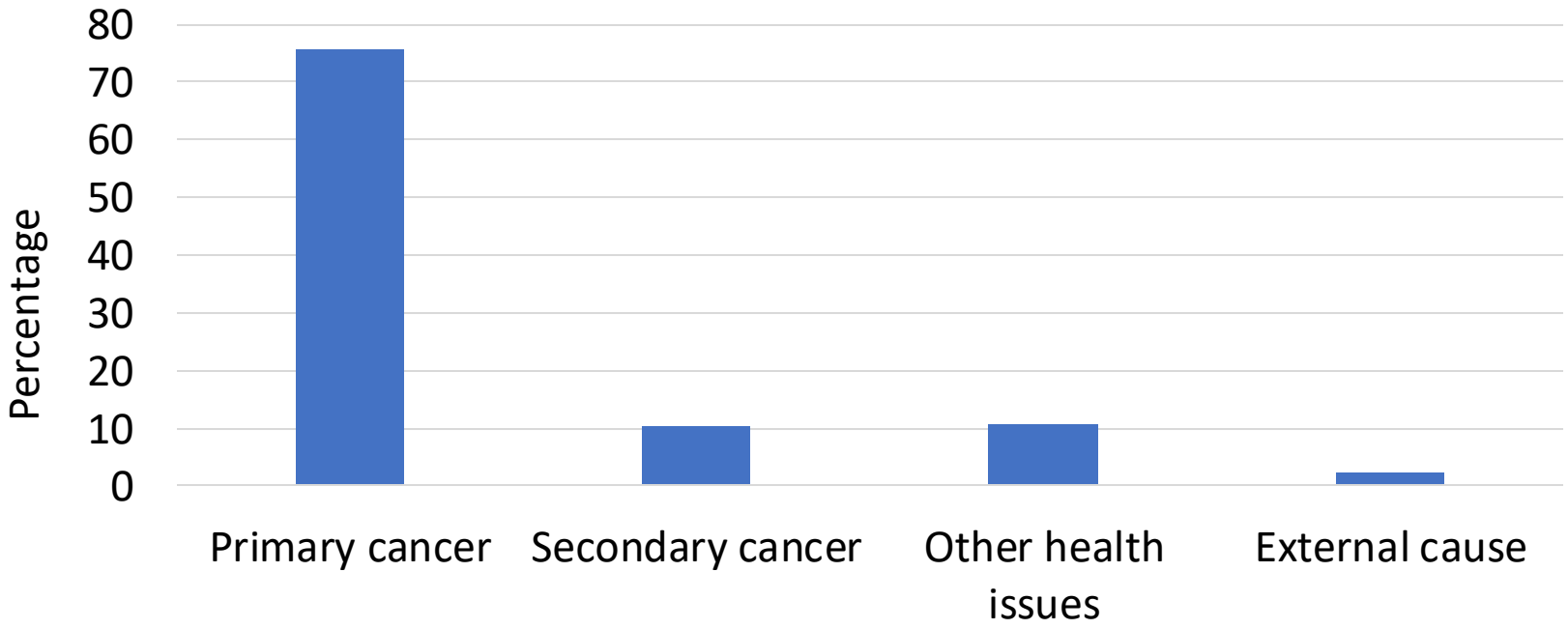
Berkman AM, et al. *Cancer Epidemiol Biomarkers Prev*. 2022;31:1176-1184.

How Long Does the Risk of Early Death Persist?

- In younger patients, acute leukemia remains the most significant cause of death until 2–3 decades after diagnosis[1]
  - The older the patient group, the earlier the impact of secondary events
  - However, older patients have poorer disease-related outcomes
- Survivors of adolescent and young adult cancer have a risk of death 10.4-fold that of aged-match controls[2]
  - This risk persists for up to 20 years following diagnosis

1. Berkman AM, et al. *Cancer Epidemiol Biomarkers Prev*. 2022;31:1176-1184; 2. Armenian SH, et al. *Cancer*. 2020;126:2305-2316.

What Are the Causes of Death for “Survivors” of Cancer?



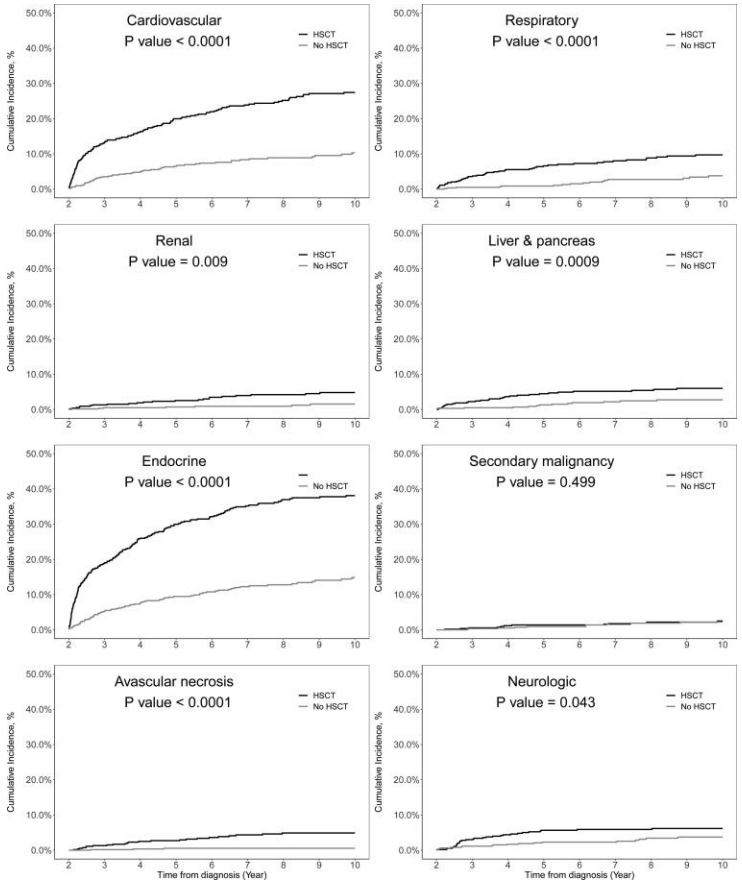
Armenian SH, et al. *Cancer*. 2020;126:2305-2316.

Survivors of AML Have Poorer Psychosocial Outcomes Compared With Their Peers

- Significantly higher rates of poor memory (RR 2.15), emotional regulation (2.08), and task efficiency (1.86)
- Worse health-related quality-of-life outcomes in physical health (RR 2.76), general health (2.89), social functioning (1.78), mental health (1.66), and bodily pain (1.31)
- Lower educational attainment and less likely to complete college (RR 1.15)
- Less likely to be in full-time work or school (RR 1.41), with an average loss of income of $20,000 annually
- Less likely to be married or partnered (RR 1.33)

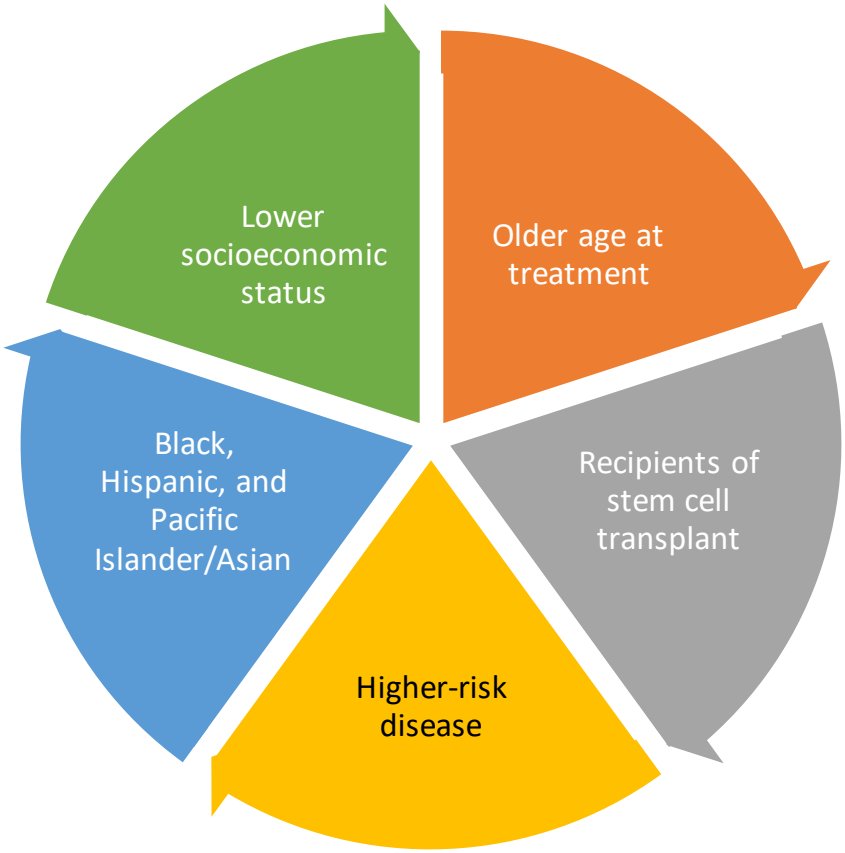
Stefanski KJ, et al. *J Natl Cancer Inst.* 2021;113:481-495.

What Particular Health Conditions in Long-Term Survivors of AML?



Abrahão R, et al. *Int J Epidemiol*. 2021;50:663-674.

Who Is Most at Risk for These Complications?



Most data on this are from the US, and there are a lack of data for our region!

Abrahão R, et al. *Int J Epidemiol.* 2021;50:663-674.

What Are We Doing at Alfred Health?

- IMPROVE study and clinic
  - Led by our leukemia nurse practitioner and allied health staff; enrolling all patients with nontransplant eligible acute leukemia 6 months from finishing intensive chemotherapy (including ALL on maintenance)
  - Evaluation of cardiovascular risk, osteoporosis risk, second cancer screening, quality of life, psychosocial outcomes, endocrine screening
  - Early intervention on physical rehabilitation and reconditioning
  - Referral for specialist management of identified health outcomes and risk factors
  - Associated tissue banking and biomarker research
- Study is coming to an end, and we plan to identify which factors are important to plan sustainment

The Long Term for Survivors of AML

- It is important to remember that AML remains a major cause of death for patients for many years following their treatment
  - Better treatments will ultimately reduce this burden
- Patients have a higher risk of poor health-related outcomes
  - Early identification and treatment of these may be important
  - However, how do we measure the effectiveness of these interventions?
- Balancing the competing demands of highly effective therapies with longer-term functioning
- The longer-term psychosocial impacts of AML need consideration
- There are a lack of local data on this to help guide what we do in our region

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Q&A

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

Shaun Fleming and Junichiro Yuda

Moderator: Naval Daver

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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 within the concept of locations 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

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ARS Questions

Naval Daver

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 + 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

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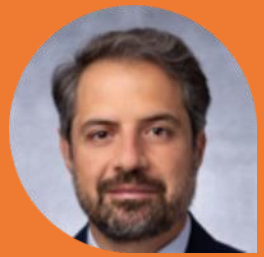
Session close

Elias Jabbour and Naval Daver



APTITUDE HEALTH

Thank you!

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

THANK YOU!

Day 2: Virtual Plenary Sessions

Time (UTC+8)	Title	Speaker
8.00 AM – 8.10 AM	Welcome to Day 2	Elias Jabbour
8.10 AM – 8.30 AM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
8.30 AM – 8.50 AM	Current treatment options for relapsed AML in adult and elderly patients	Junichiro Yuda
8.50 AM – 9.20 AM	Case-based panel discussion • Case AML (10 min) – Rithin Nedumannil • Case ALL, high risk or elderly (10 min) – Huai-Hsuan Huang • Discussion (10 min) – panelists: all faculty	Naval Daver and all faculty
9.20 AM – 9.30 AM	Break	
9.30 AM – 9.50 AM	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	Daniel DeAngelo
9.50 AM – 10.20 AM	Current and future role of transplantation in acute leukemias • Jae Park (in general) (10 min) • Shaun Fleming (in the JAPAC region) (10 min) • Discussion (10 min)	Jae Park/Shaun Fleming
10.20 AM – 10.50 AM	Panel discussion: How treatment in first line influences further approaches in ALL and AML • Will CAR T and bispecifics change the landscape? • Role of HSCT – is it still confirmed? • What does the future look like?	Elias Jabbour and all faculty
10.50 AM – 11.00 AM	Session close	Elias Jabbour and Naval Daver

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SEE YOU TOMORROW!

10–11 September 2023 – Japan and Asia-Pacific Region

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Please join the next meeting in our regional series