Global Leukemia Academy

# GLOBAL LEUKEMIA ACADEMY

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

16–17 November 2023 – Europe

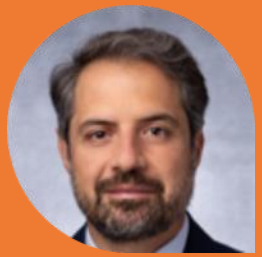
Meeting sponsors AMGEN astellas

APTITUDE HEALTH

Global Leukemia Academy

# Welcome and meeting overview

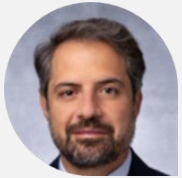
Elias Jabbour



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

**Nicola Gökbuget, MD**
University Hospital Frankfurt
Frankfurt, Germany

**Stephane De Botton, MD, PhD**
Gustave Roussy Cancer Center
Paris, France

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

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

# Objectives of the program

Learn about the latest clinical advances and sequencing considerations for ALL and AML

Understand the role of risk stratification and the clinical usage of MRD on treatment

Gain insight on the management of ALL and AML, including AYA ALL and *FLT3*+ AML

Engage in patient case-based panel discussions

Discuss sequencing strategies for acute leukemias

Explore regional challenges in the treatment of acute leukemias across Europe

# Day 1: Virtual Plenary Sessions

| Time (CET) | Title | Speaker |
|---|---|---|
| 18.00 – 18.10 | Welcome and meeting overview; introduction to the voting system | Elias Jabbour |
| 18.10 – 18.25 | Review of prognostic value of MRD in leukemias (focusing on ALL) | Josep-Maria Ribera |
| 18.25 – 18.40 | Latest achievements in ALL and AML developments | Elias Jabbour |
| 18.40 – 18.55 | 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 | Nicola Gökbuget |
| 18.55 – 19.25 | ALL case-based panel discussion<br>• Case ALL – Jacopo Nanni on behalf of Christina Papayannidis<br>• Case ALL AYA – Fabian Lang<br>• Discussion – panelists: all faculty | Elias Jabbour and all faculty |
| 19.25 – 19.35 | Break | |
| 19.35 – 19.50 | Genetic characterization and risk stratification of AML | Stephane De Botton |
| 19.50 – 20.05 | Therapeutic approaches in high-risk and frail AML patients | Naval Daver |
| 20.05 – 20.20 | Maintenance and time-limited treatment strategies in leukemias (focusing on ALL) | Josep-Maria Ribera |
| 20.20 – 20.50 | Panel discussion: Open questions in ALL and AML – regional specificities<br>• Nicola Gökbuget – Germany<br>• Stephane De Botton – France | Naval Daver and all faculty |
| 20.50 – 21.00 | Session close | Elias Jabbour and Naval Daver |

# Day 2: Virtual Plenary Sessions

| Time (CET) | Title | Speaker |
|---|---|---|
| 18.00 – 18.10 | Welcome to Day 2 | Naval Daver |
| 18.10 – 18.25 | Frontline approaches and the role of genetic variants in ALL – Ph+ and Ph-like | Elias Jabbour |
| 18.25 – 18.45 | Current treatment options for relapsed ALL in adult and elderly patients | Josep-Maria Ribera |
| 18.45 – 19.05 | Current treatment options for relapsed AML in adult and elderly patients | Charles Craddock |
| 19.05 – 19.35 | AML case-based panel discussion<br>• Case AML: young, high risk – Vitor Botafogo<br>• Case AML: elderly – Justin Loke<br>• Discussion – panelists: all faculty | Naval Daver and all faculty |
| 19.35 – 19.45 | Break | |
| 19.45 – 20.05 | Long-term safety considerations for AML and ALL | Stephane De Botton |
| 20.05 – 20.35 | Current and future role of transplantation in acute leukemias (including regional insights)<br>• AML – Charles Craddock<br>• ALL – Nicola Gökbuget<br>• Discussion | Charles Craddock and Nicola Gökbuget |
| 20.35 – 21.05 | Panel discussion: How treatment in first line influences further treatment approaches in ALL and AML<br>• Will CAR T and bispecifics change the landscape?<br>• Role of HSCT – is it still confirmed?<br>• What does the future look like? | Elias Jabbour and all faculty |
| 21.05 – 21.15 | Session close | Elias Jabbour and Naval Daver |

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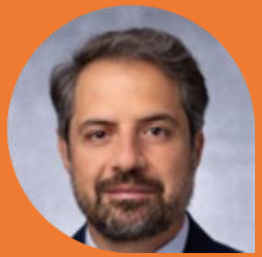
# Introduction to the voting system

Elias Jabbour



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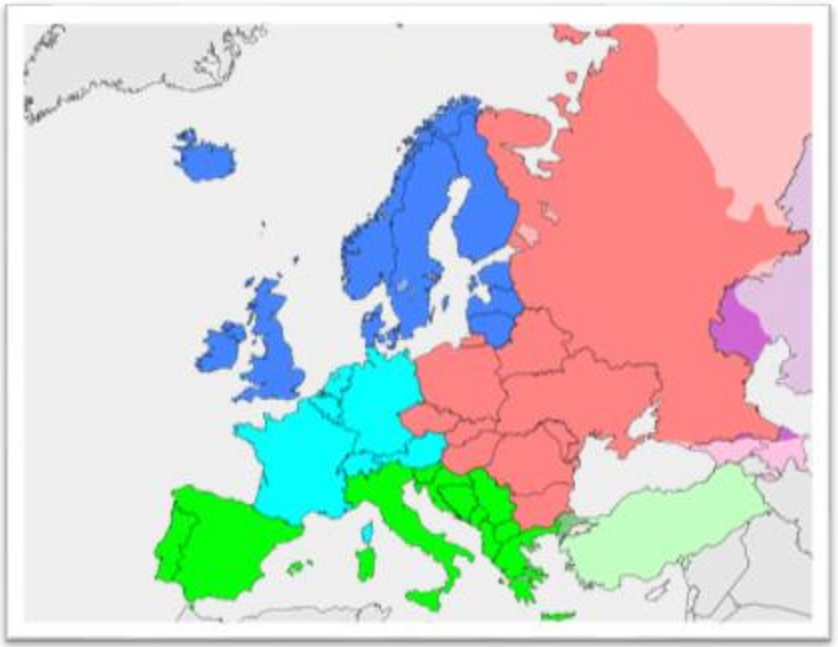
# Question 1

**In which region of Europe do you currently practice?**

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





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

# Question 2

**Which leukemias do you primarily treat?**

A. AML

B. ALL

C. Both

# Question 3

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

A. After induction/consolidation

B. Prior to allogeneic hematopoietic cell transplant

C. After transplant

D. All of the above

# Question 4

**Which of the following is NOT true for treating ALL?**

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

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

C. MRD– CR does not correlate strongly with outcome

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

Instituto de Investigación CONTRA LA LEUCEMIA Josep Carreras

FUNDACIÓN PETHEMA Para el tratamiento de la Leucemia y el Linfoma

ICO Institut Català d'Oncologia Hospital Germans Trias i Pujol

Global Leukemia Academy

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

Josep-Maria Ribera

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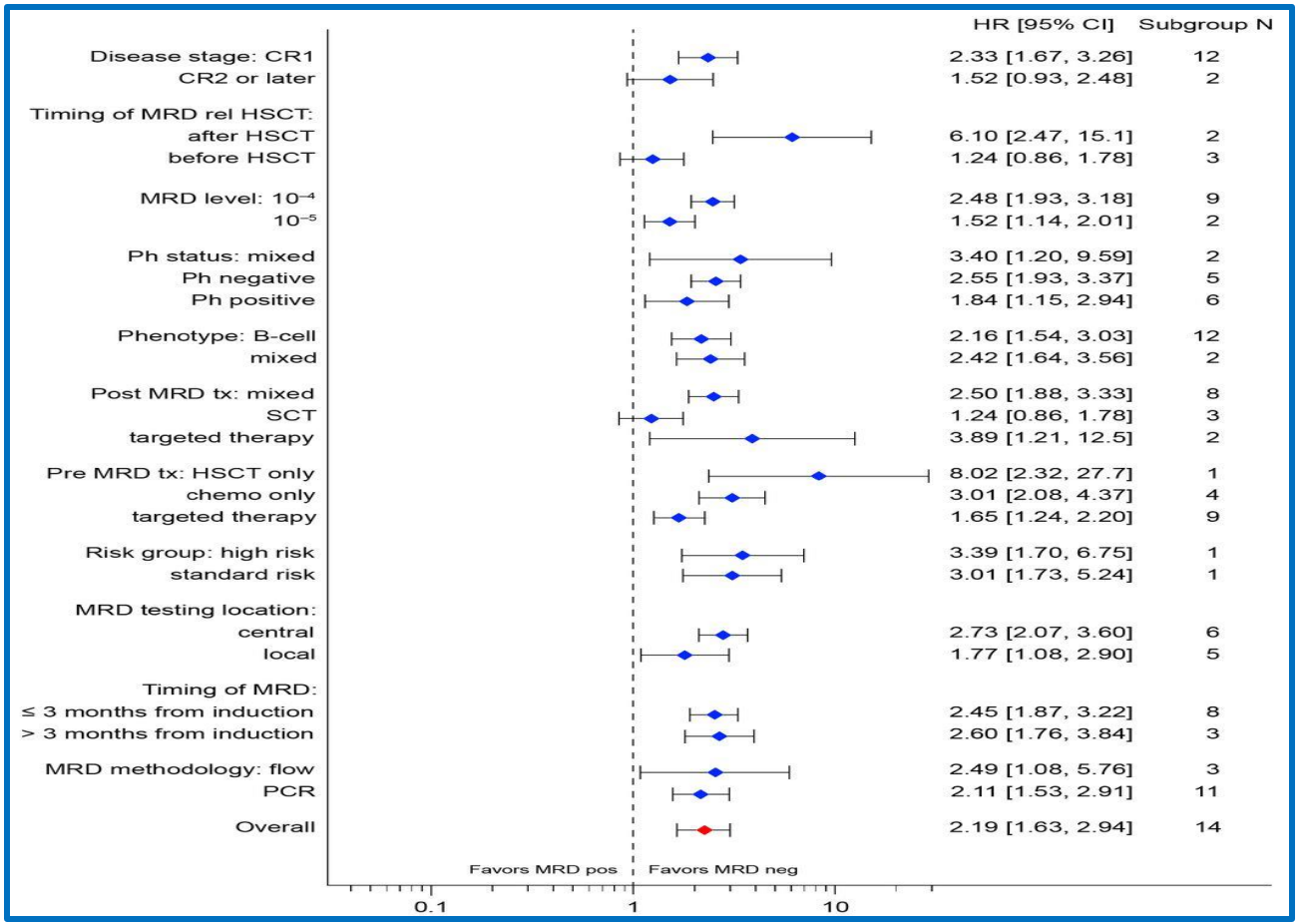
# Disclosures

- 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

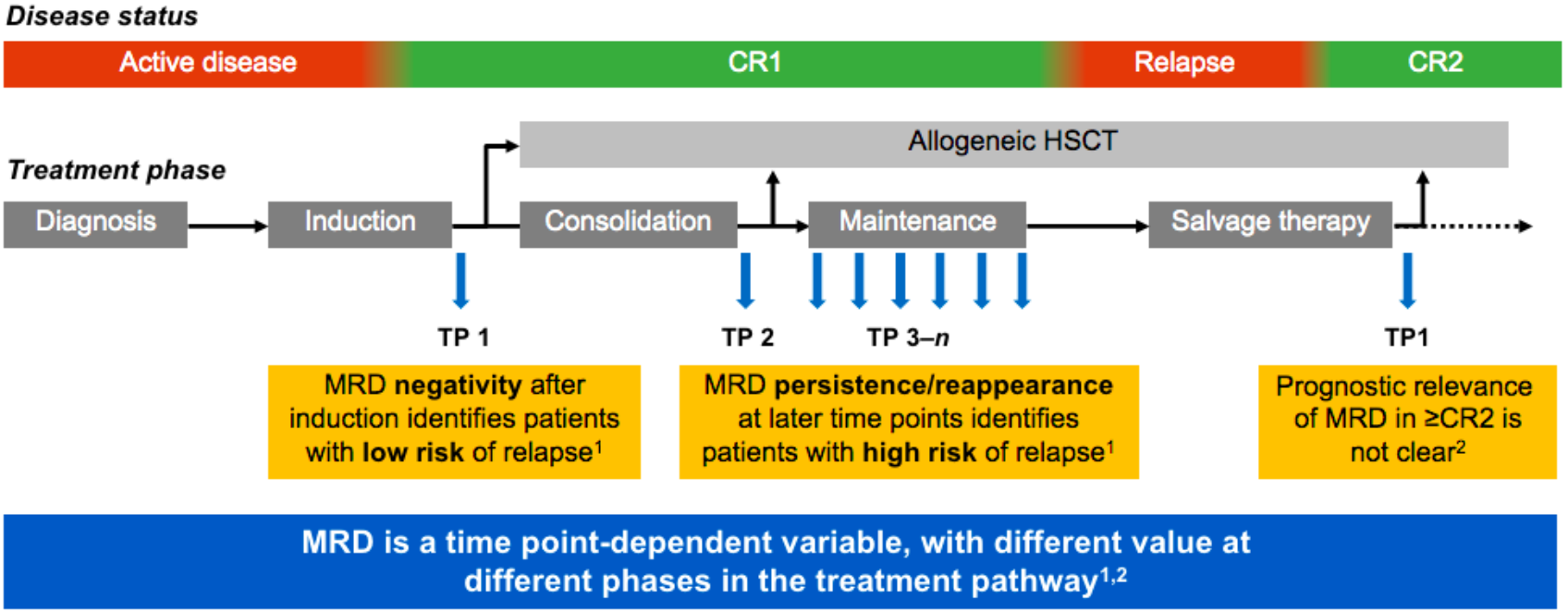
# Prognostic value of MRD in the chemotherapy era

# Prognostic value of MRD in all situations of ALL




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

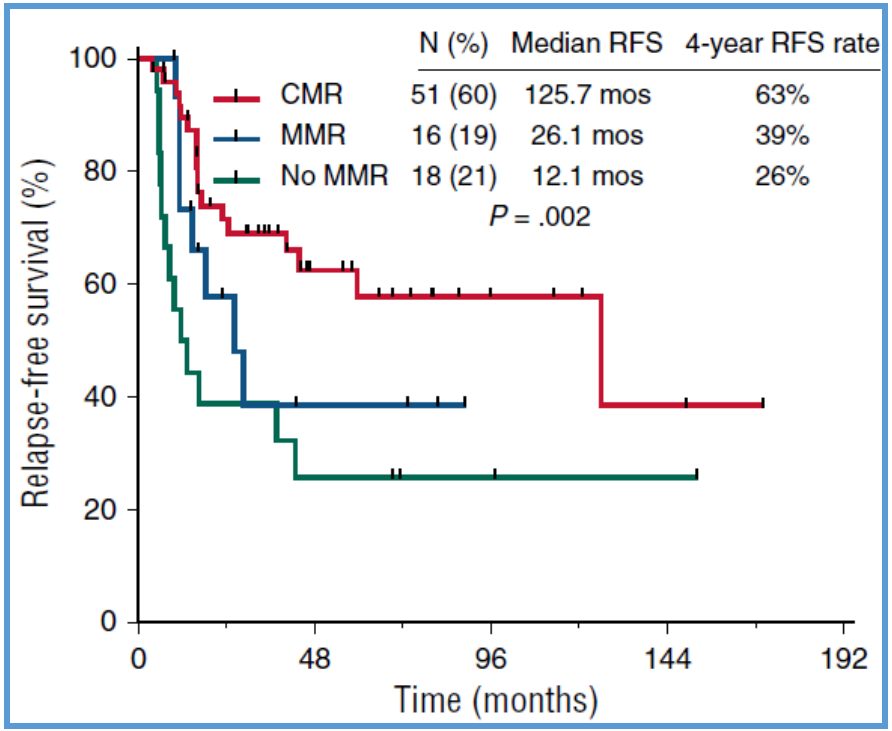
# Timepoint to MRD detection

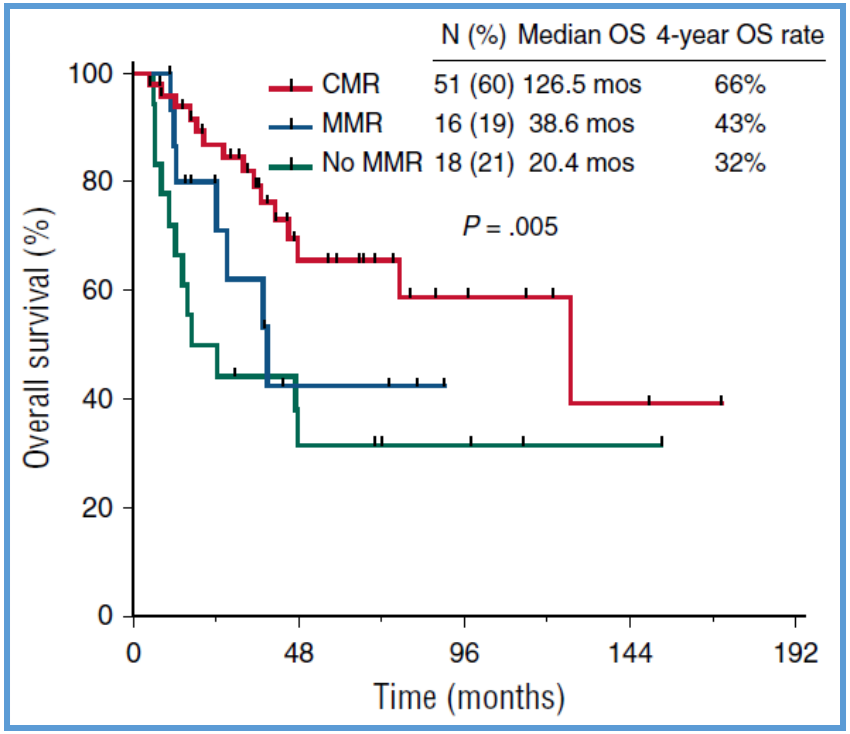



- **Negative** MRD at **TP1**: useful for recognizing patients with **low risk** of relapse
- **Positive** MRD at **TP2**: useful for recognizing patients with **high risk** of relapse

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

# CMR at 3 months: The best prognostic factor in Ph+ ALL

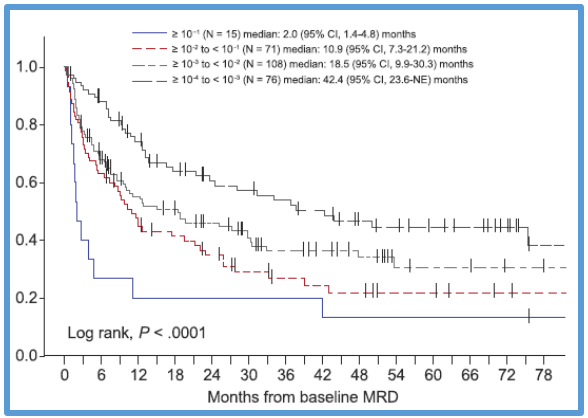


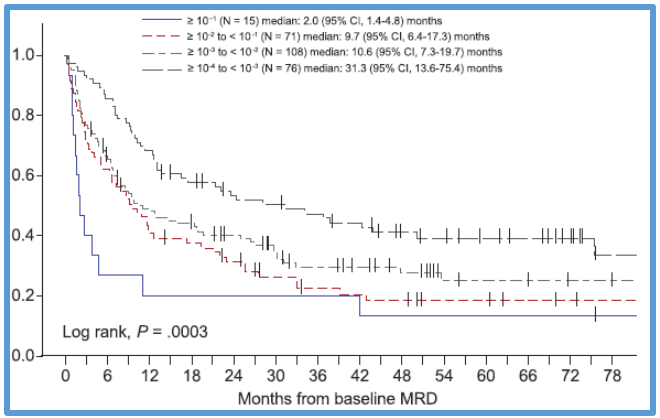



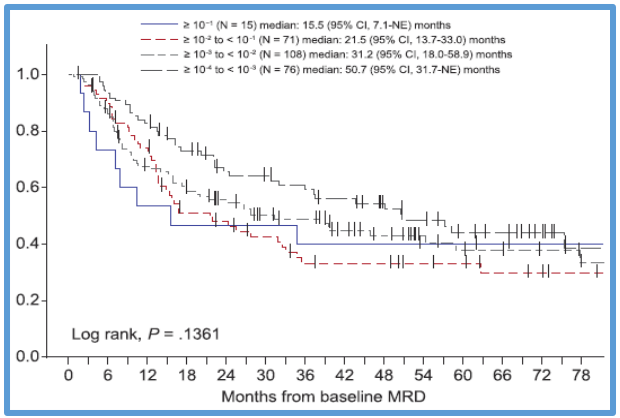

Short NJ, et al. *Blood*. 2016;128:504-507.

# Impact of End-Induction MRD Level on Prognosis in Ph– ALL

## Survey From 7 EU Cooperative Groups




### Duration of Remission

$\geq 10^{-1}$ (N = 15) median 2 months
$\geq 10^{-1}$ to $<10^{-2}$ (N = 71) median 10.9 months
$\geq 10^{-2}$ to $<10^{-3}$ (N = 108) median 18.5 months
$\geq 10^{-3}$ to $<10^{-4}$ (N = 76) median 42.4 months

### RFS

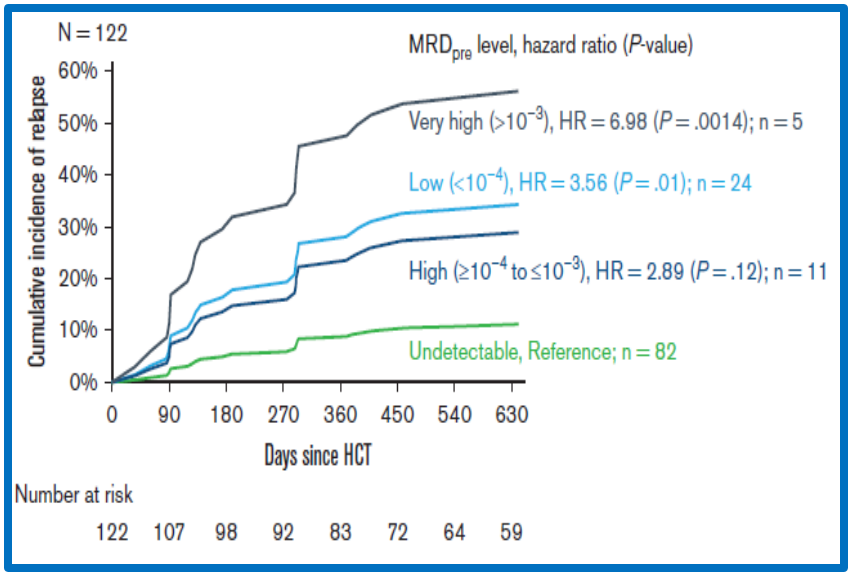
$\geq 10^{-1}$ (N = 15) median 2 months
$\geq 10^{-1}$ to $<10^{-2}$ (N = 71) median 9.7 months
$\geq 10^{-2}$ to $<10^{-3}$ (N = 108) median 10.6 months
$\geq 10^{-3}$ to $<10^{-4}$ (N = 76) median 31.3 months

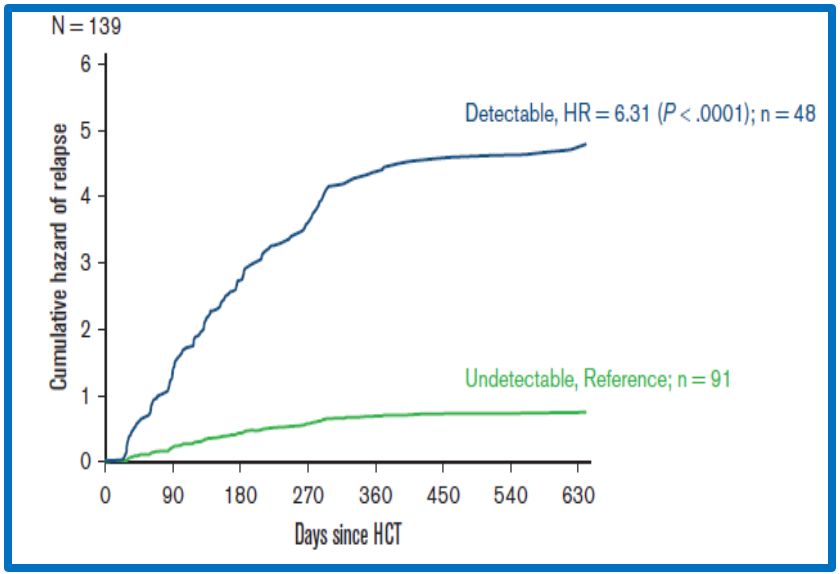
### OS

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

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

# Detectable pre-HSCT MRD, even at level of <$10^{-4}$, and any detectable post-HSCT MRD increase the risk of post-HSCT relapse

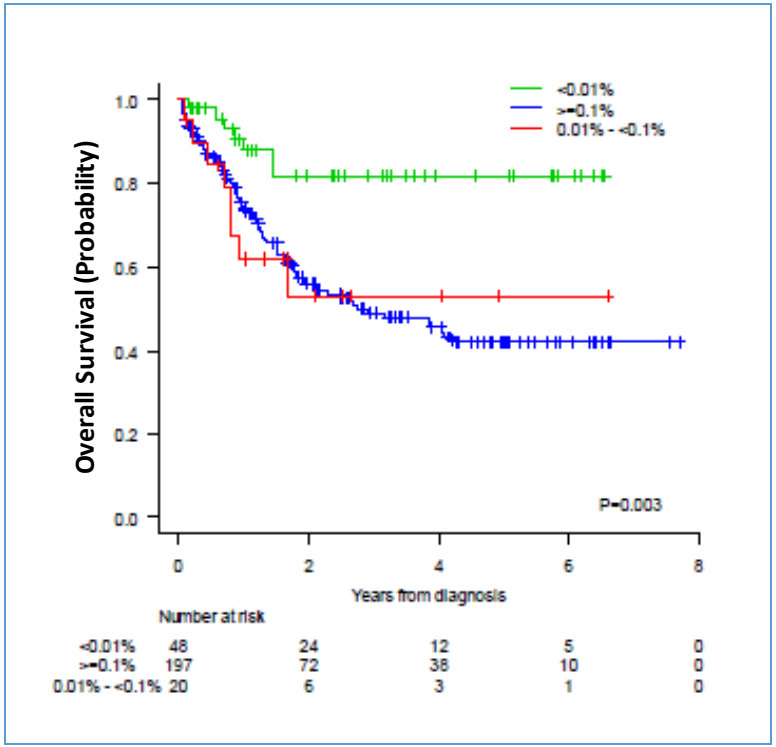


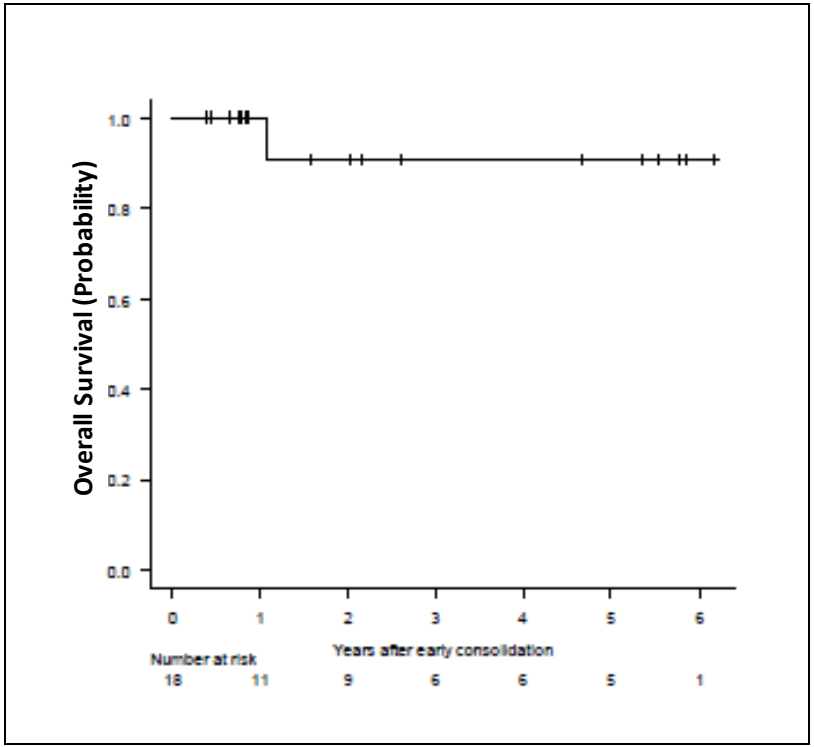

Liang EC, et al. *Blood Adv*. 2023;7:3395-3402.

# Outcomes by MRD centrally assessed by next-generation FCM (sensitivity 2 × $10^{-6}$)

## According to post-induction MRD level

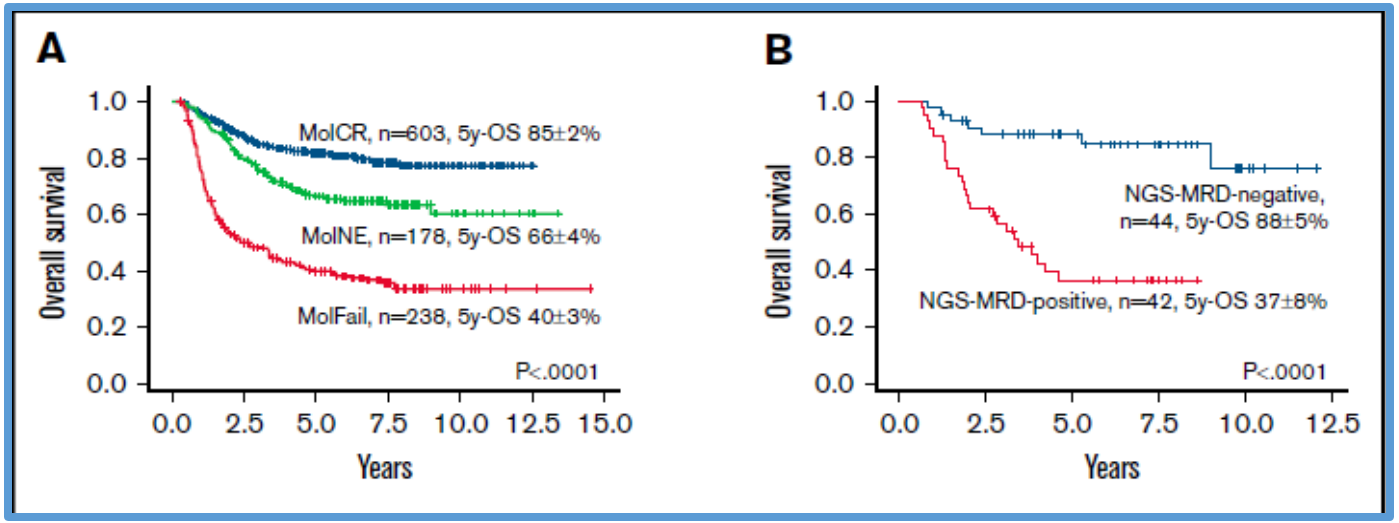



## Patients with MRD <0.01% from d14




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

# End-of-consolidation low-level MRD (RQ-PCR) is refined by NGS

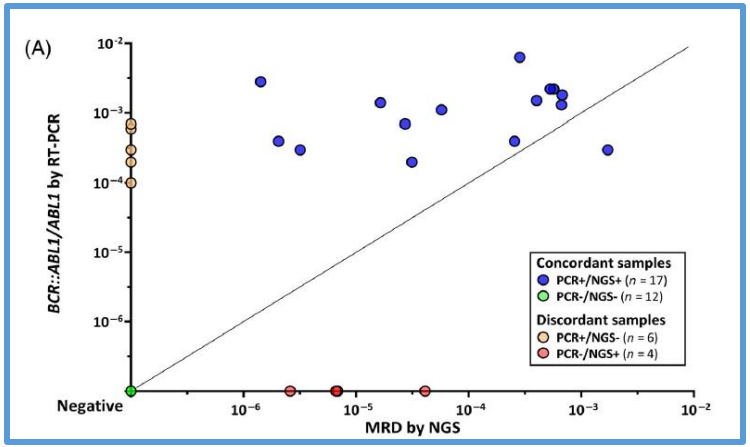


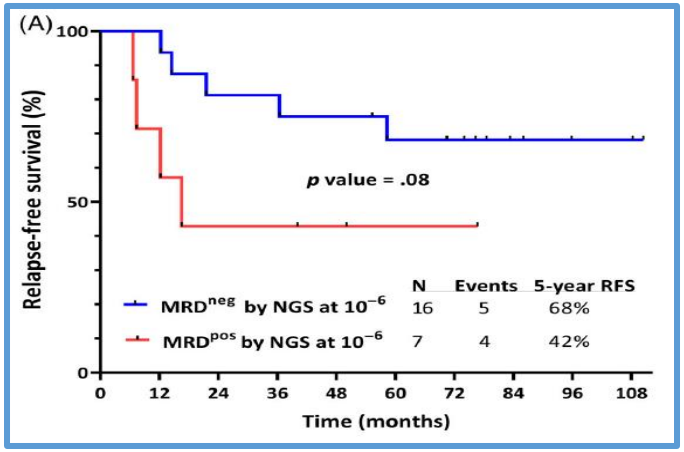

RQ-PCR negativity confirmed by NGS MRD

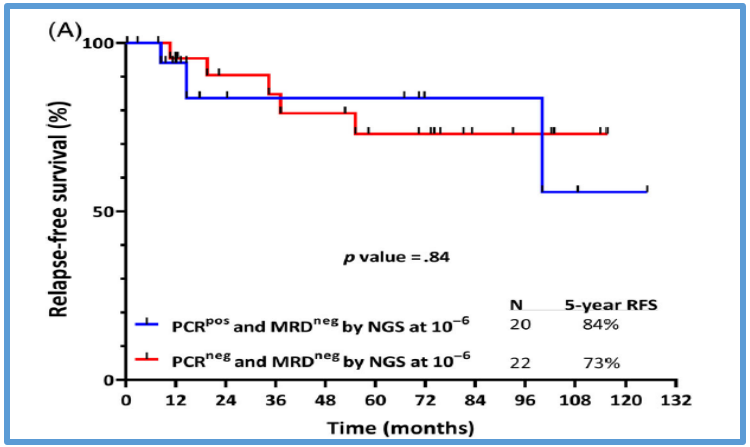
26/67 (39%) of RQ-PCR low-level MRD samples were NGS MRD negative

Kotrová M, et al. *Blood Adv*. 2022;6:3006-3010.

# Ultrasensitive NGS MRD assessment in Ph+ ALL: Prognostic impact and correlation with RT-PCR for *BCR::ABL1*



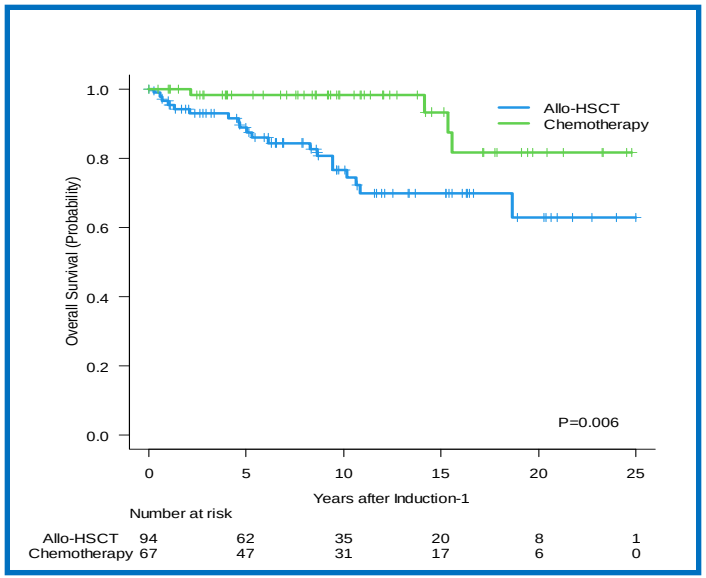



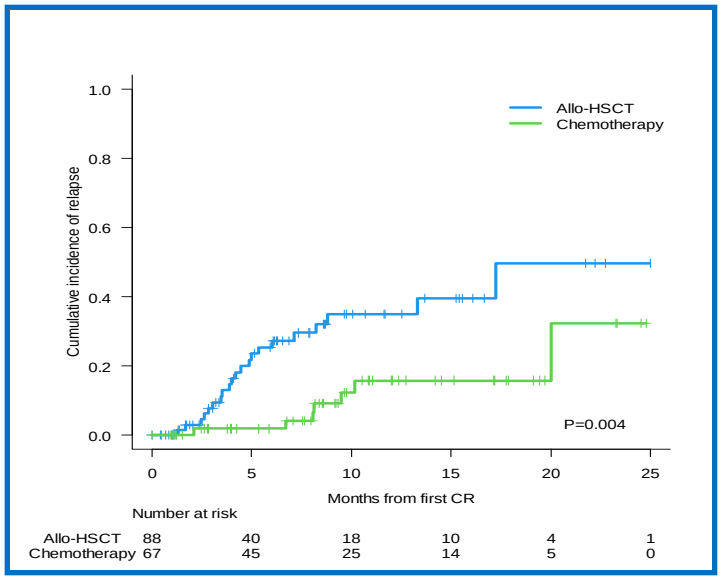

- PCR for BCR::ABL1 did not provide additional prognostic information in patients with NGS MRD negativity
- NGS-based MRD is prognostic in Ph+ ALL. Patients with low-level detectable BCR::ABL1 are unlikely to relapse
- NGS-based assays could eventually supplant MRD monitoring by RT-PCR for BCR::ABL1 in Ph+ ALL

Short NJ, et al. *Am J Hematol*. 2023;98:1196-1203.

# Post-consolidation decision according to MRD and genetic background: ALL 2019 trial

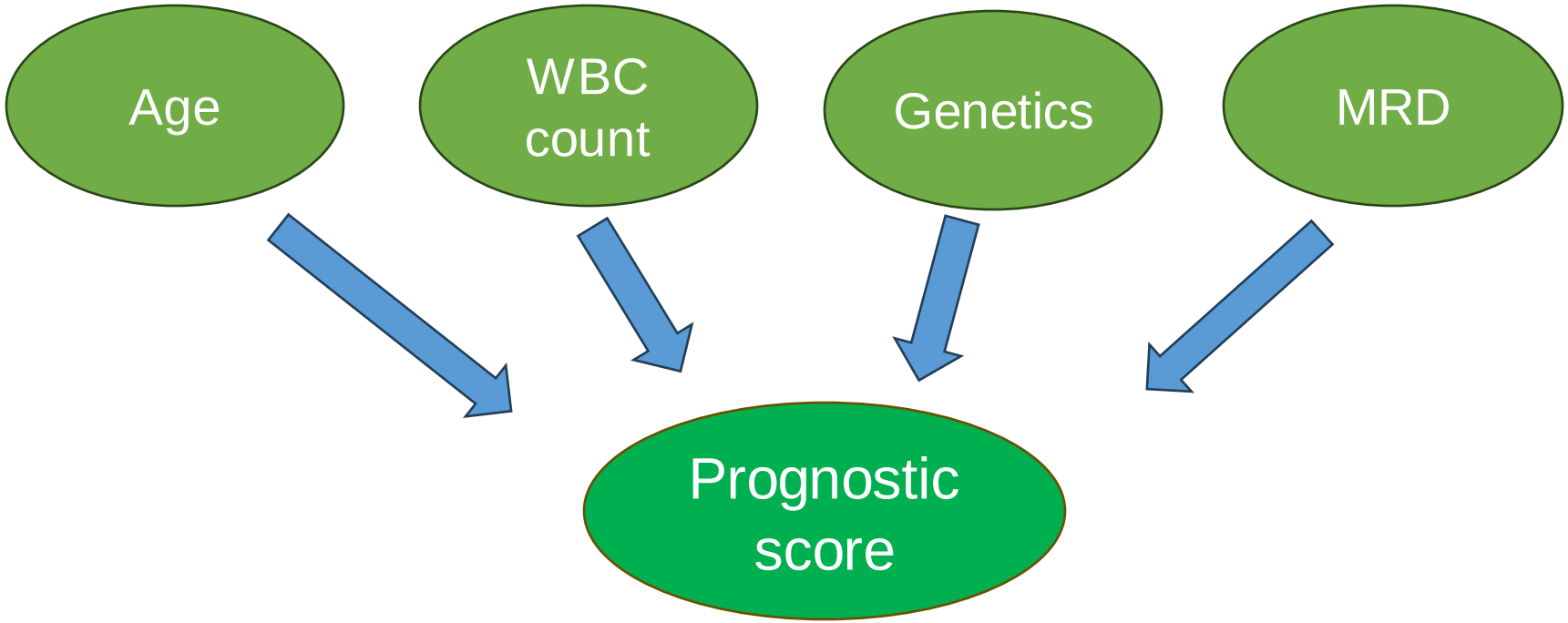
End-of-induction MRD <0.01% **and** no high-risk genetics: **chemotherapy**
End-of-induction MRD ≥0.01% **and/or** high-risk genetics: **alloHSCT**



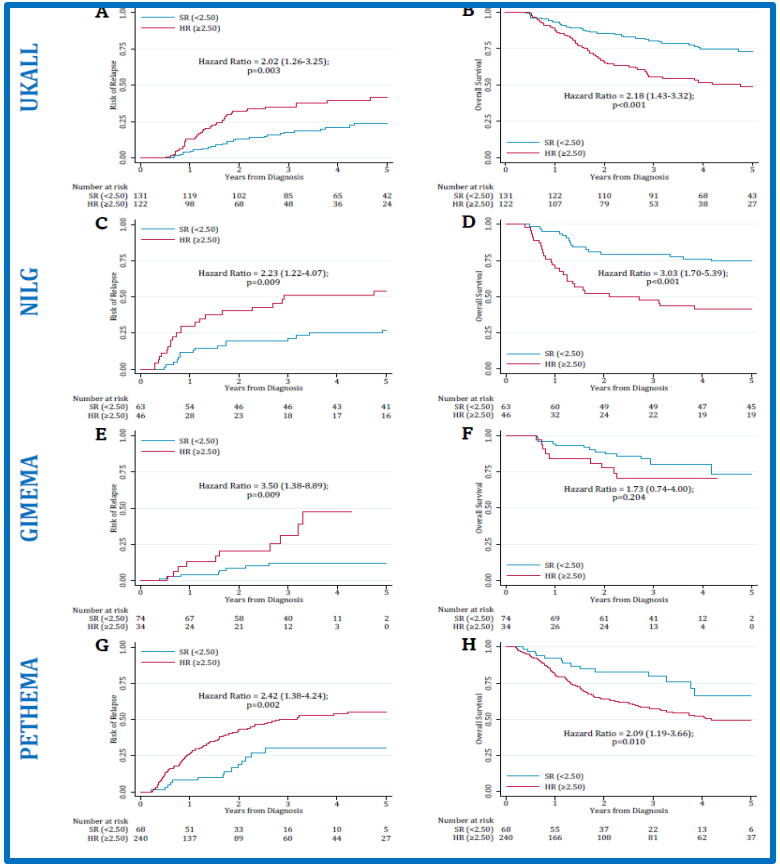

ClinicalTrials.gov identifier: NCT04179929. PETHEMA data on file.

# Need of prognostic score for adult ALL



# EWALL risk score for adult ALL

$$PI_{UKALL} = \tau(MRD) \times -0.218 + CYTO\text{-}GR \times -0.440 + CYTO\text{-}HR \times 1.066 + \tau(WCC) \times 0.138$$




**2.5 score separates SR and HR ALL**

Enshaei A, et al. Submitted.

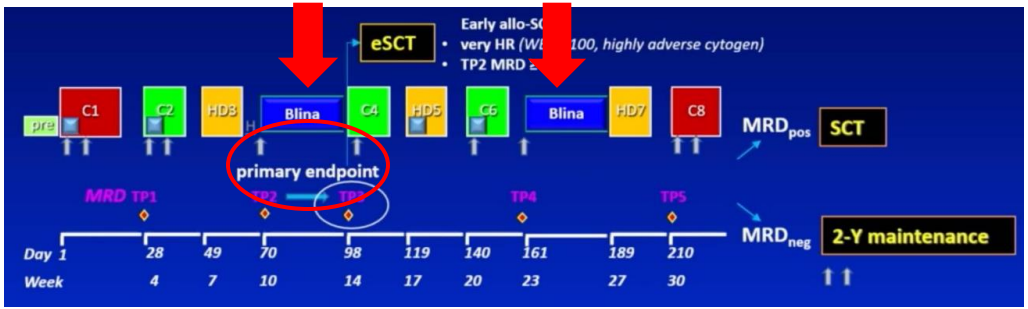
# Impact of MRD in the immunochemotherapy era

Early use of immunotherapy (MRD+, CR1)

Less use of alloHSCT in CR1

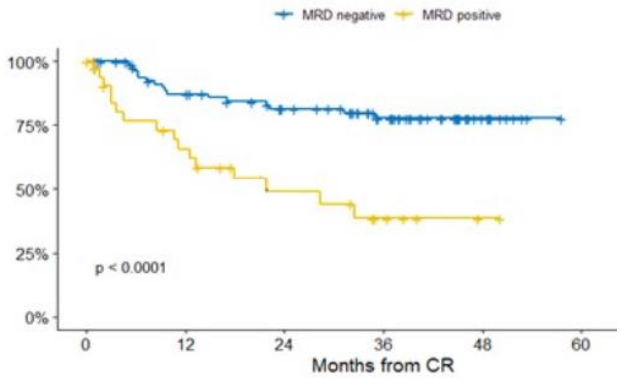
Use of CAR T in early phases? Before HSCT?

# GIMEMA LAL2317 (18-65y): Blinatumomab consolidation

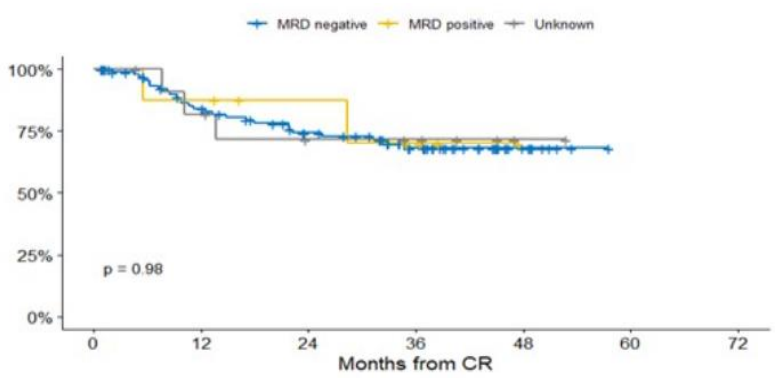



| Patients | Overall | 18–40 y | 41–55 y | >55 y | *P* |
|---|---|---|---|---|---|
| CR TP1 | **88%** | **94%** | **92%** | **64%** | **Sig** |
| MRD– TP2 | 70% | - | - | - | - |
| MRD– TP3 (Blin) | **93%** | - | - | - | - |
| OS 3 yr | 71% | **76%** | **74%** | **49%** | **Sig** |
| DFS 3 yr | 66% | 71% | 62% | 42% | N |
| CIR | **27.5%** | - | - | - | |

**DFS TP2 (EOC)**




**DFS TP3 (Blin)**




Median FU 37.5 months

MRD neg at TP2 has impact in MV analysis for OS/DFS

Bassan R, et al. EHA 2021. Abstract S114.

Chiaretti S, et al. ASH 2023. Abstract 826.

# Frontline blinatumomab and inotuzumab combinations in young adults with newly dx ALL

| | Agent | N | Median Age, yr (range) | CR, % | MRD Negativity, % | OS, % (x-yr) |
|---|---|---|---|---|---|---|
| HCVAD-blina | Blinatumomab | 38 | 37 (17–59) | 100 | 97 | 81 (3-yr) |
| HCVAD-blina-inotuzumab | Blinatumomab and inotuzumab | 25 | 24 (18–47) | 100 | 91 | 100 (1-yr) |
| GIMEMA LAL1913 | 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) |

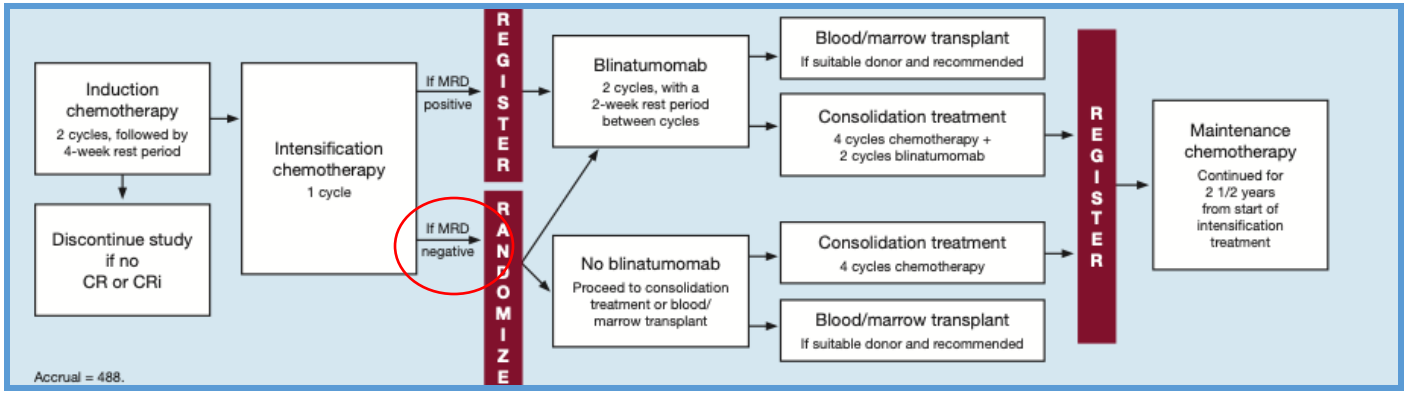
Short. *Blood.* 2021;138:1223; Bassan R, et al. EHA 2022. Abstract S113; Boissel N, et al. *Blood.* 2021;138(suppl 1):1232; Fleming S, et al. *Blood.* 2021;138(suppl 1):1234.

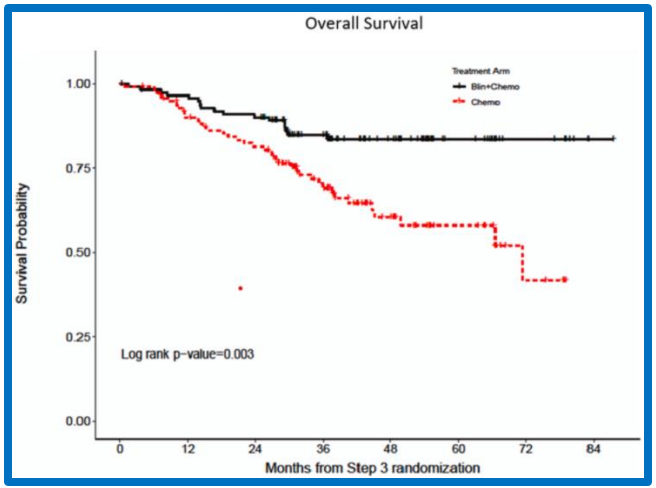
# Frontline blinatumomab and inotuzumab combinations in older adults with newly dx ALL

| | 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;40:1574-1582; Chevallier P, et al. *Blood*. 2021;138(suppl 1):511; Goekbuget N, et al. *Blood*. 2021;138(suppl 1):3399; Stelljes M, et al. *Blood*. 2021;138(suppl 1):2300.

# ECOG 1910: Blinatumomab consolidation for MRD-negative B-ALL



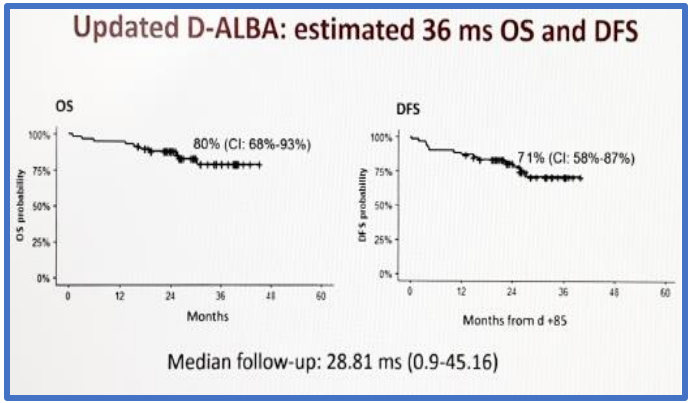

N = 488 enrolled in Step 1
N = 224 randomized 1:1 in Step 2 (negative MRD)

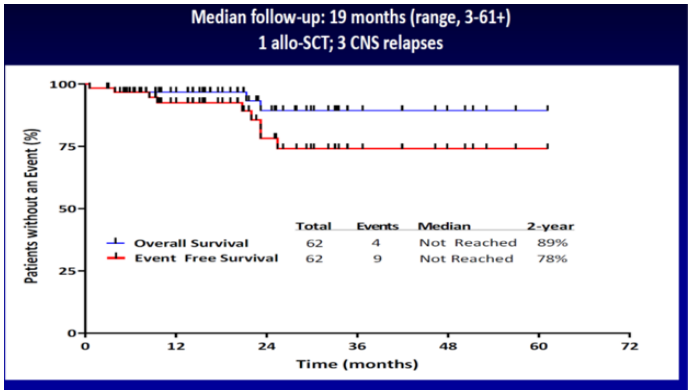
Addition of blinatumomab significantly improved OS (HR 0.42, 95% CI: 0.24-0.75; *P* = .003)
**Effect particularly evident in pts <55 yr and undetectable MRD**

Litzow M, et al. ASH 2022. Abstract LBA1; Litzow M, et al. EHA 2023. Abstract S115.

# Immunotherapy in early phases of Ph+ ALL: Results from phase II trials

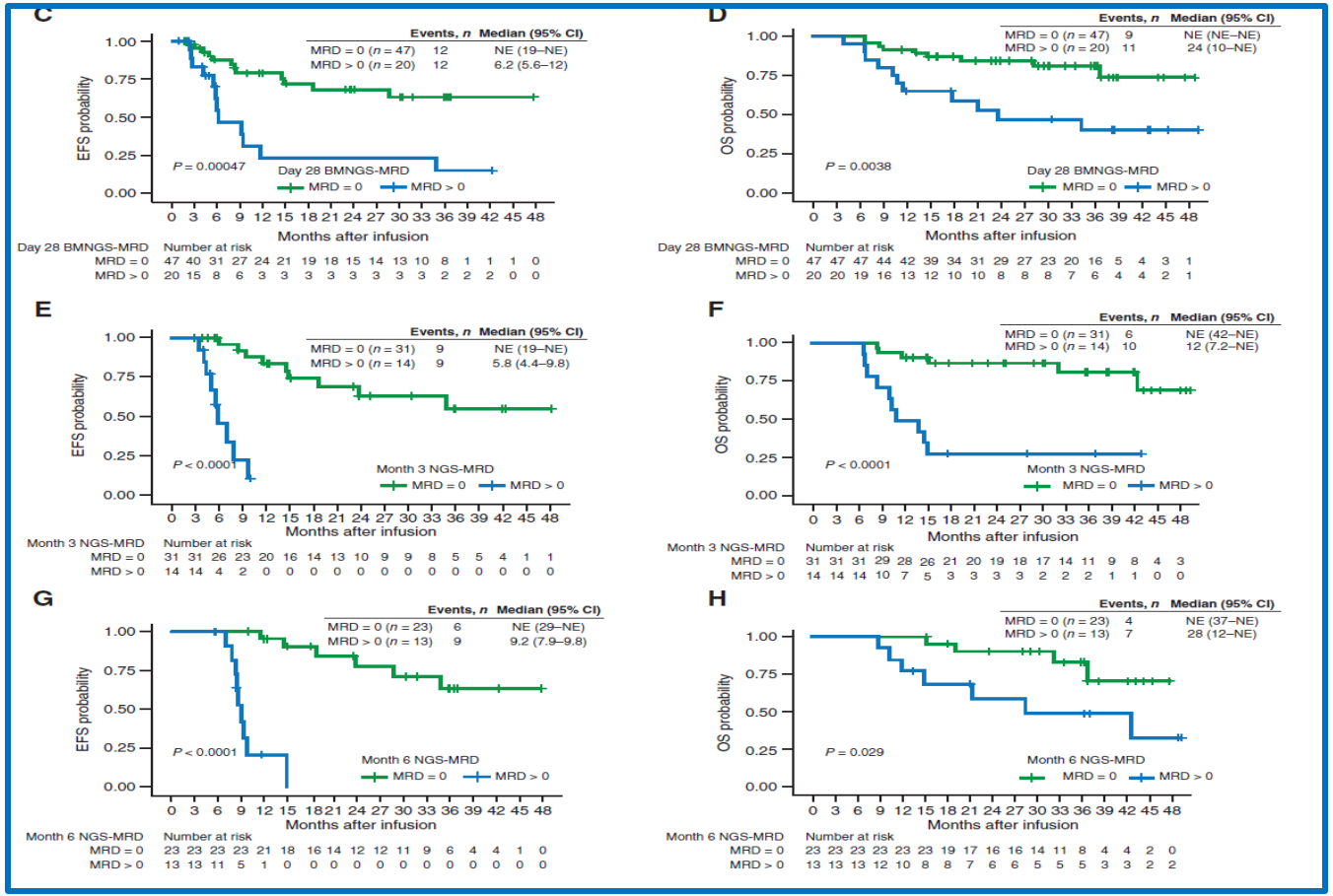
| Reference | TKI | Immunotherapy | N | Median Age (range) | CR, % | CMR, % | OS, % (95% CI) yr |
|---|---|---|---|---|---|---|---|
| Foa et al[1] | Dasatinib | Blinatumomab | 63 | 54 (24–82) | 98 | 29 (ponatinib) 60 (blinatumomab) | 80 (68–93) 2-yr |
| Short et al[2] | Ponatinib | Blinatumomab | 30 | 62 (34–83) | 94 | 81 (CMR + MMR) | 93 2-yr |
| Advani et al[3] | Dasatinib | Blinatumomab | 24 | 73 (62–87) | 92 | 31 | 85 (58–95) 3-yr |




1. Foa R, et al. *N Engl J Med.* 2020;383:1613-1623; 2. Short N, et al. *Blood.* 2021;138(suppl 1): abstract 2299;
3. Advani A, et al. *Blood.* 2021; 138(suppl 1): abstract 3397.

# NGS MRD on d28, months 3 and 6 after tisa-cel predicts outcome




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

# Conclusions

- MRD is the best prognostic factor in children and adults with ALL
- Prognostic significance at any time point (after induction, consolidation, before and after HSCT)
- Independent additional impact of oncogenetic factors (± age and WBC). Development of integrated prognostic models necessary
- NGS: the reference tool for MRD assessment in near future
- **Early use of immunotherapy: promising results with deeper MRD negativity and on the decision strategy** of treatment of newly diagnosed patients with ALL


Thank you
jribera@iconcologia.net

Global Leukemia Academy

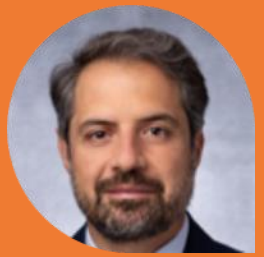
# Q&A

APTITUDE HEALTH

Global Leukemia Academy

# Latest achievements in ALL and AML developments

Elias Jabbour



APTITUDE HEALTH

# Recent Developments in Leukemias

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

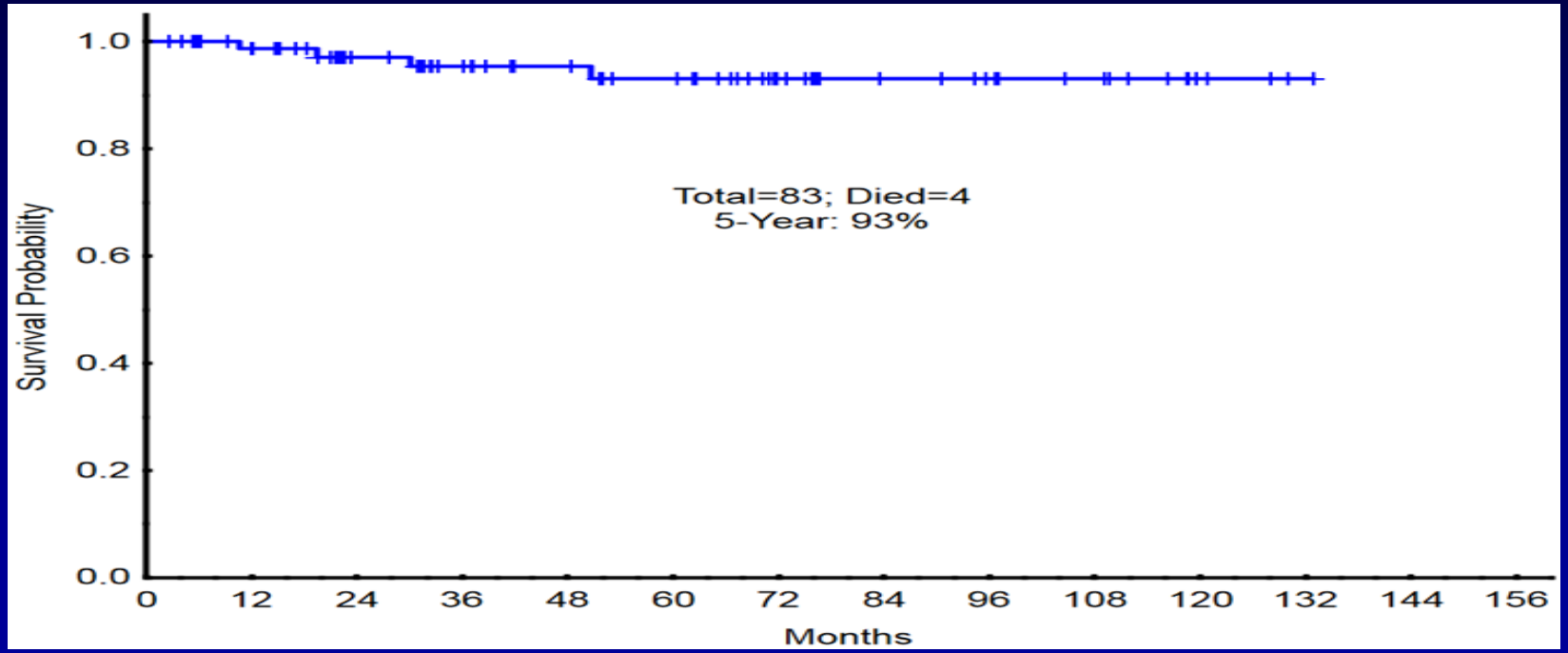
| Disease | Therapies | % cure/10-yr survival |
|---|---|---|
| Hairy cell leukemia | CDA + rituximab | 90 |
| APL | ATRA + arsenic | 80–90 |
| CBF AML | FLAG-GO/IDA | 80–90 |
| AML – younger | FLAG-IDA-VEN and CLIA-VEN + FLT3i/IDHi; MoAbs | 60+ |
| AML – older | Triple-nucleoside + venetoclax low intensity 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%



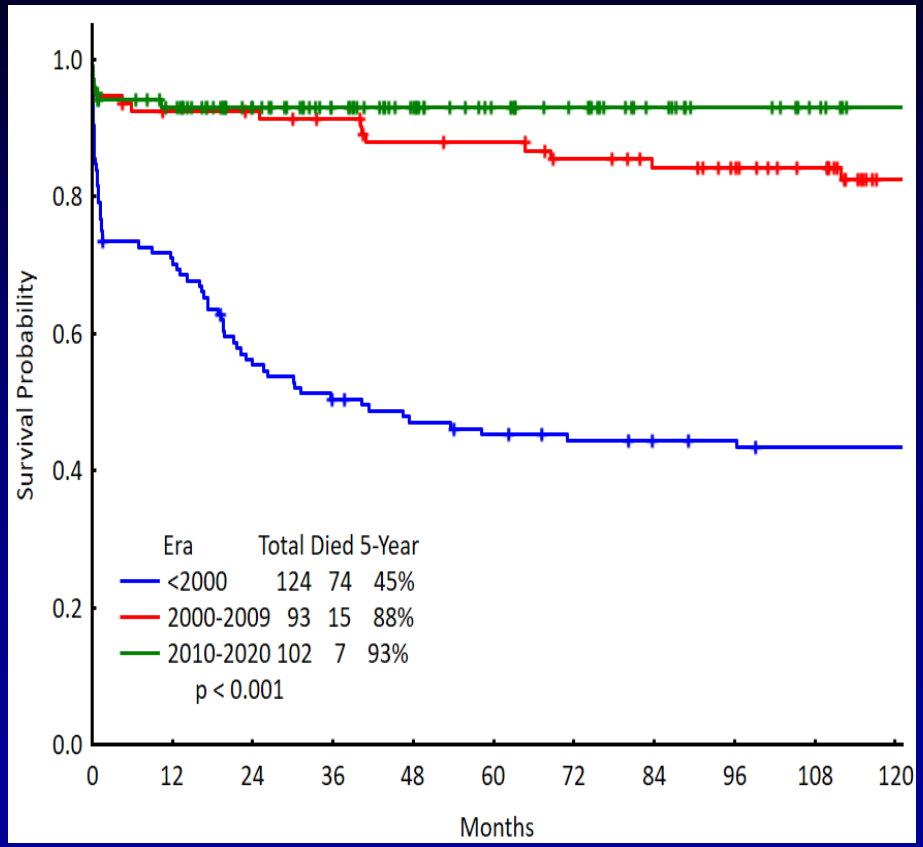

Chihara D, et al. *Br J Haematol*. 2016;174(5):760-766.

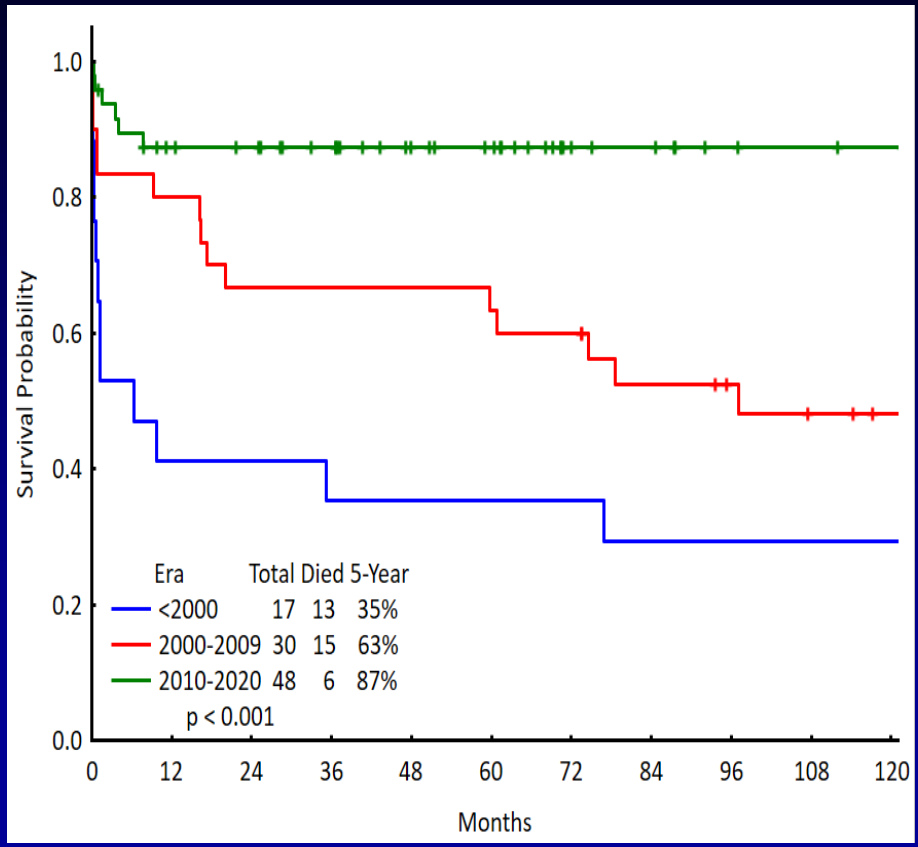
# ATRA + $As_2O_3$ Without Chemotherapy in APL: MD Anderson Experience

- **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.

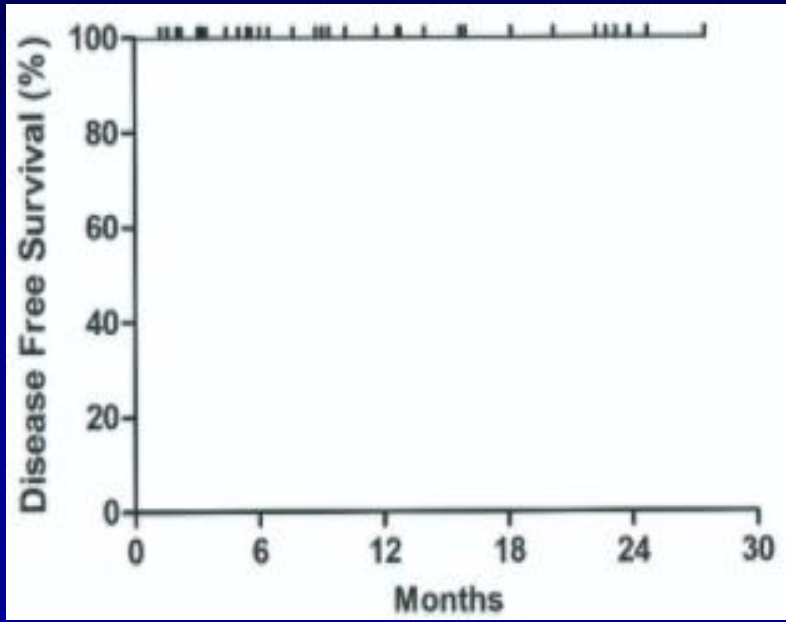
# APL Young and Old: MDACC

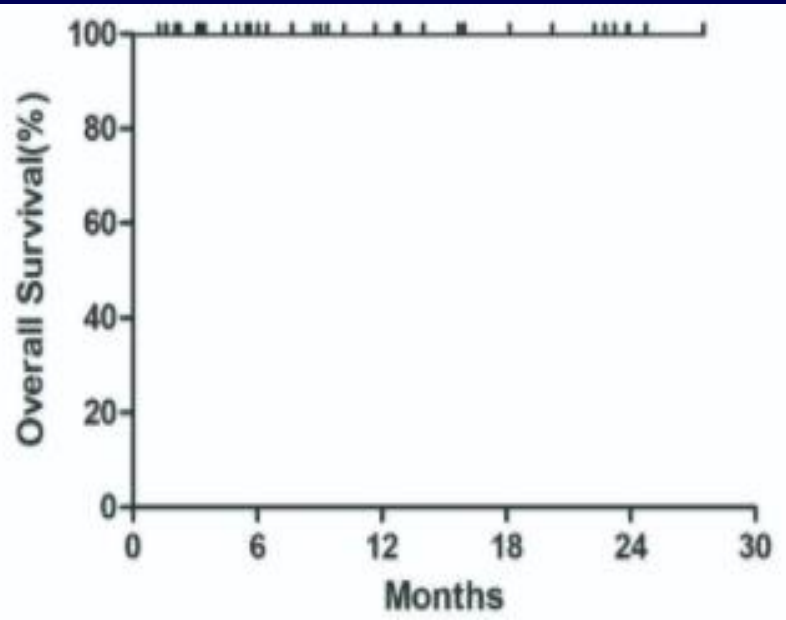


# ATRA + Realgar Indigo (oral arsenic) in APL

- 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



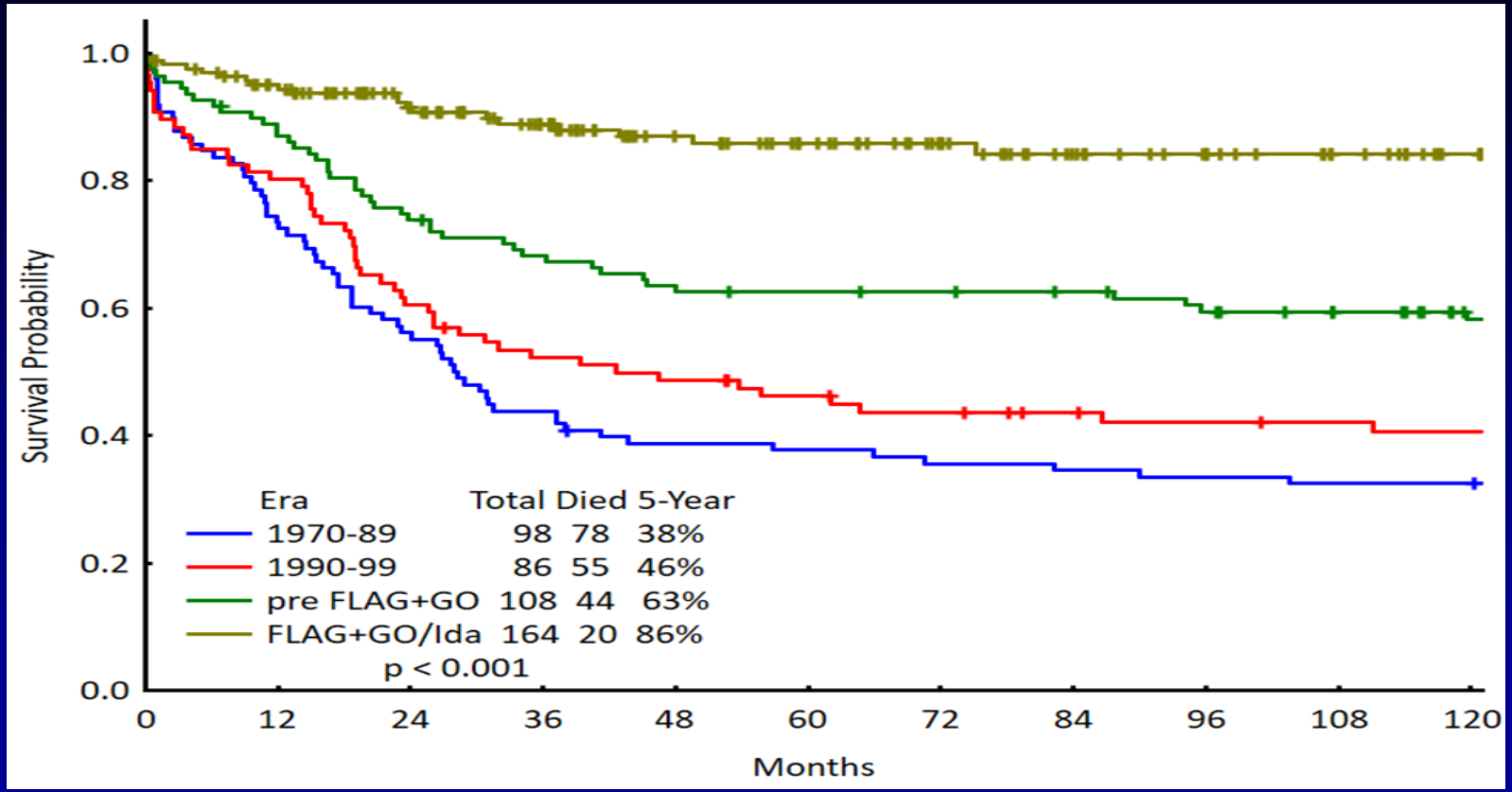




Zhu et al. *Blood*. 2021;138:abstract 873.

# 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

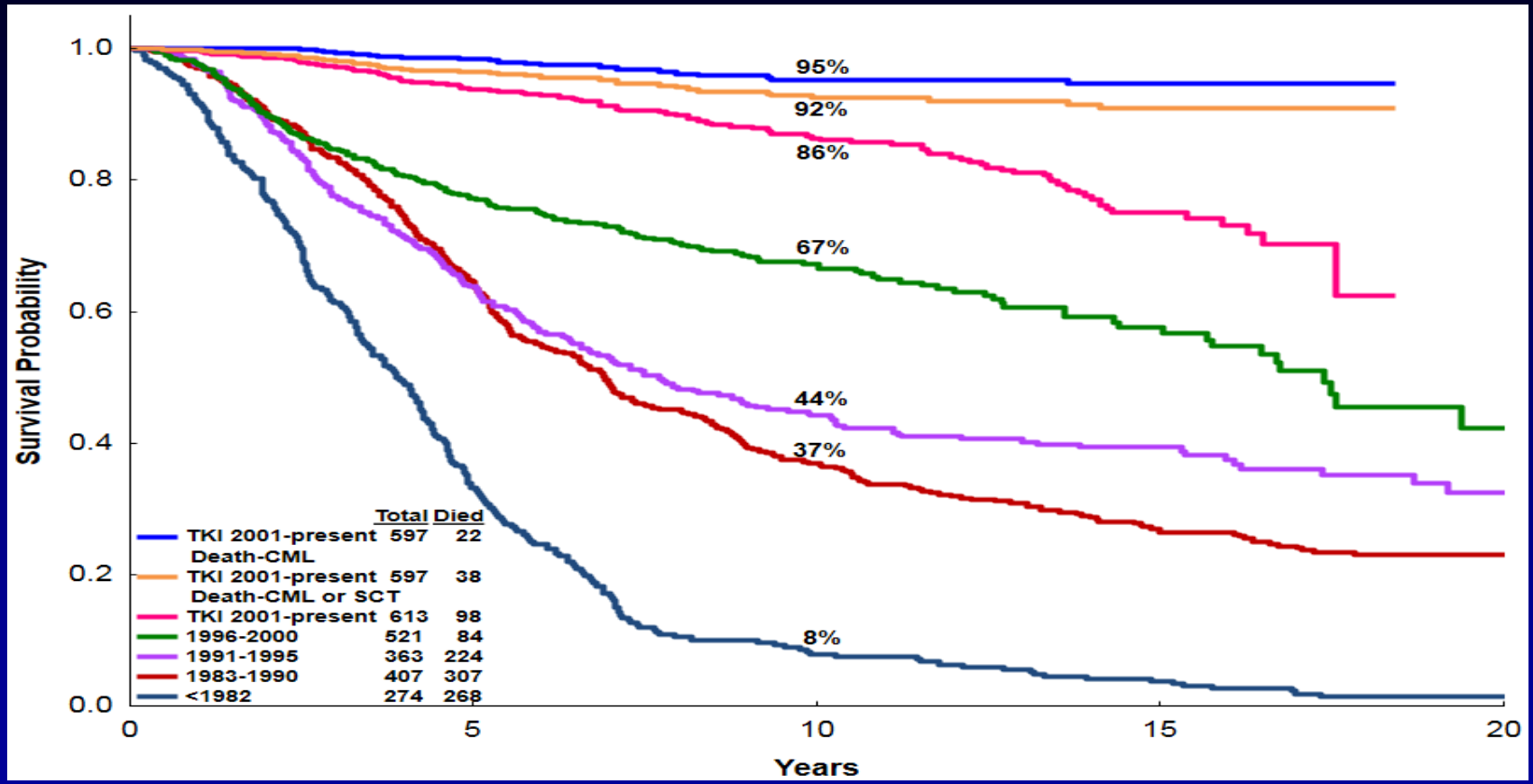
# FLAG-GO/IDA in CBF-AML: Survival



# Therapy of CML in 2023

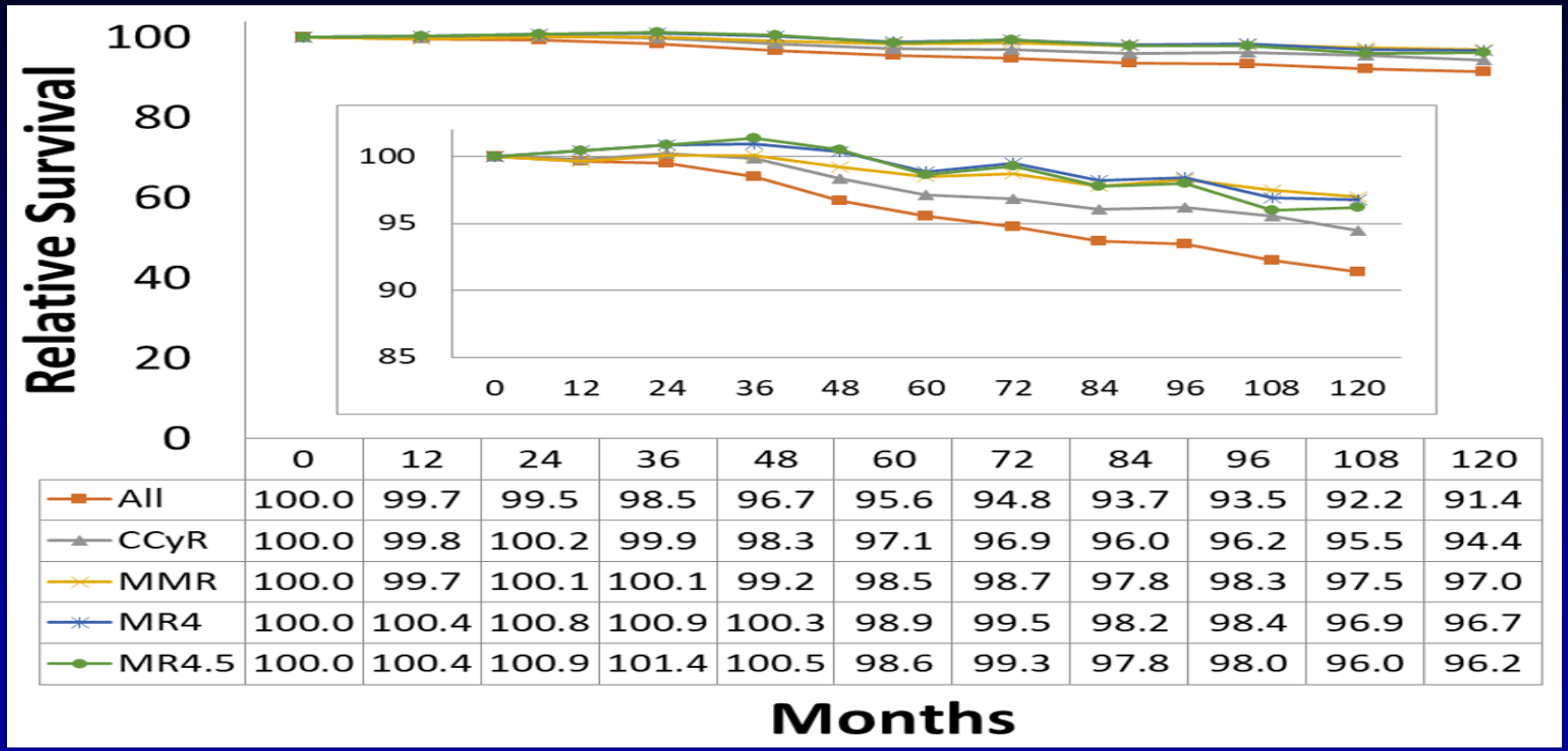
- Frontline
  - Imatinib 400 mg daily
  - Dasatinib 100 mg daily (50 mg at MD Anderson)
  - Nilotinib 300 mg BID
  - Bosutinib 400 mg daily
- Second/third line
  - Nilotinib, dasatinib, bosutinib, ponatinib, asciminib, omacetaxine
  - Allogeneic SCT
- Other
  - Decitabine, peg IFN, omacetaxine (only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



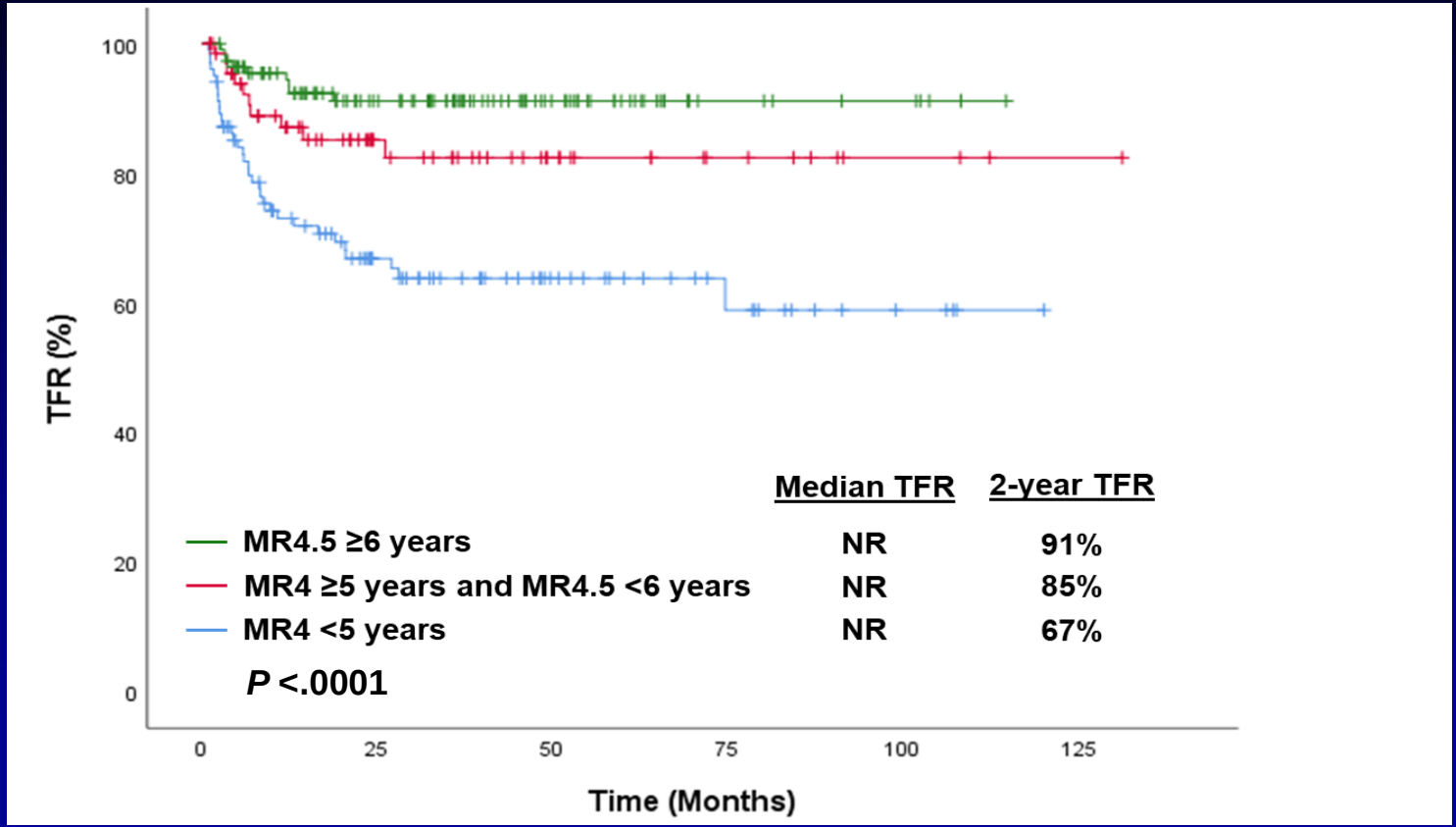

| | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All | 100.0 | 99.7 | 99.5 | 98.5 | 96.7 | 95.6 | 94.8 | 93.7 | 93.5 | 92.2 | 91.4 |
| CCyR | 100.0 | 99.8 | 100.2 | 99.9 | 98.3 | 97.1 | 96.9 | 96.0 | 96.2 | 95.5 | 94.4 |
| MMR | 100.0 | 99.7 | 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



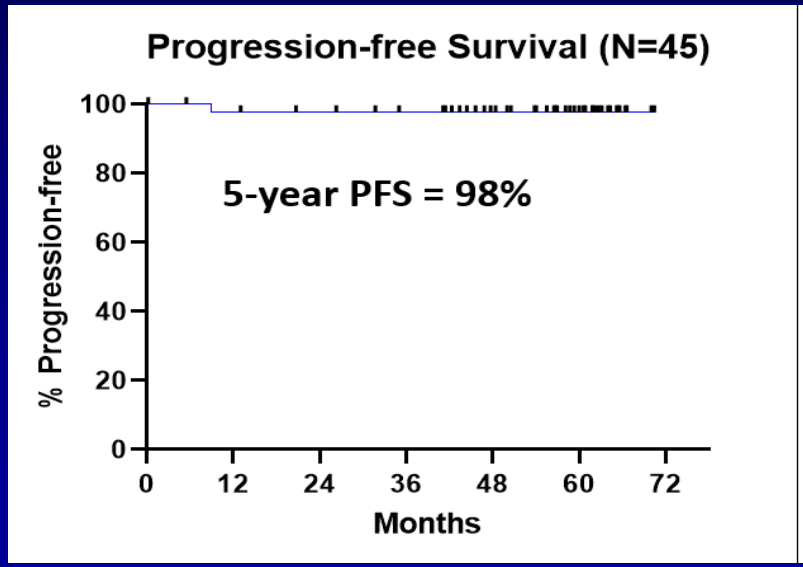

Haddad. *Blood*. 2021;138:abstract 1480.

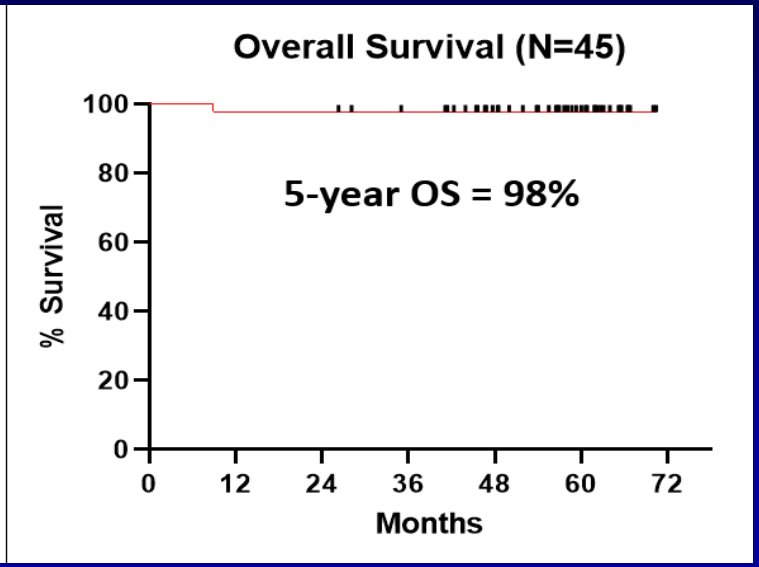
# Frontline CML Therapy in 2023+

- 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. Abstract S149.

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

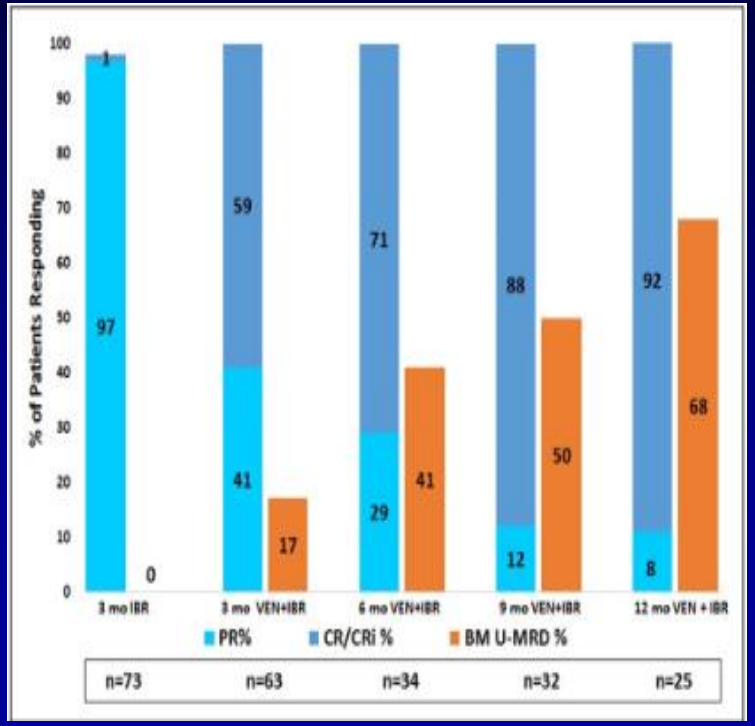
# Cure of CLL – Couplets vs Triplets

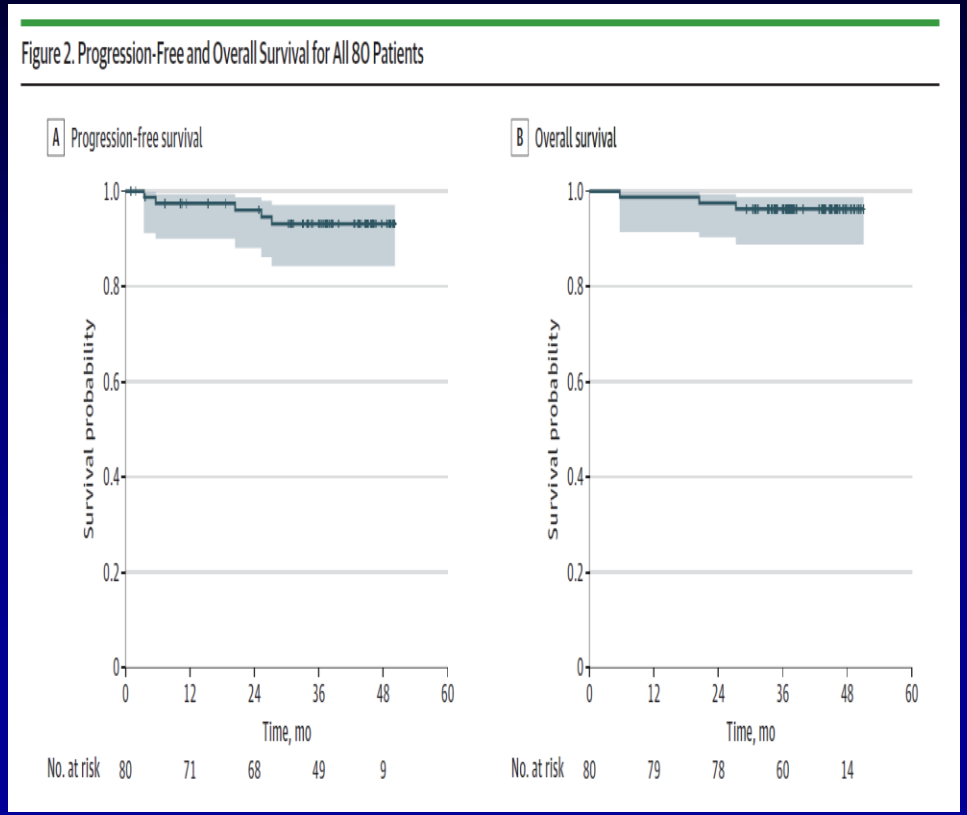
- Ibrutinib-venetoclax finite Rx duration = cure
- Questions: duration (2 vs more years); couplets vs triplets

| 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

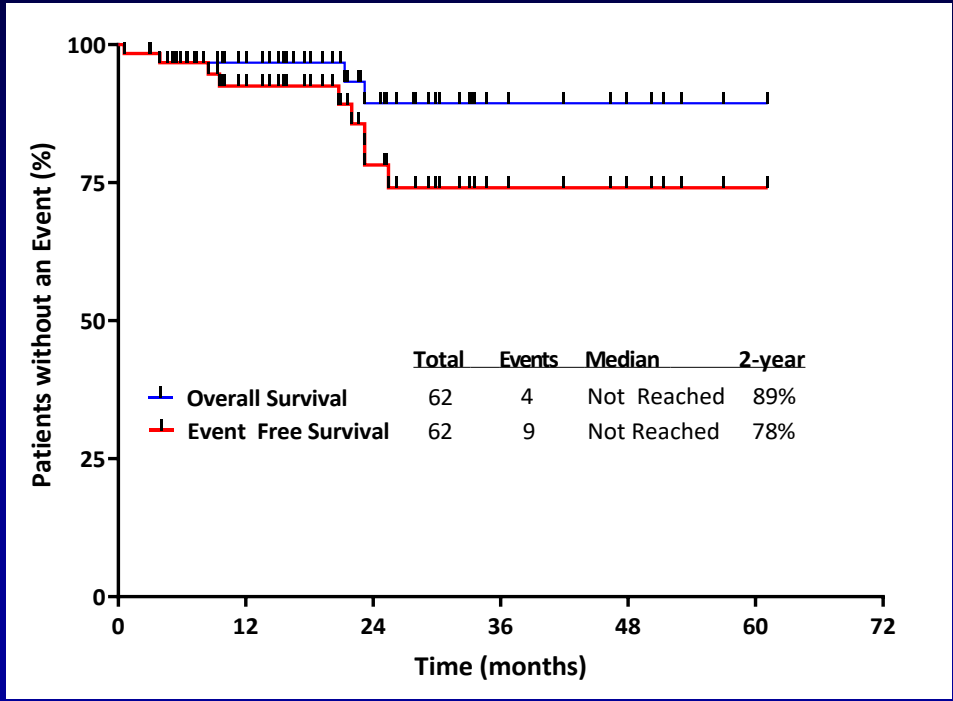
# Reasons for Recent Success in Adult ALL

- 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

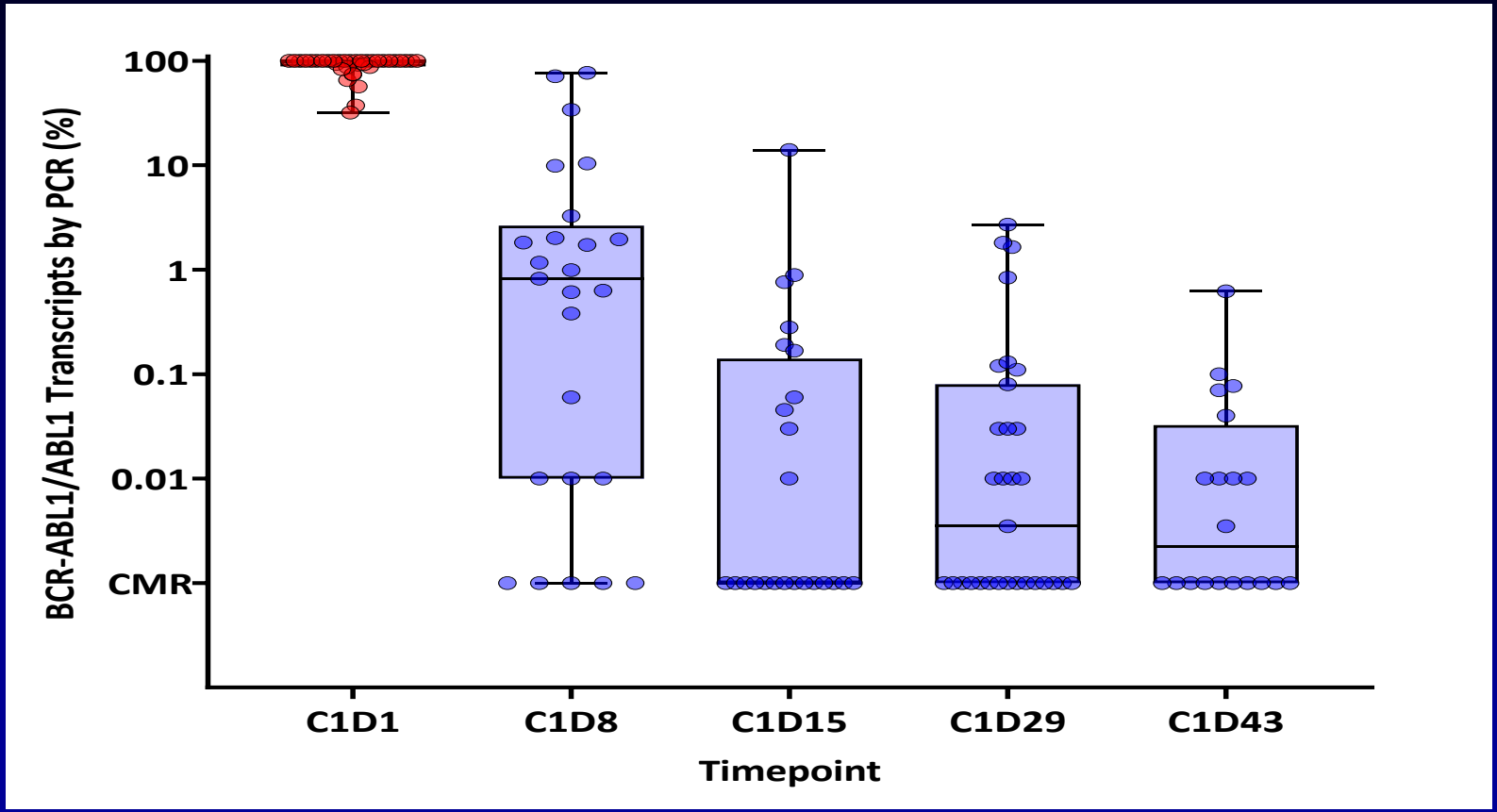
- 62 pts Rx with simultaneous ponatinib 30–15 mg/D and blinatumomab ×5 courses. 12–15 ITs
- Only 1 pt had SCT(2%)
- Median F/U 19 months. 2-yr EFS 78%, OS 89%
- 6 relapses (all p190): 3 CNS, 1 CRLF2+ (Ph–), 2 systemic

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



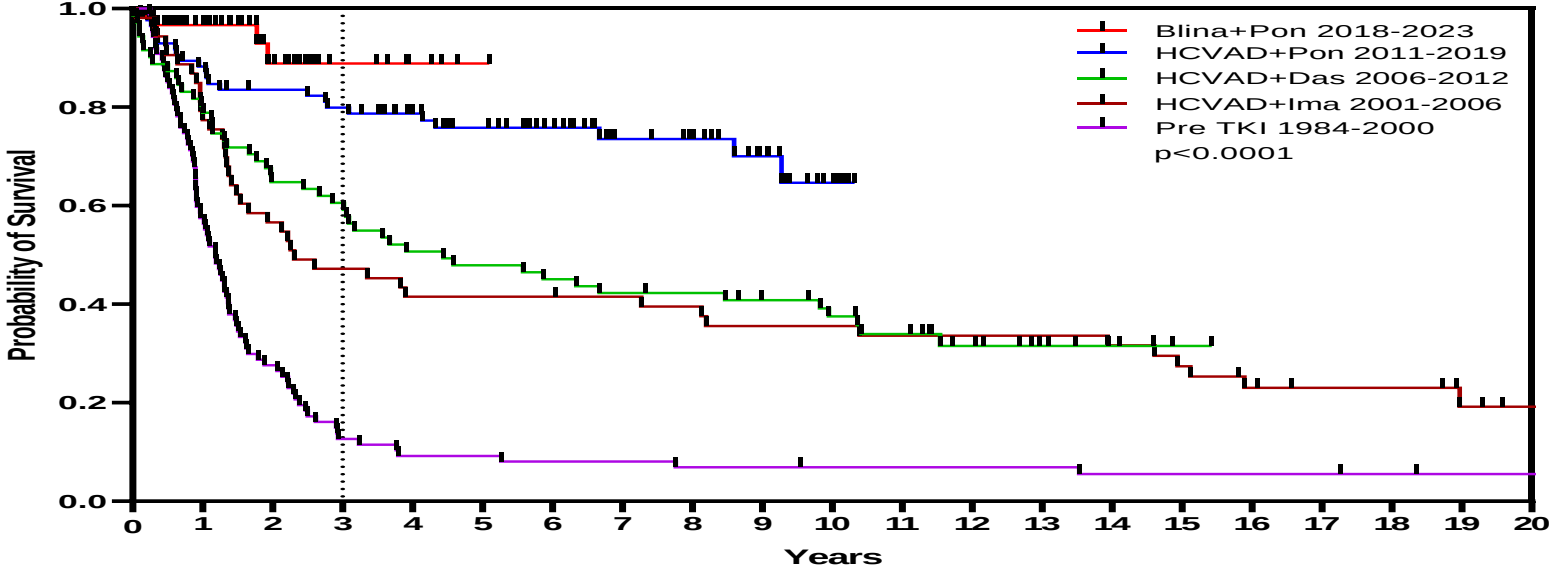

Short N, et al. *HemaSphere.* 2023;7:abstract S118 (updated August 2023).

# Ponatinib + Blinatumomab in Ph+ ALL: Early MRD Responses




Short N, et al. *HemaSphere.* 2023;7:abstract S118 (updated August 2023).

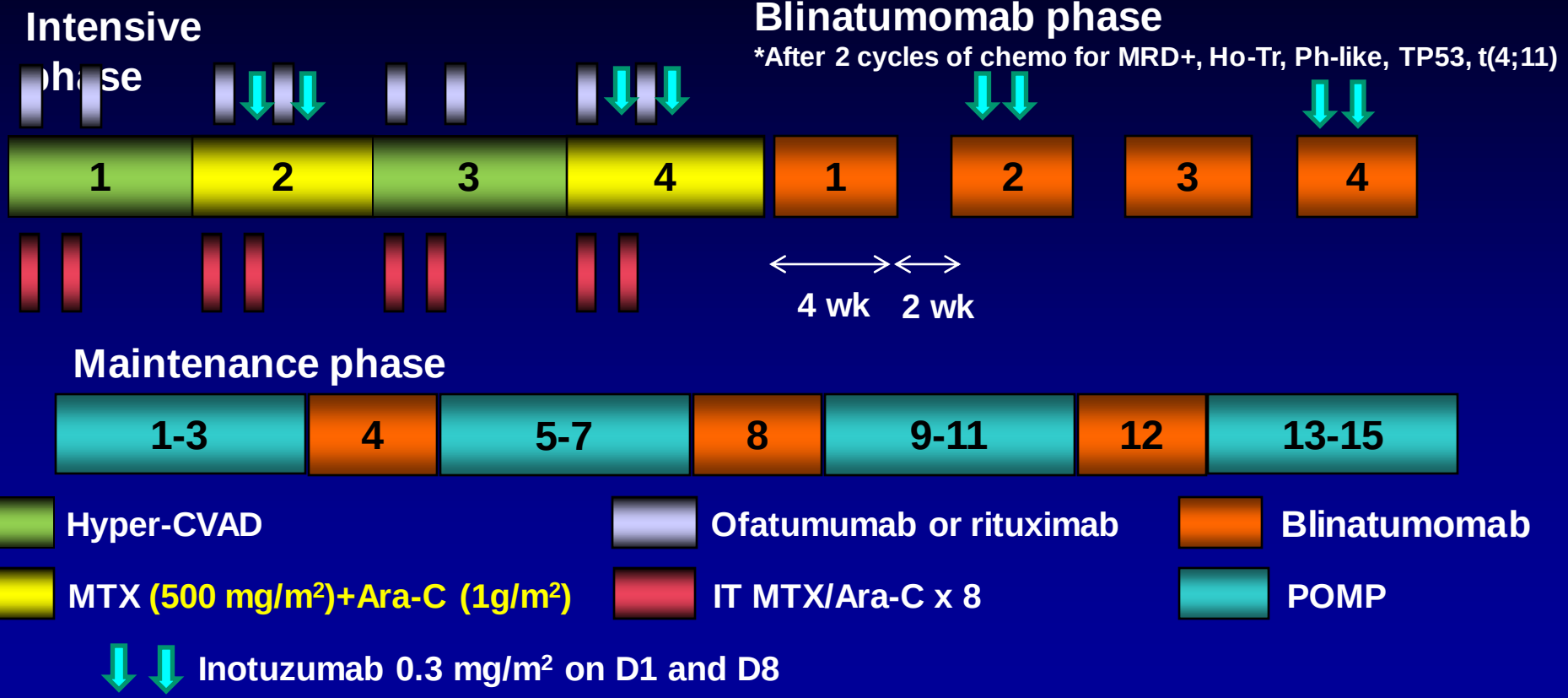
# Ph+ ALL: Survival by Decade (MDACC 1984–2023)




| | 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

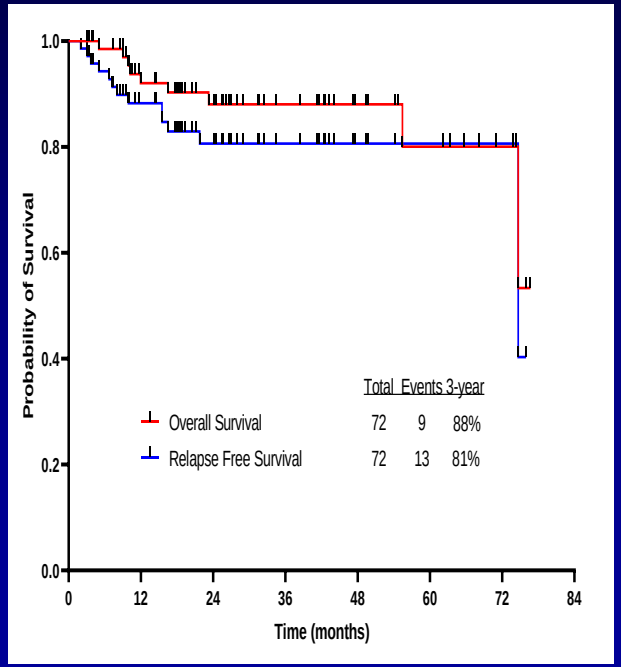
# Hyper-CVAD + Blina + InO in B-ALL: Regimen

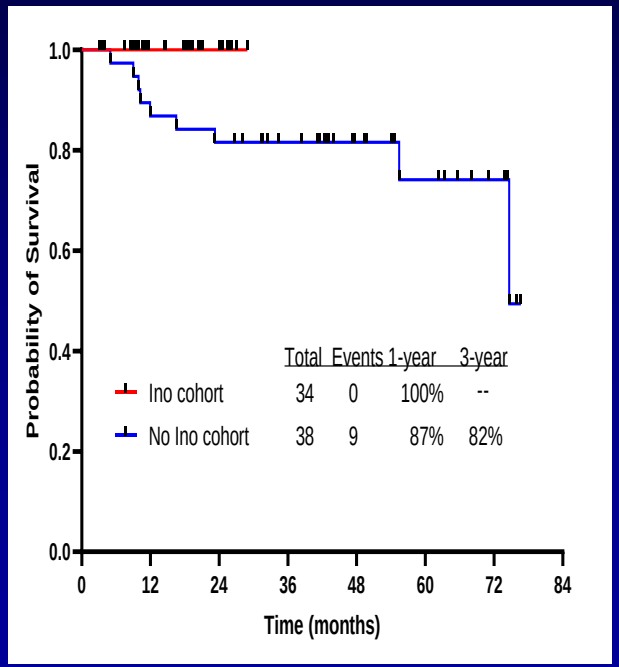


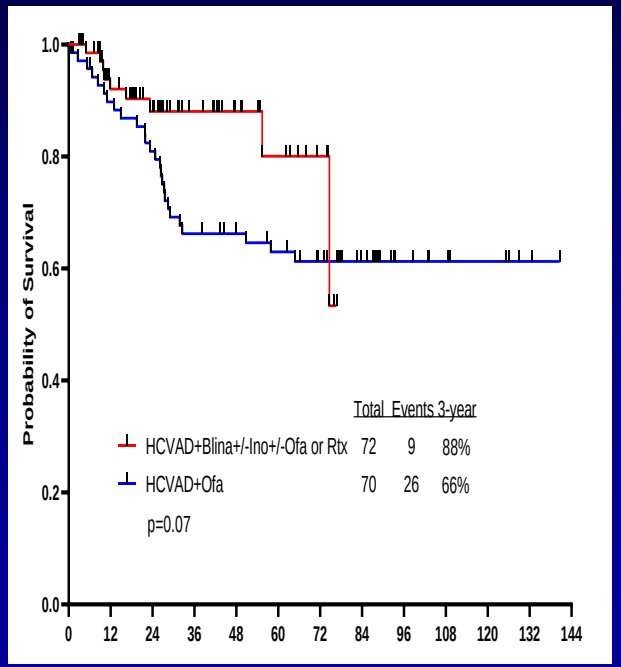

Short N, et al. *HemaSphere.* 2023;7:abstract P358.

# 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



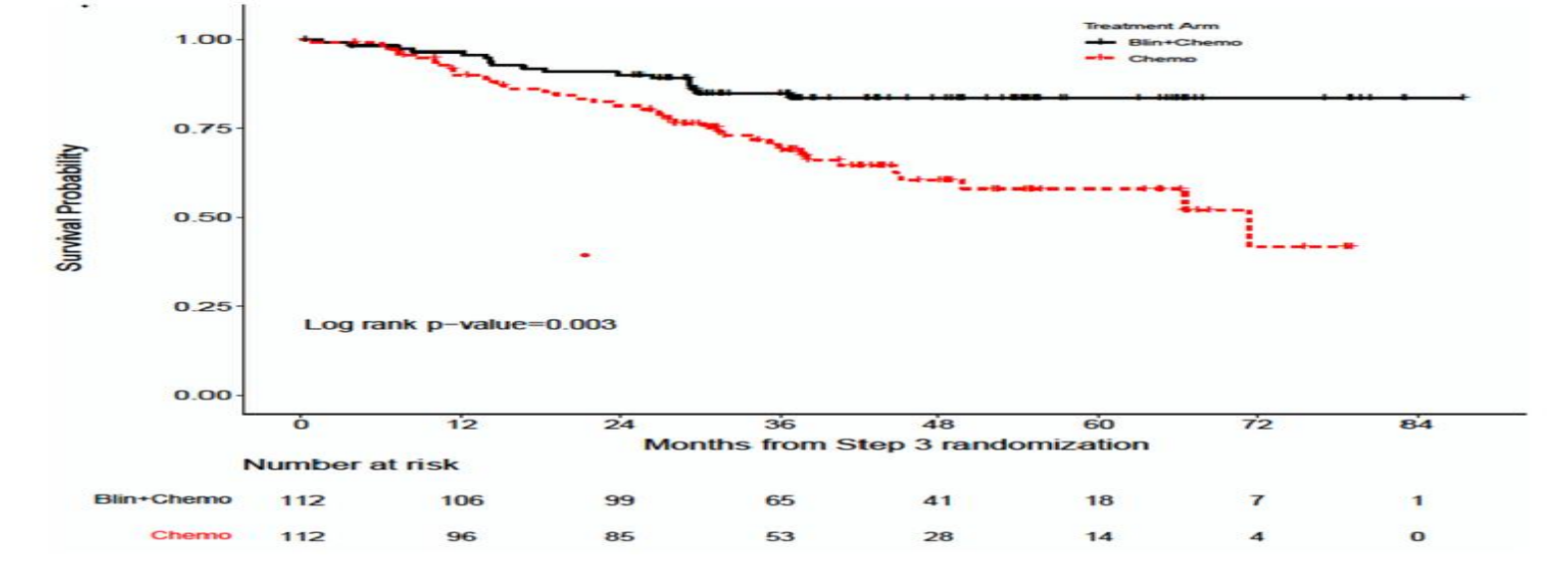




Short N, et al. *HemaSphere.* 2023;7:abstract P358.

# 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)

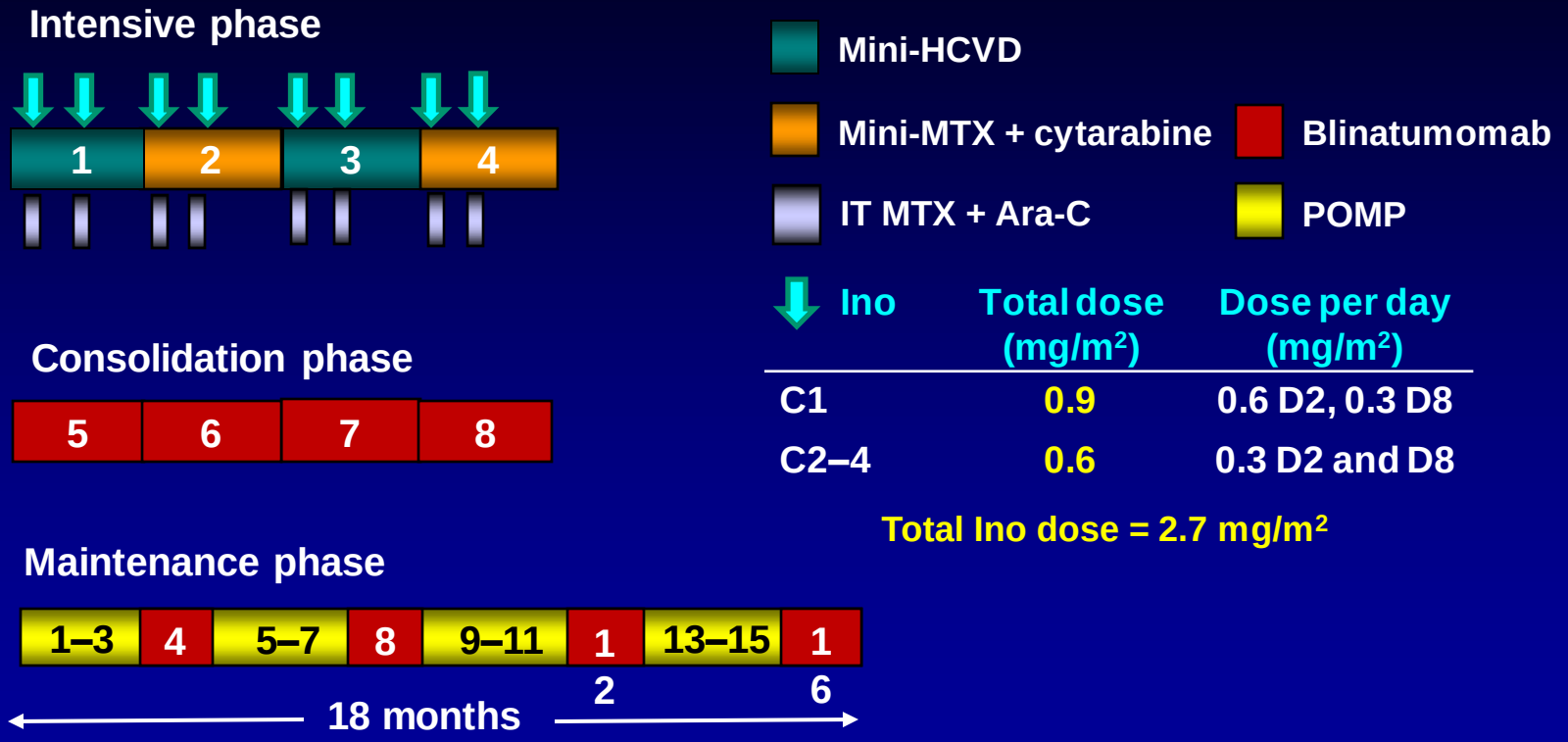



Litzow MR, et al. *Blood*. 2022;140(suppl 2): abstract LBA-1.

# The “Intermediate” Leukemias

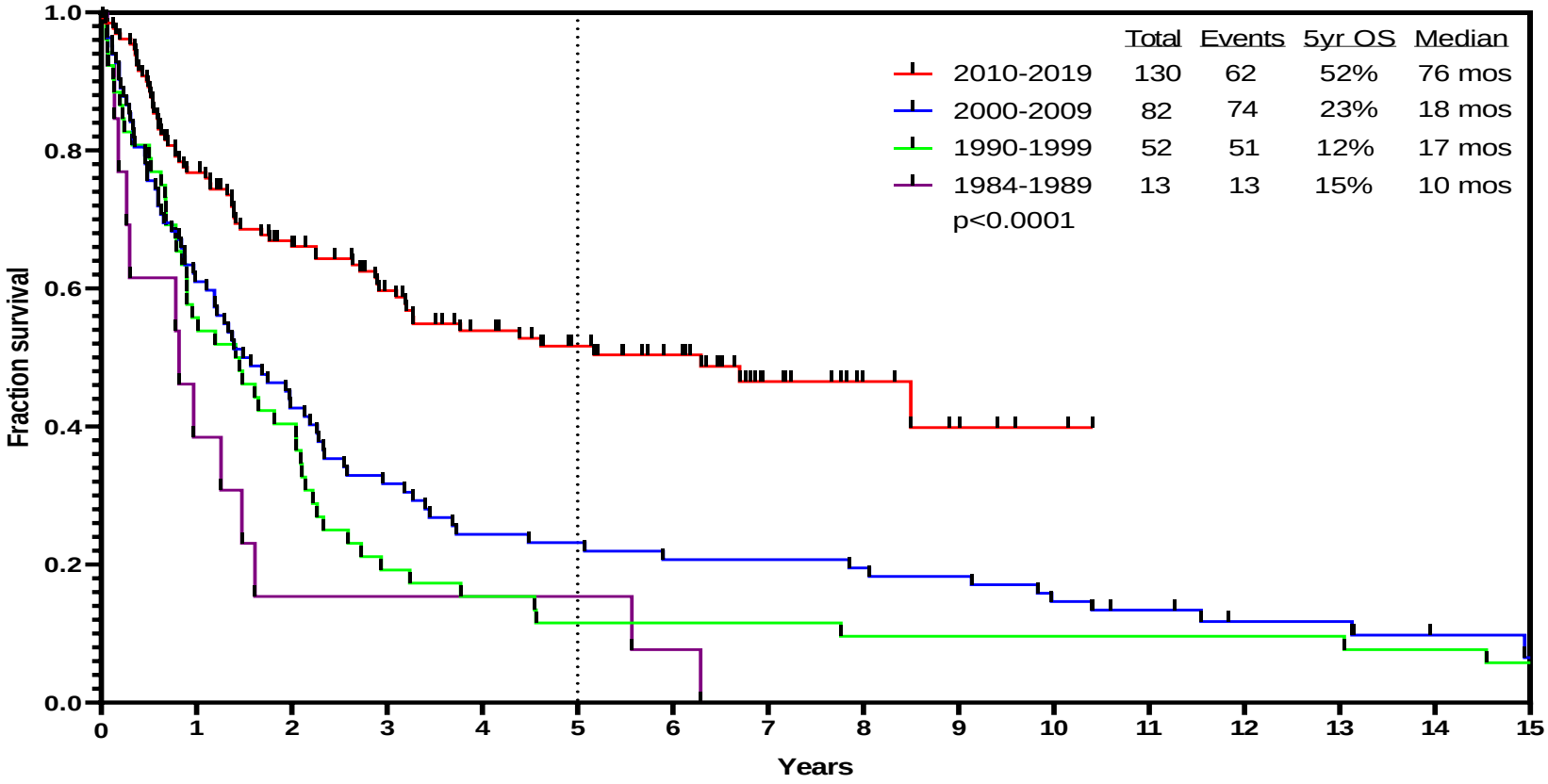
- Older ALL
- Younger AML

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



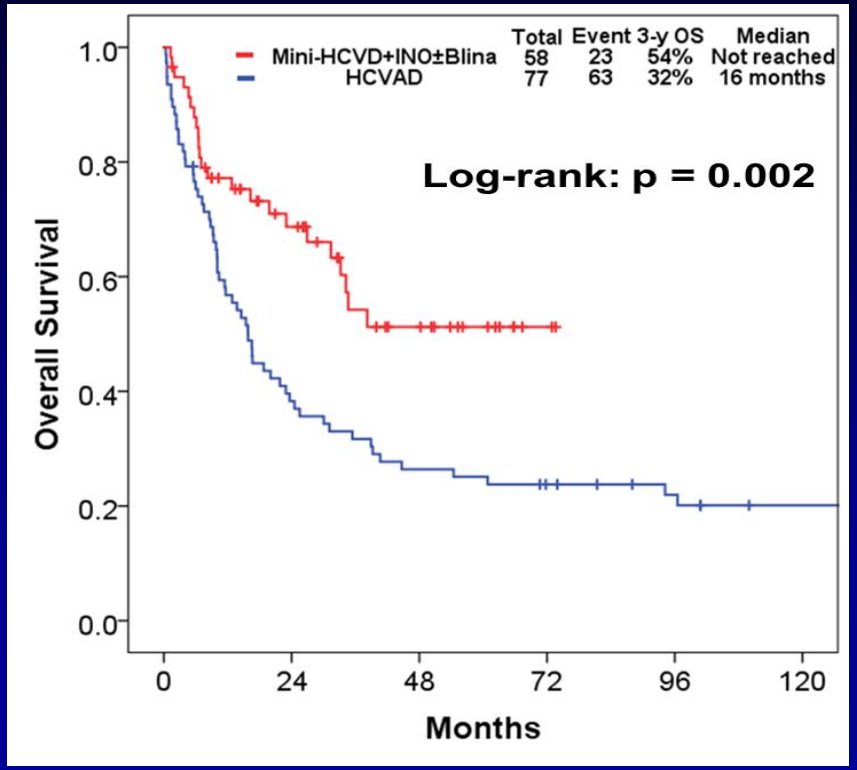

Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Short N, et al. *Blood*. 2018;132:abstract 36.

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

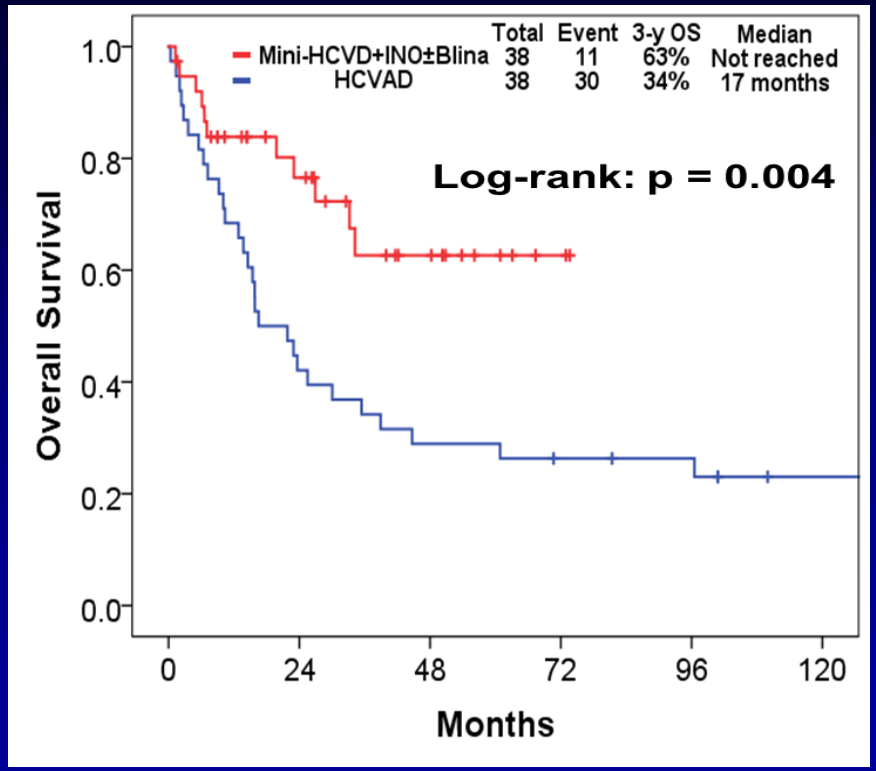


# Mini-HCVD + INO ± Blina vs HCVAD in Older ALL: Overall Survival

## 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)

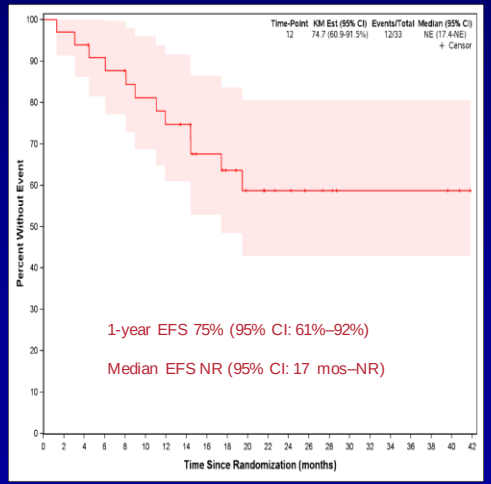
- 33 pts; median age 71 yrs (60–84). Median CD22 92%. **F/U 22 months**
- Induction: INO 0.8 mg/m$^2$ D1, 0.5 mg/m$^2$ D8 & 15 (1.8 mg/m$^2$)
- Maintenance: If CR-CRi INO 0.5 mg/m$^2$ D1, 8, 15 (1.5 mg/m$^2$) ×2 then BLINA ×2
- If no CR-CRi—BLINA 28 mcg/D ×21 then ×28 ×3
- IT ×8
- **CR 85% post INO ×3;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

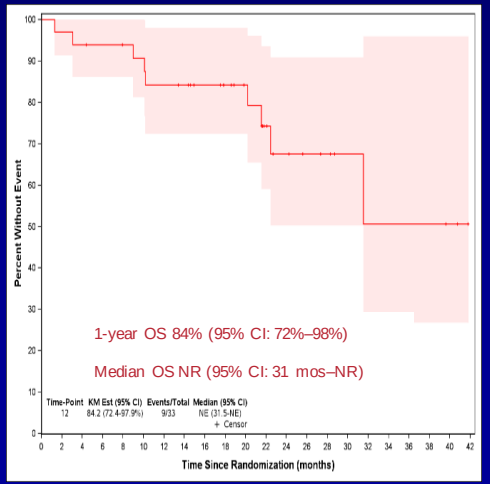
*CR+CRh+CRi

* 1 completed IA only, 2 proceeded to course II

**EFS**




**OS**

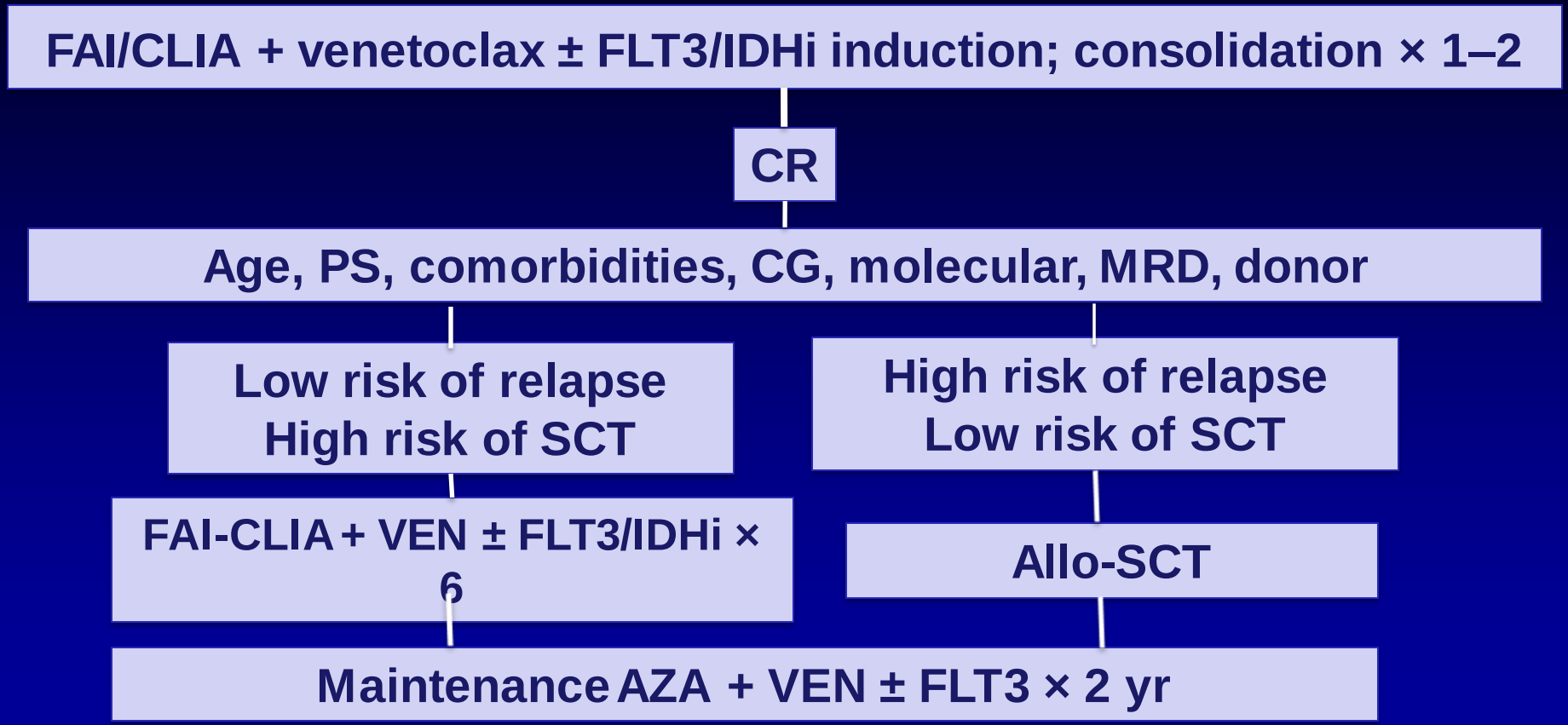



Wieduwilt et al. *HemaSphere.* 2023;7:abstract S117.

# AML in 2017–2023 – 12 Agents FDA Approved

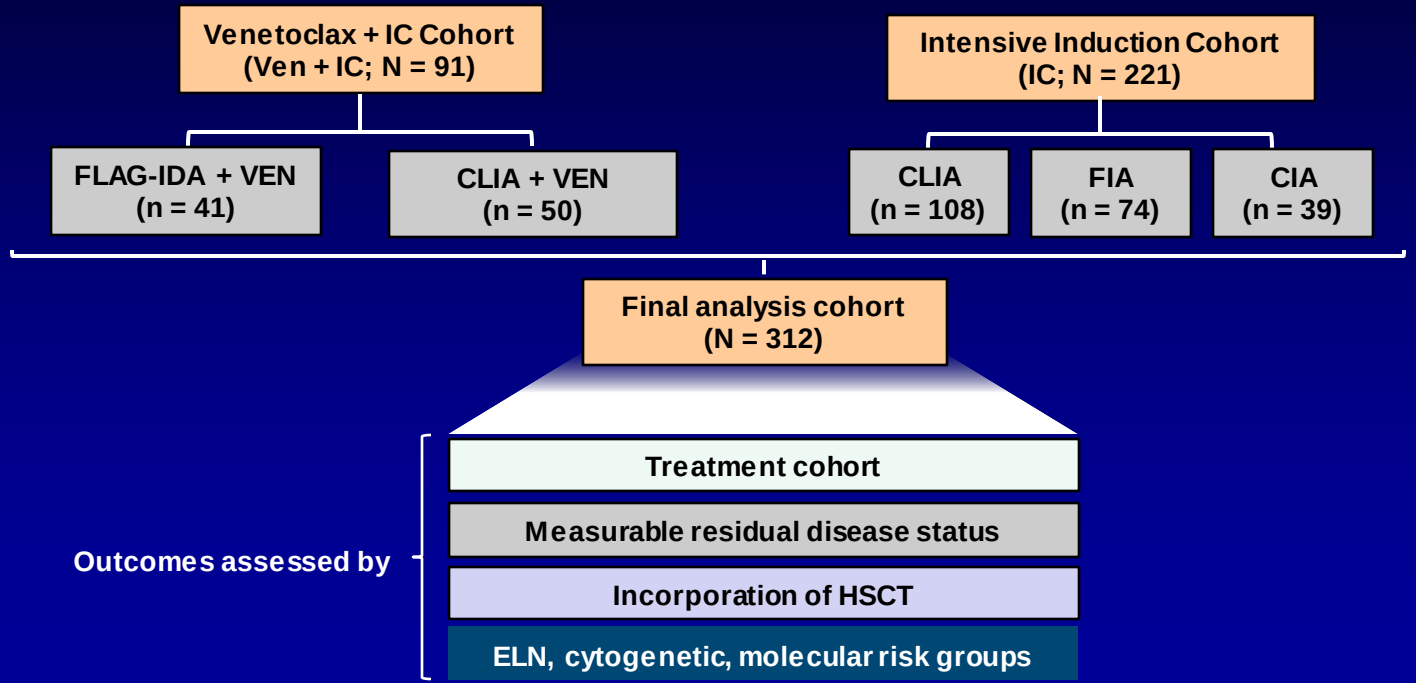
- **Midostaurin** (RYDAPT) – de novo younger AML (≤60 yrs), FLT3 mutation – April 2017
- **Gilteritinib** (FLT3 inhibitor) – FLT3 + R/R AML
- **Enasidenib** (AG-221; IDHIFA) – R/R AML and *IDH2* mutation – August 2017
- **Ivosidenib** (AG-120) – R/R AML and *IDH1* mutation – August 2018
- **CPX 351** (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+



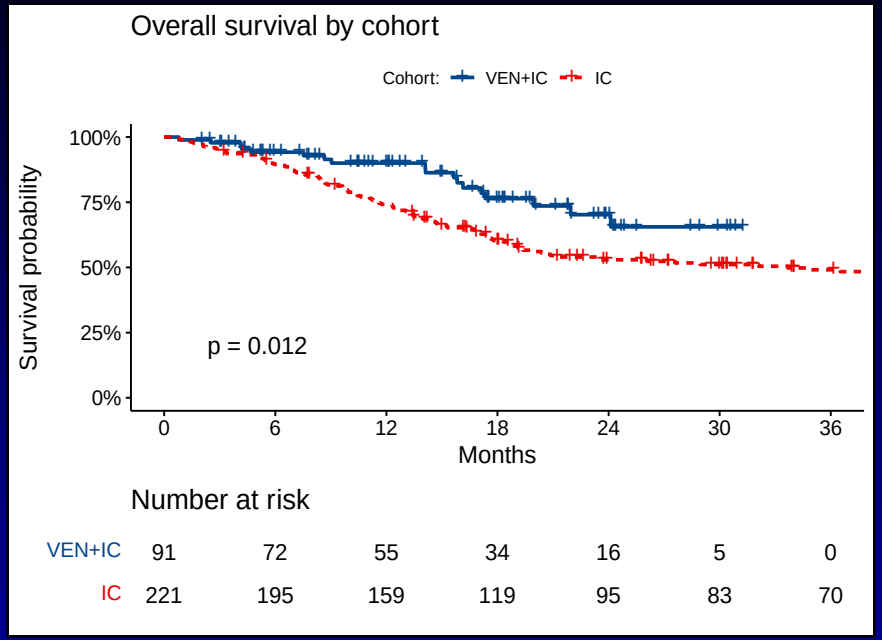
# VEN + IC in AML – Study Design

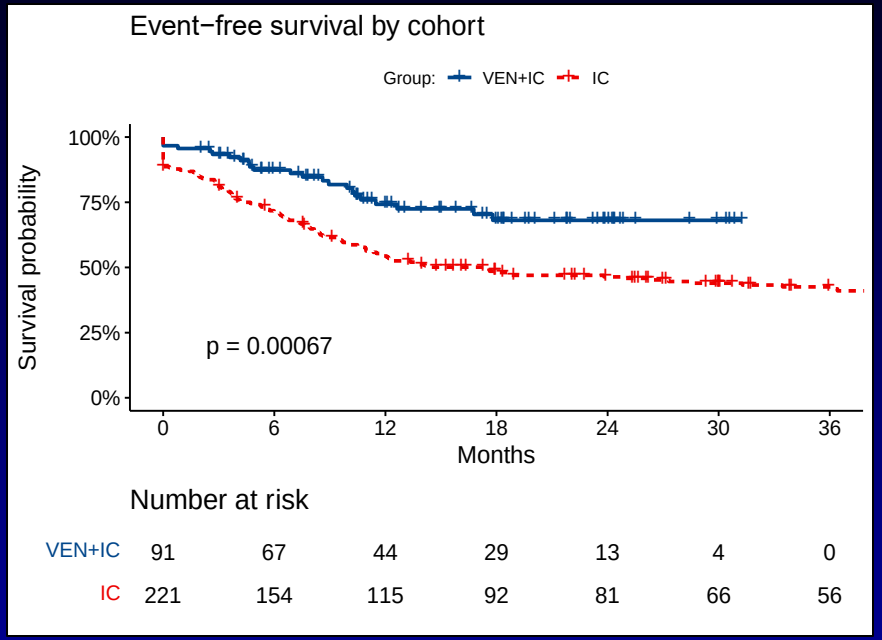
**Patients with ND-AML (de novo, sAML, tAML, stAML) treated with intensive chemotherapy (IC) at MDACC on prospective clinical trial protocols**




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

# AML – Outcome With Intensive ChemoRx ± Venetoclax



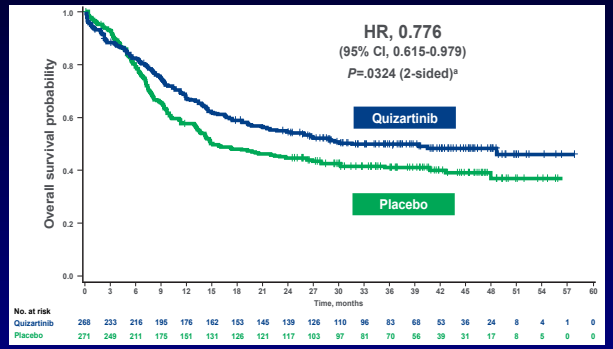

| Demographic<br>Median (95% CI) or %(SE) | Ven + IC | IC |
|---|---|---|
| **Median OS, months** | **NR (–)** | **34 (20–NR)** |
| 12-Month OS | 90 (3) | 74 (3) |
| 24-Month OS | 70 (6) | 52 (4) |

| Demographic<br>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) |

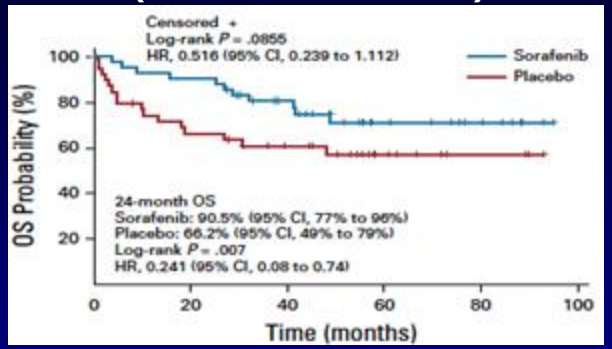
Lachowiez CA, et al. *Lancet Haematol.* 2022;9:e350-e360.

# FLT3 Inhibitors Improve OS in AML

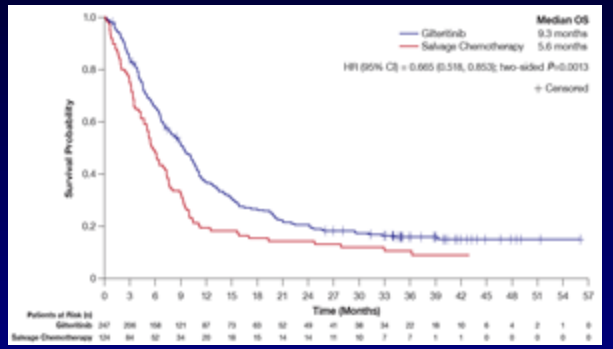
## New Dx AML
## intensive chemoRx + TKI/placebo

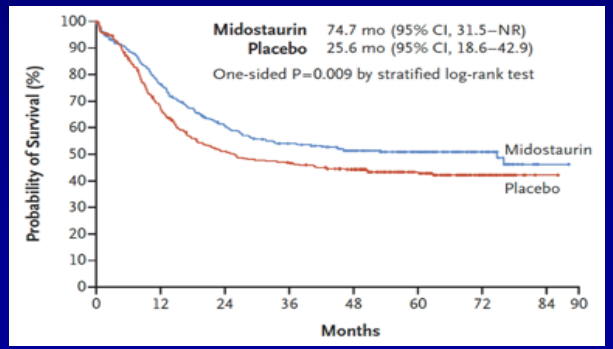


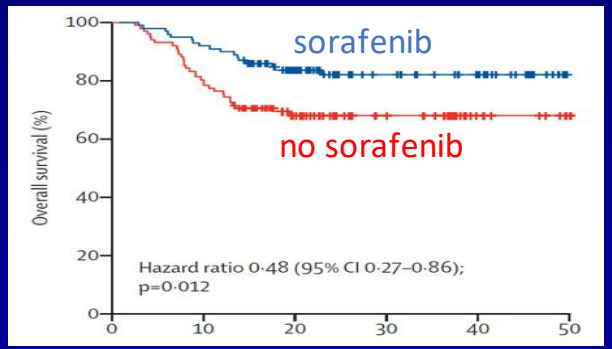

## TKI post allo SCT
## (sorafenib 2 studies)

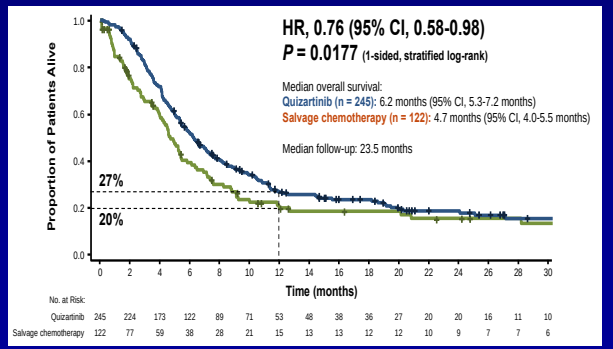



## R/R AML
## TKI vs chemoRx



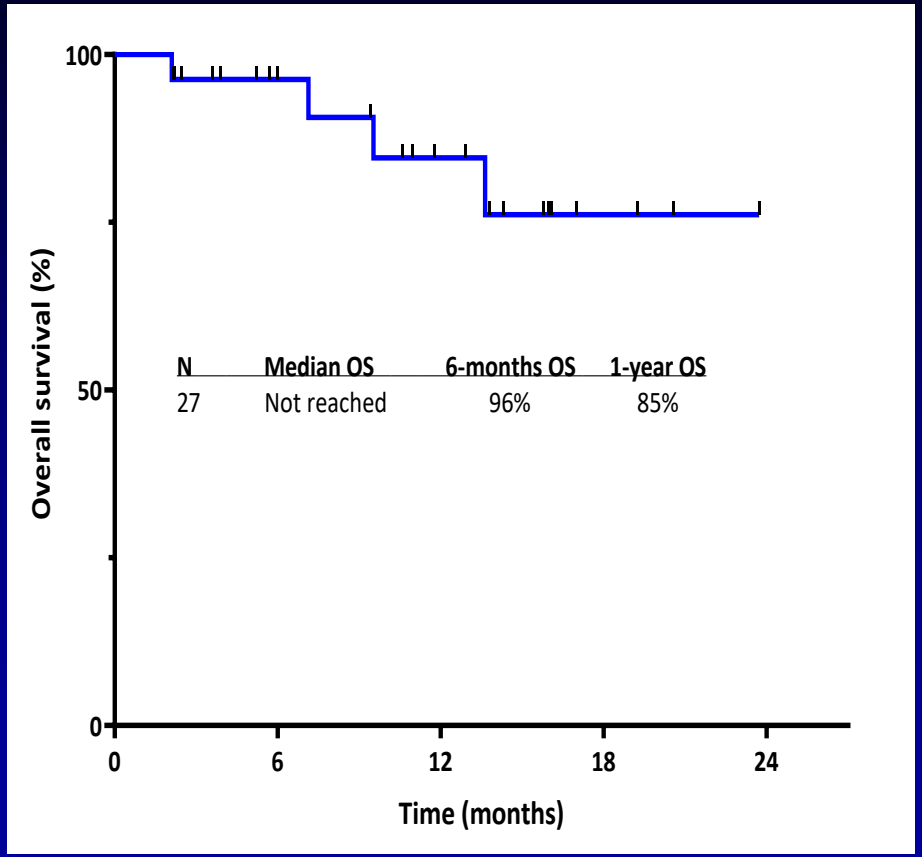




Erba HP, et al. EHA 2022. Abstract S100; Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464; Burchert A, et al. *J Clin Oncol.* 2020;38(26):2993-3002; Xuan Y, et al. *Lancet Oncol.* 2020;21(9):1201-1212; Perl AE, et al. *Blood.* 2022;139(23):3366-3375; Cortes JE, et al. *Lancet Oncol.* 2019;20(7):984-997.

# 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 |

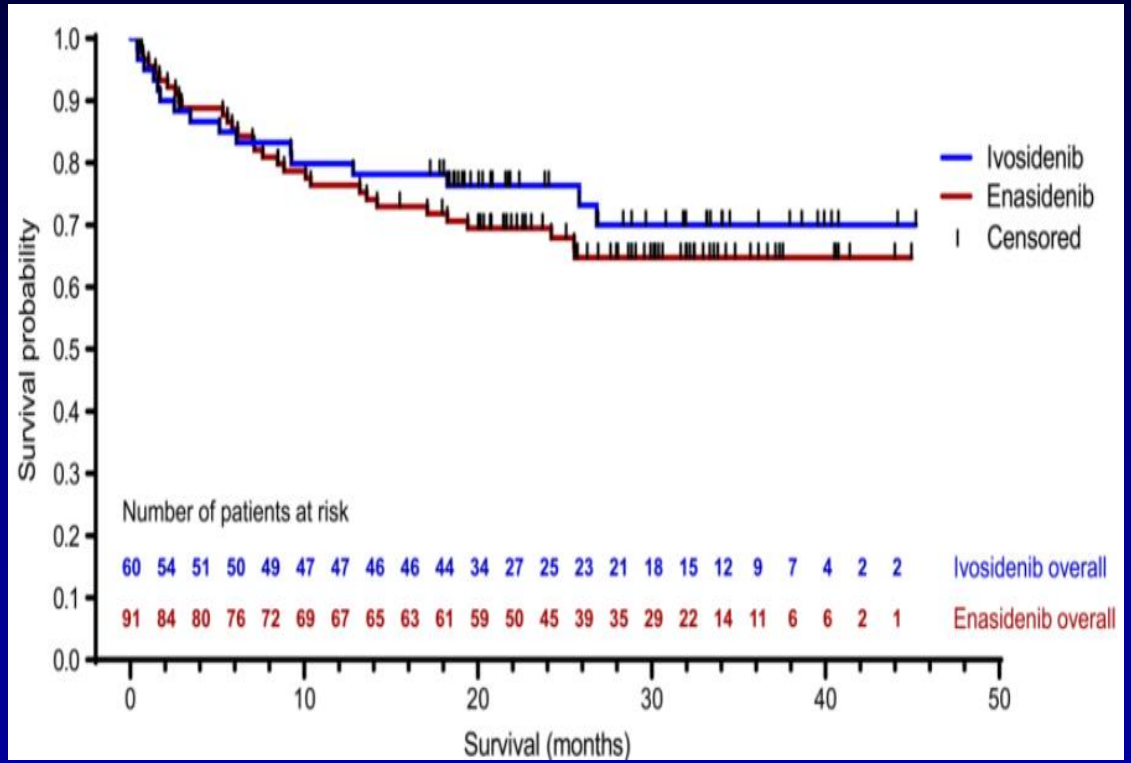



Short N, et al. *Blood*. 2022;140:abstract 831.

# 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

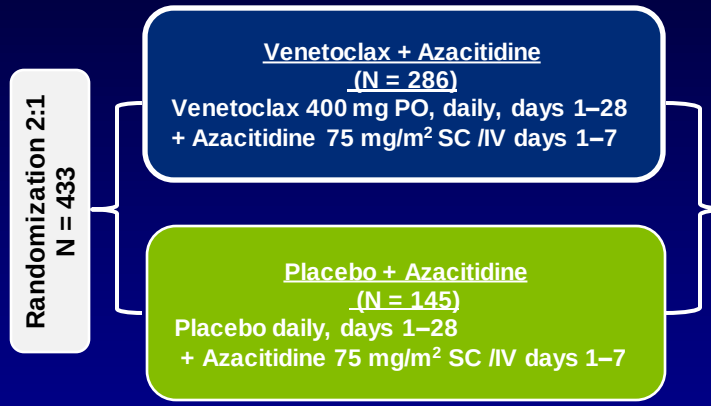
**Inclusion**

- 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**

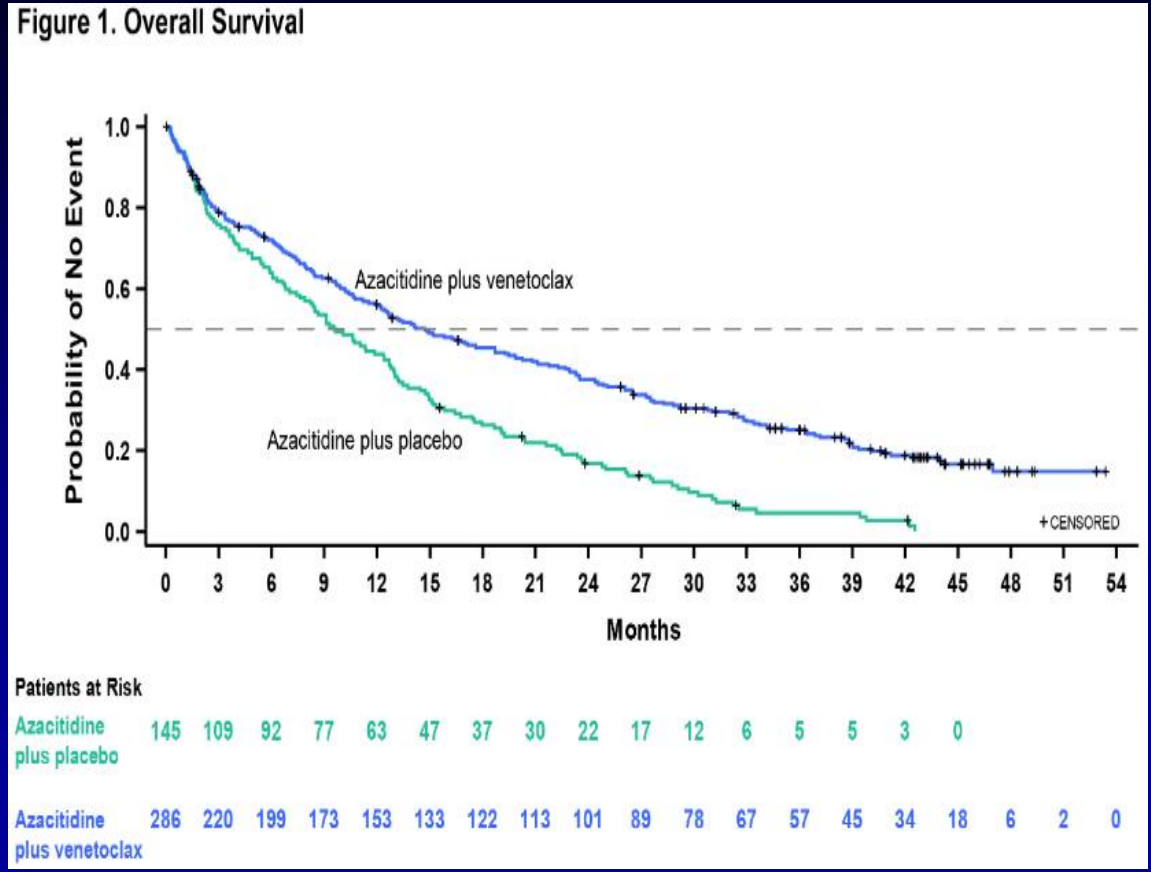
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

| | |
|---|---|
| **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<br>**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

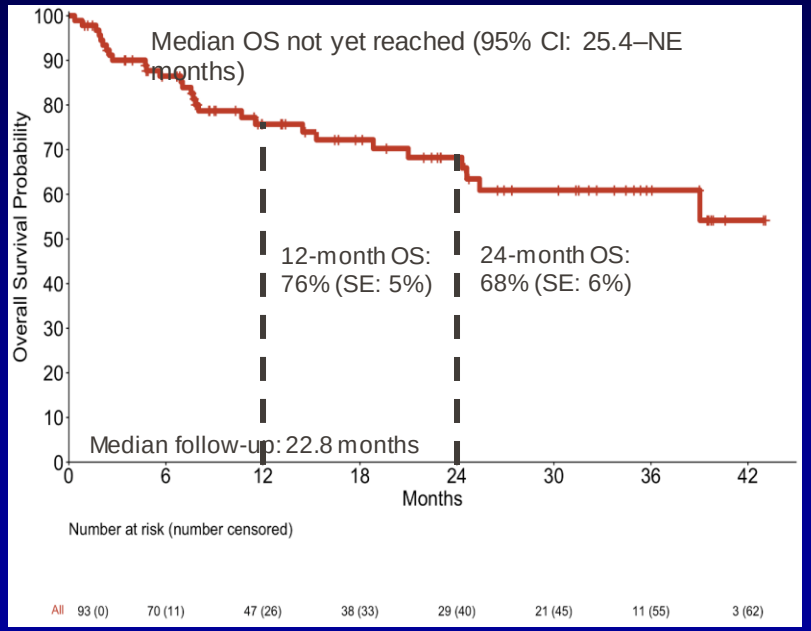
- 431 pts older, unfit with newly Dx AML randomized 2:1 to AZA-VEN (n = 286) or AZA (n = 145)
- 3-yr OS ≈7% with AZA; ≈25% with AZA-VEN
- Interpretation – HMA + VEN suboptimal

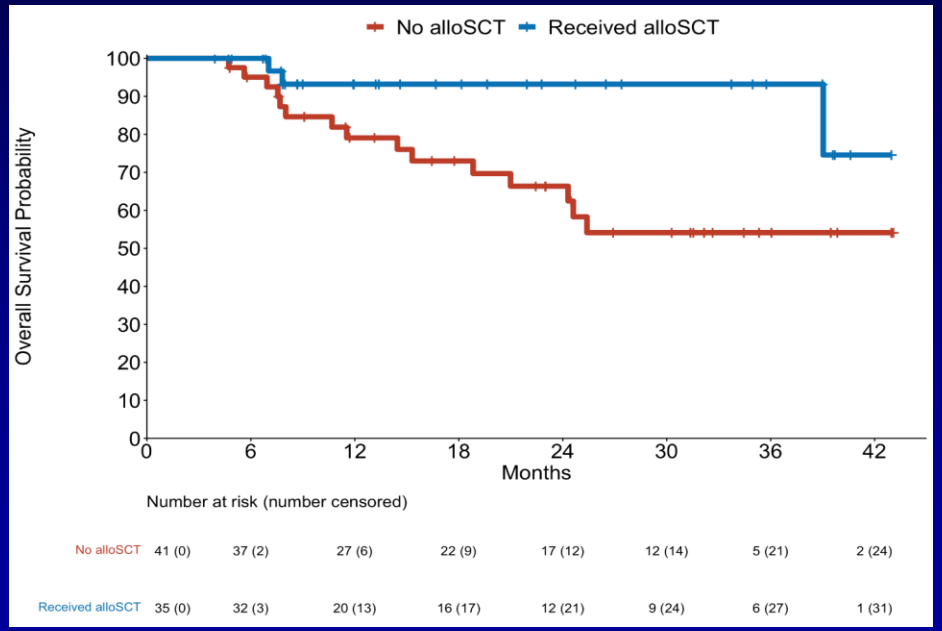



Pratz KW, et al. ASH 2022. Abstract 219.

# 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 T, et al. *J Clin Oncol.* 2022;21 and update in 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?


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

Global Leukemia Academy

# Q&A

APTITUDE HEALTH

Global Leukemia Academy

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

Nicola Gökbuget

APTITUDE HEALTH

# AYA: Adolescents and Young Adults

**Nicola Gökbuget**

Goethe University Hospital, Department of Medicine II, Frankfurt

GMALL Study Coordinator

UNIVERSITÄTS KLINIKUM FRANKFURT
GOETHE-UNIVERSITÄT

GMALL
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

DKTK German Cancer Consortium

uct Universitäres Centrum für Tumorerkrankungen Frankfurt
University Cancer Center

MED2

FRANKFURT CANCER INSTITUTE

# Potential conflicts of interest

Speaker honoraria, travel support, or advisory board

- Amgen
- Celgene
- Gilead
- Novartis
- Pfizer
- Jazz Pharmaceuticals
- Incyte
- Cellestia
- Erytech
- MorphoSys
- Autolus

Research support

- Amgen
- Pfizer
- Novartis
- Shire/Servier
- Jazz Pharmaceuticals
- Incyte

# Thoughts about adolescents, young adults, adults, and elderly . . .

- ***Origin of the discussion***
- Comparative data
- Definition of age groups
- Role of comorbidities
- GMALL approach
- What to learn from pediatric approaches
  - ASP
  - Maintenance
- What to learn from adult approaches
  - Immunotherapy
  - Ph+ ALL
- Specific support for young adults

Charles A. Schiffer. *J Clin Oncol.* 2003;21:760-761.

EDITORIAL

# Differences in Outcome in Adolescents With Acute Lymphoblastic Leukemia: A Consequence of Better Regimens? Better Doctors? Both?

# Outcome of adolescents (~14-21 yr) with ALL in "pediatric" vs "adult" ALL trials

| | | Pts | Age | CR | EFS/DFS |
|---|---|---|---|---|---|
| | *Stock, ASH 2008* | | | | |
| | CCG | 177 Ch | 16-21 | 90% | 63% |
| Insurance? | CALGB | 112 Ad | | 90% | 34% |
| | *Boissel, BLOOD 2003* | | | | |
| | FRALLE 93 | 77 Ch | 15-20 | 94% | 72% |
| SCT? | LALA 96 | 100 Ad | | 83% | 49% |
| | *De Bont, LEUKEMIA 2004* | | | | |
| | SKION | 47 Ch | 15-18 | 98% | 69% |
| SCT? | HOVON 93-99 | 44 Ad | | 91% | 34% |
| | *Ramanujachar, PED BLOOD CANCER 2006* | | | | |
| | ALL97 | 61 Ch | 15-17 | 98% | 65% |
| SCT? | UKALLXII | 67 Ad | | 94% | 49% |
| | *Testi, ASH 2004* | | | | |
| | AIEOP | 150 Ch | 14-18 | 94% | 80% |
| Similar | GIMEMA | 95 Ad | | 89% | 71% |
| | Usvasalo, Haematologica 2008 | | | | |
| | Pediatric | 128 Ch | 10-16 | 96% | 67% |
| Similar | Adult | 97 Ad | 17-25 | 97% | 60% |

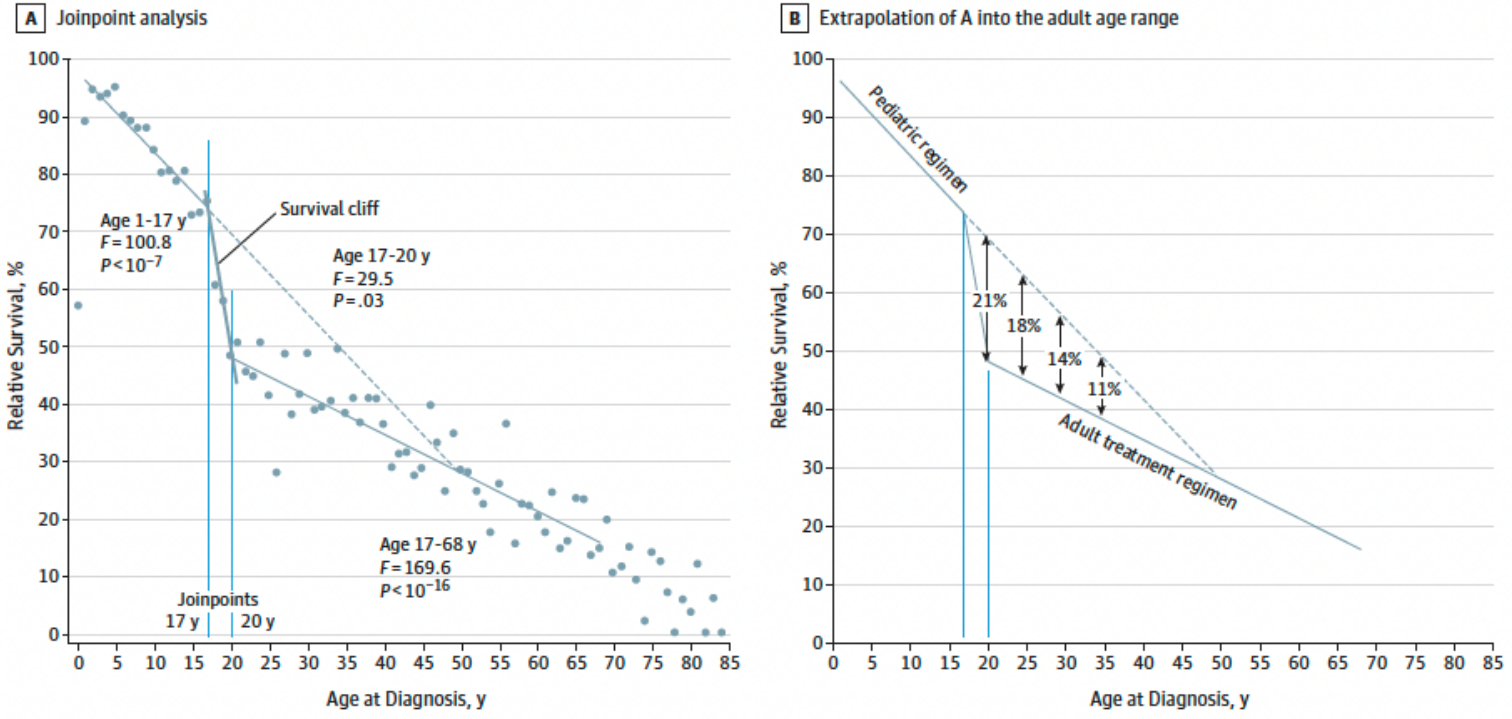
34%
49%
34%
49%

- Adult protocols had extraordinarily poor results; reason for comparison?
- Selection factors?
- Age group: 14-21 yr!

# Survival of younger adults with ALL in USA, 2000-2007

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

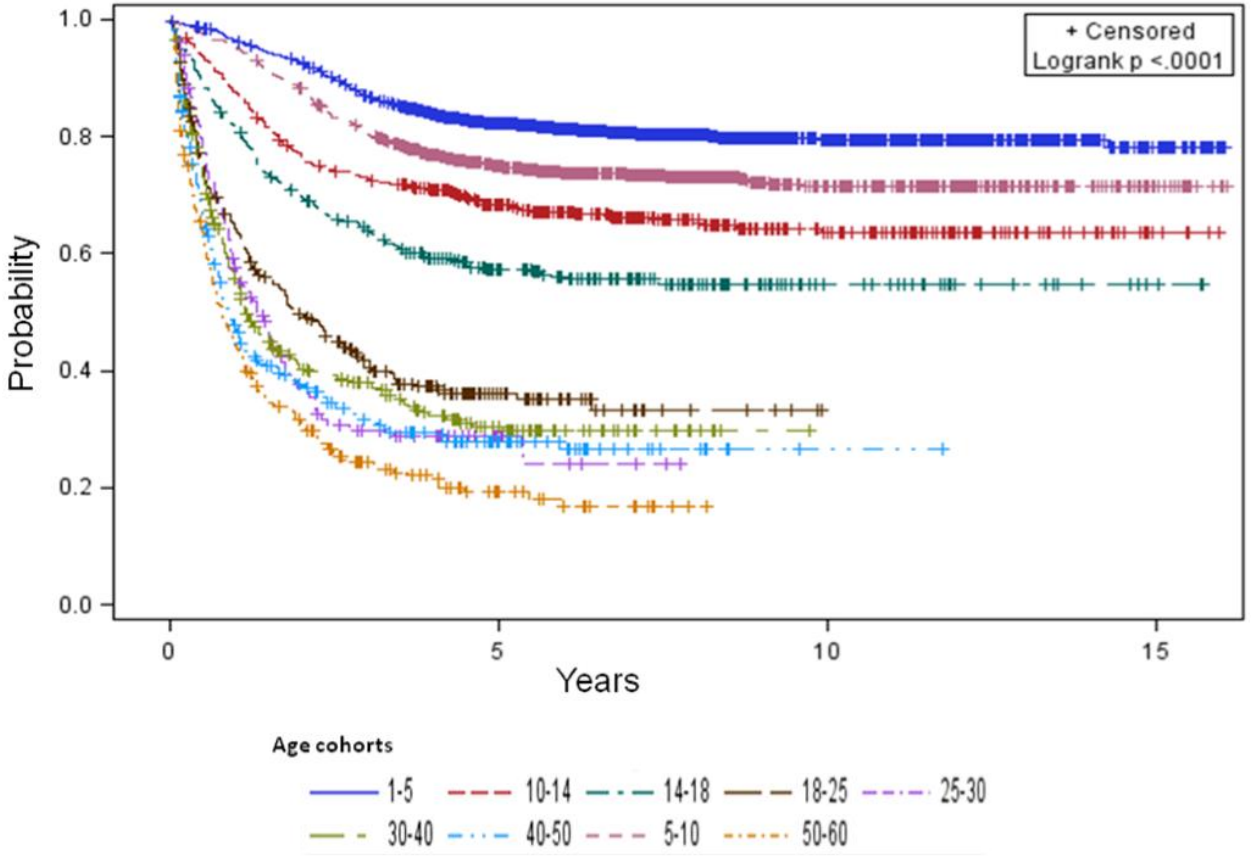
**Figure 2. Five-Year Relative Survival Rate of Patients With Acute Lymphoblastic Leukemia by Single Year of Age at Diagnosis, 2000 to 2007, From the Surveillance, Epidemiology, and End Results 18 Data[3]**



# Thoughts about adolescents, young adults, adults, and elderly . . .

- Origin of the discussion
- ***Comparative data***
- Definition of age groups
- Role of comorbidities
- GMALL approach
- What to learn from pediatric approaches
  - ASP
  - Maintenance
- What to learn from adult approaches
  - Immunotherapy
  - Ph+ ALL
- Specific support for young adults

# Treatment results in ALL depend on age
# CHILDREN vs ADULTS



# Potential reasons for poorer outcome of ALL with increasing age

1. **Poor prognostic features increase with age**
   - **Early T-ALL, hypodiploid ALL**
2. **Favorable prognostic features decrease with age**
3. **Tolerance to chemotherapy decreases with age**
   - **Morbidity (eg, due to acquired infections)**
   - **Mortality**
4. **Poorer time and dose compliance**
   - **Treatment delays due to complications**
   - **Prolonged hematologic regeneration**
5. **More (too much) SCT compared with children?**
   - **Treatment-related mortality**
5. **Multidrug resistance**
6. **Different chemotherapy**
   - HDMTX, steroids, vincristine, asparaginase
   - Fewer reinduction/consolidation courses
   - Shorter maintenance

# Treatment results of children compared with adolescents (Austrian BFM protocol)

Pichler H, et al. *Br J Haematol*. 2013;161:556-565.

## Distribution of Biological Features

| | 15-17 y | 1-14 y | |
|---|---|---|---|
| Total | 67 | 1058 | |
| Immunophenotype | | | |
| BCP-ALL | 70% | 88% | <.001 |
| T-ALL | 30% | 12% | |
| Hyperdiploid | 15% | 25% | .02 |
| **ETV6-RUNX1** | **1%** | **23%** | **<.001** |
| BCR-ABL | 3% | 2% | ns |
| MLL-rearr. | 1% | 2% | ns |

## Response and Risk Stratification

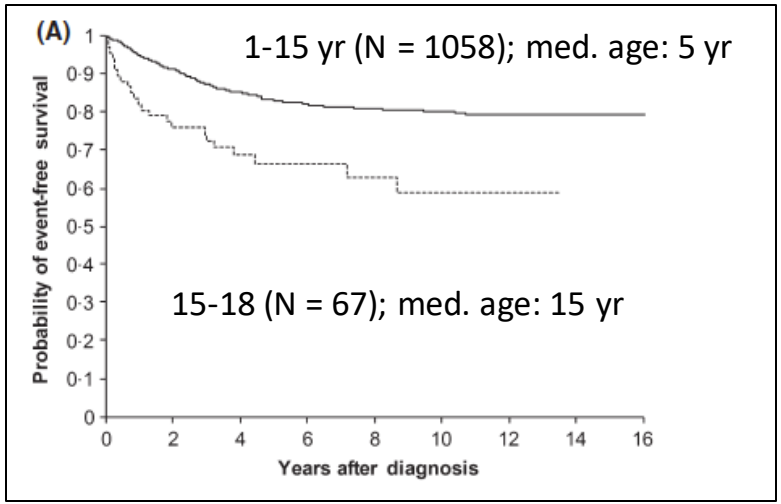
| | 15-17 y | 1-14 y | |
|---|---|---|---|
| Prednisone Poor | 18% | 9% | .01 |
| D15 M3 marrow | 31% | 9% | <.001 |
| CR day 33 | 91% | 98% | <.001 |
| **Risk group** | | | |
| SRG | 10% | 31% | <.001 |
| MRG | 61% | 56% | |
| **HRG** | **29%** | **12%** | |
| **MRD** | | | |
| LR | 9% | 32% | |
| IMR | 74% | 63% | |
| **HR** | **18%** | **5%** | <.001 |

# Treatment results of children compared with adolescents (Austrian BFM protocol)

Pichler H, et al. *Br J Haematol*. 2013;161:556-565.

**Adolescents: 6%**

## Overall Survival

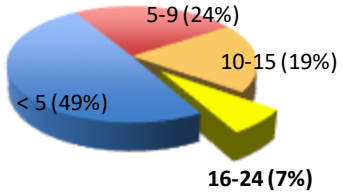



| | 15-17 y | 1-14 y | |
|---|---|---|---|
| Total | 67 | 1058 | |
| Relapse | 18% | 15% | ns |
| **Death** | | | |
| **Induction** | **3%** | **1%** | **.04** |
| **First CR** | **12%** | **2%** | **<.001** |
| OS 5 y | 76% | 91% | <.001 |
| RR 5 y | 19% | 13% | ns |

# UKALL 2003 in children and young adults

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

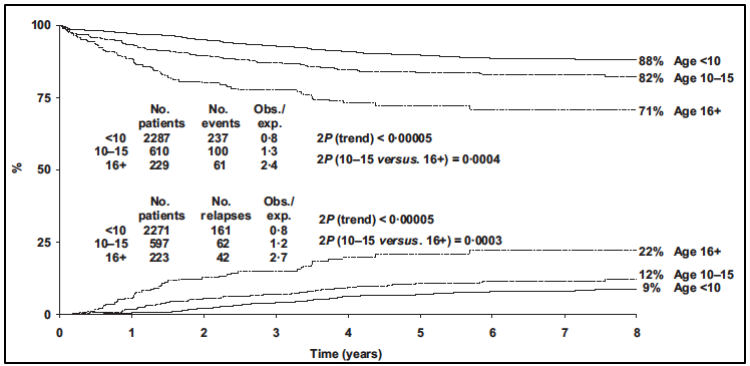
## Age Distribution




## Patient Characteristics

| Age Group | <5 y | 5-9 y | 10-15 y | 16-24 |
|---|---|---|---|---|
| T-ALL | 5% | 14% | 23% | **28%** |
| Good Cy | 72% | 64% | 37% | **25%** |
| MRD high | 28% | 35% | 37% | **48%** |

## EFS and RR by Age Groups




## EFS and RR by Age Groups

| Age Group | <10 y | 10-15 y | 16-24 |
|---|---|---|---|
| EFS | 90% | 84% | **72%** |
| OS | 94% | 87% | **76%** |
| RR | 7% | 11% | **21%** |
| TRM | 2% | 3% | **6%** |

# UKALL 2003 in children and young adults

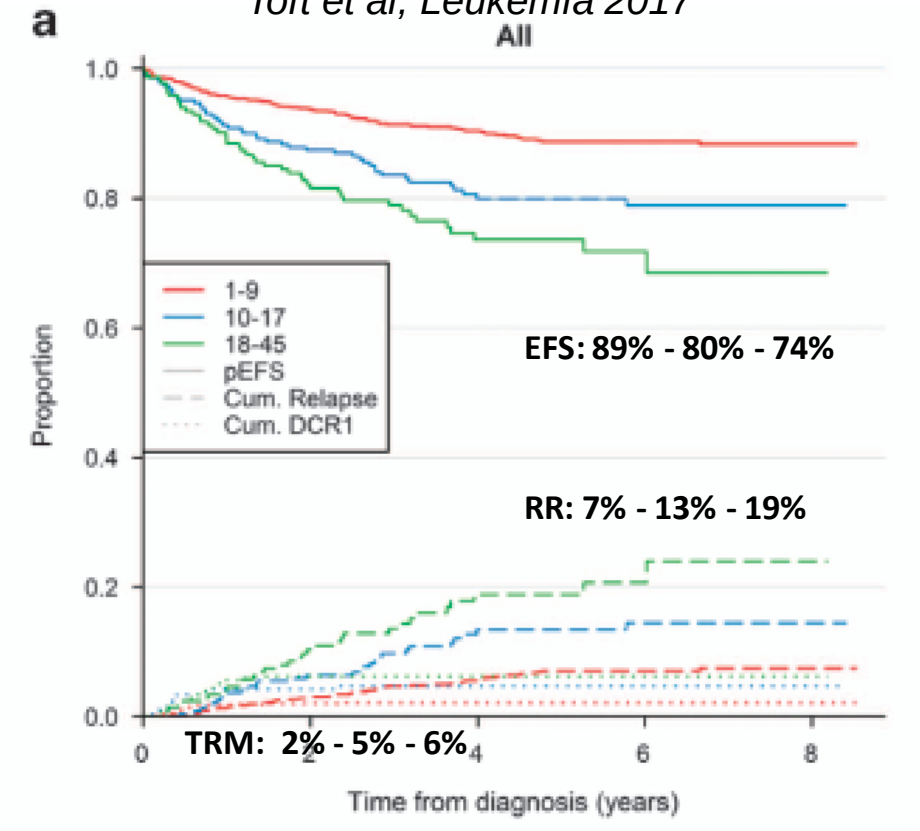
Hough R, et al. *Br J Haematol.* 2016;172:439-451.

**Impact of Age on SAE Frequency**

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

# NOPHO ALL2008: Pediatric treatment 1-45 yr for Ph/BCR-ABL–positive ALL

*Toft et al, Leukemia 2017*



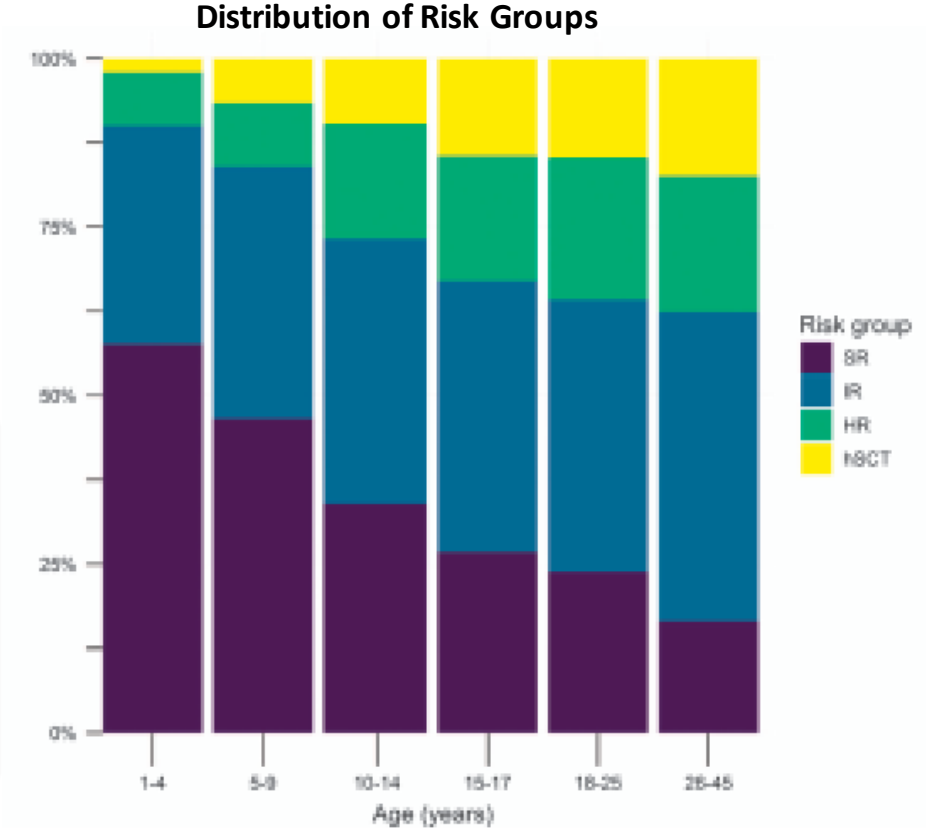
# NOPHO ALL2008: Pediatric treatment 1-45 yr for Ph/BCR-ABL–negative ALL

Toft N, et al. *Leukemia*. 2018;32:606-615.

Period: 7/2008-12/2014
Patients: 1509
Age: 1-45 yr

1-9 yr: 1022 (68%)
10-17 yr: 266 (18%)
**18-45 yr: 221 (15%)**

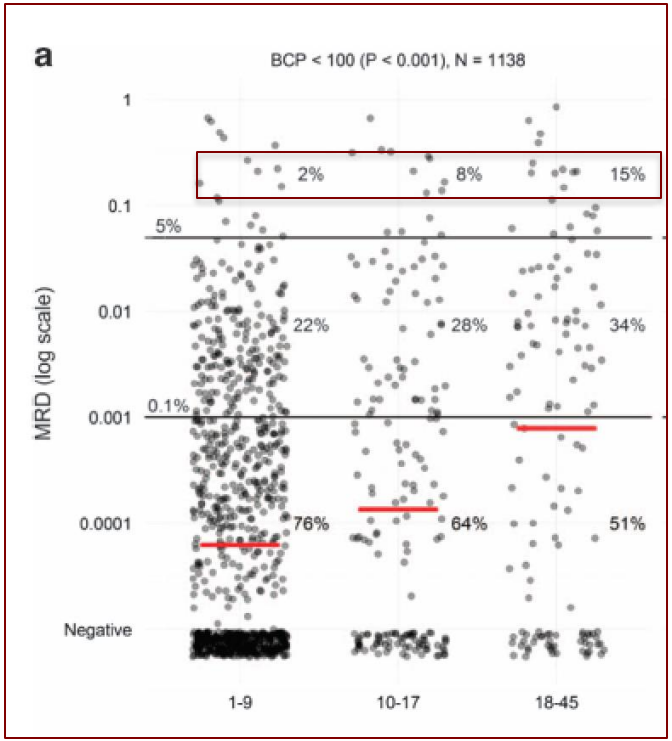
| | T-ALL | *KMT2A* t(12;21) | |
|---|---|---|---|
| **1-9 yr:** | **9%** | **3%** | **28%** |
| **10-17 yr:** | **25%** | **5%** | **6%** |
| **18-45 yr:** | **32%** | **6%** | **2%** |

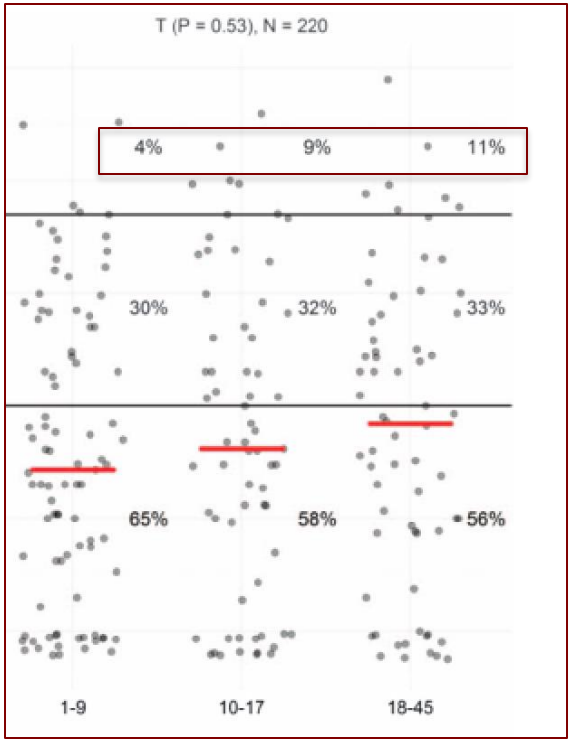


# NOPHO ALL2008: Pediatric treatment 1-45 yr for Ph/BCR-ABL–positive ALL

Toft N, et al. *Leukemia*. 2018;32:606-615.

## MRD Day 29

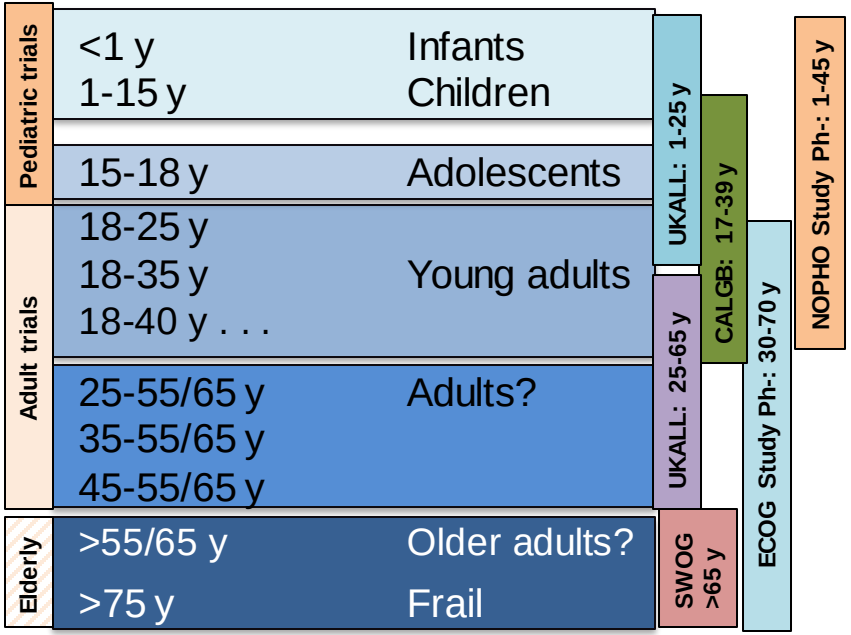


# Thoughts about adolescents, young adults, adults, and elderly . . .

- Origin of the discussion
- Comparative data
- ***Definition of age groups***
- Role of comorbidities
- GMALL approach
- What to learn from pediatric approaches
  - ASP
  - Maintenance
- What to learn from adult approaches
  - Immunotherapy
  - Ph+ ALL
- Specific support for young adults

# What is the meaning of “young” and "old" in the ALL world?




**Age cuts are not evidence based, eg**

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

**Severe consequences, eg**

- **Non-comparability of clinical trials**
- **Marketing authorization for CTL019 up to 25 yr**
- **Broad age group of "so-called" adults (40-80?) without clear treatment strategy**

# Thoughts about adolescents, young adults, adults, and elderly . . .

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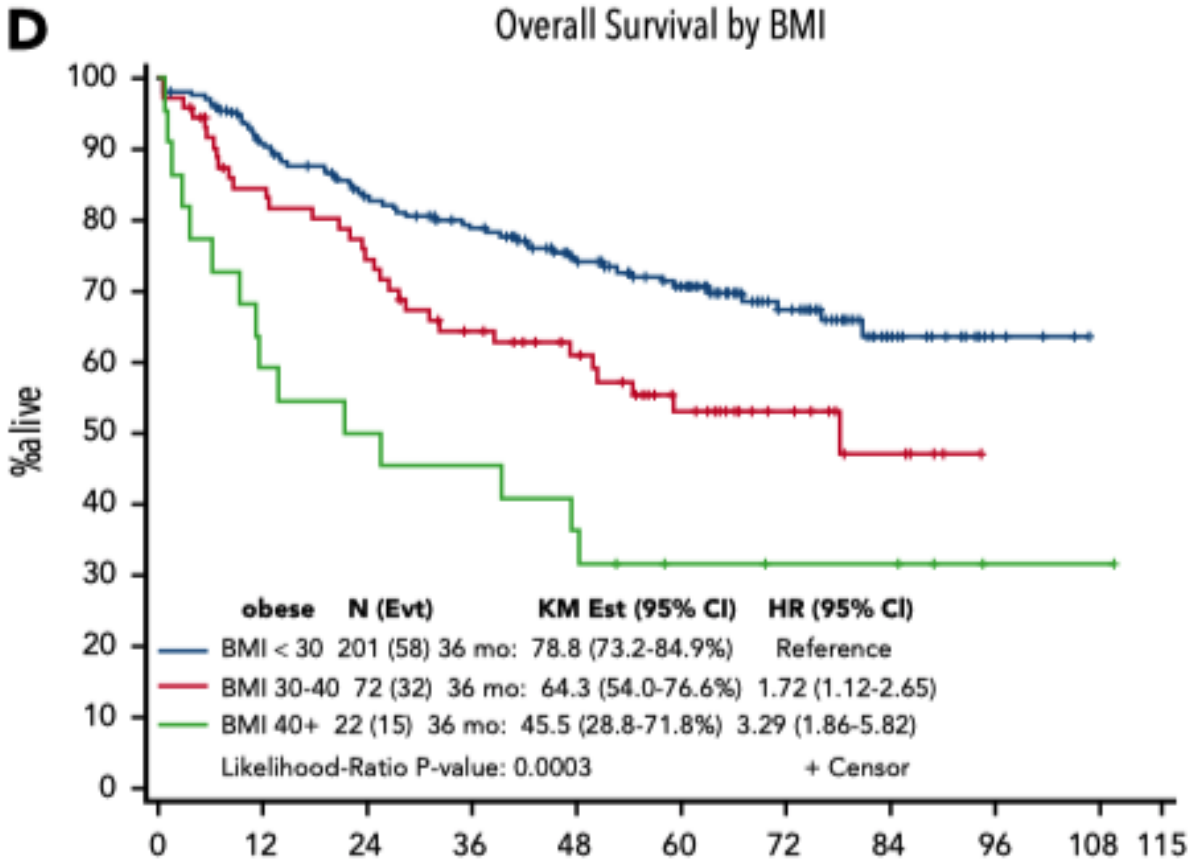
  - Ph+ ALL
- Specific support for young adults

# Pediatric regimen in AYA (17-39 yr)

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



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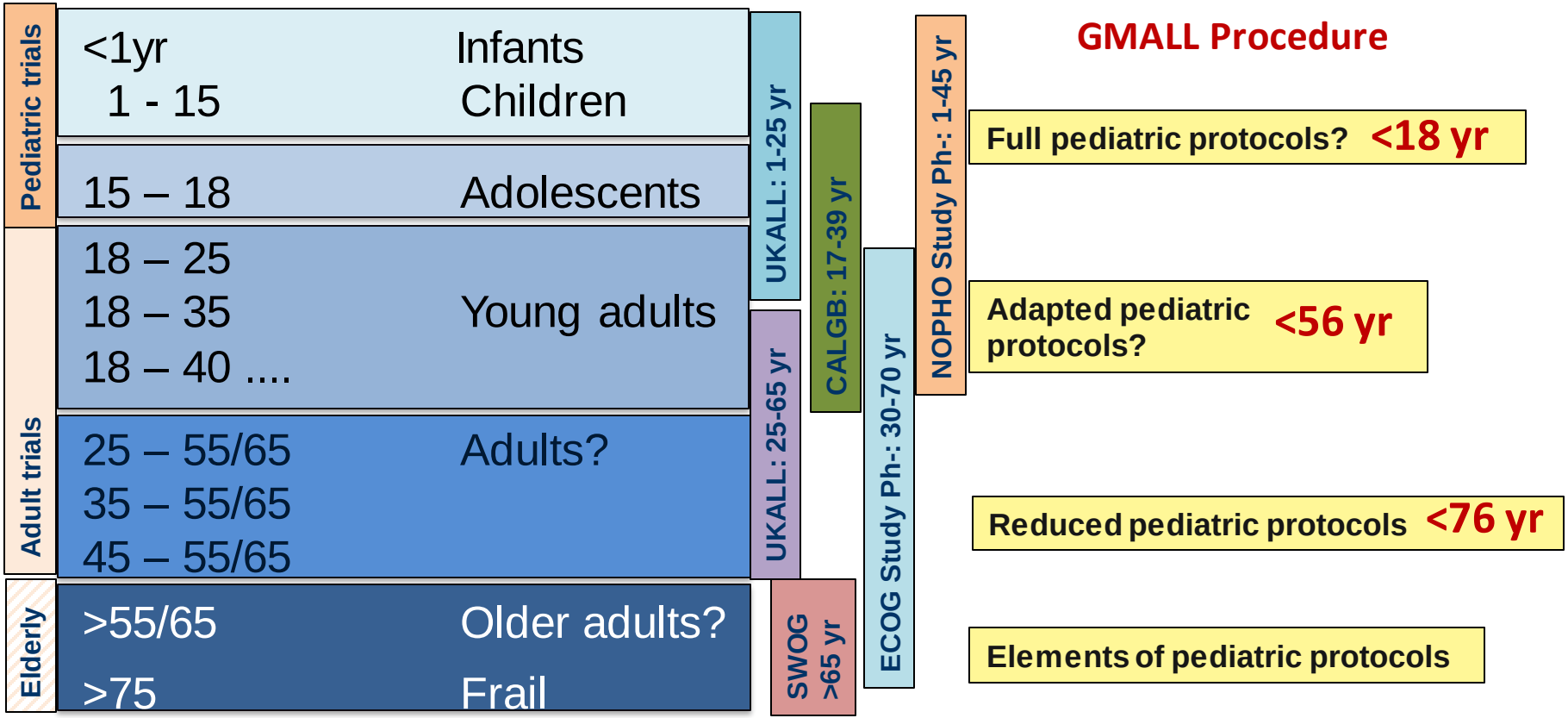
# Outcome of younger adults with pediatric/pediatric-based/pediatric-inspired therapies

| Author | N | Age | CR | OS |
|---|---|---|---|---|
| **Ribera, 2008** | **81** | **29 (15-30)** | **98%** | **69% (6 y)** |
| **Huguet, 2009** | **225** | **31 (15-60)** | **93%** | **60% (3 y)** |
| **Haiat, 2011** | **40** | **33 (18-55)** | **90%** | **75% (3 y)** |
| **Rijneveld, 2011** | **54** | **26 (17-40)** | **91%** | **72% (2 y)** |
| **Stock, 2014** | **296** | **24 (17-39)** | **nr** | **78% (2 y)** |
| **Rytting, 2014** | **85** | **21 (13-39)** | **94%** | **74% (3 y)** |
| **De Angelo, 2015** | **92** | **28 (18-50)** | **85%** | **67% (4 y)** |

**Many adult ALL study groups have used pediatric-based regimens for several decades**

Adapted from Boissel N, et al. *J Adolesc Young Adult Oncol*. 2015;4:118-128.

# Definition of target population:
# What is the meaning of "young" in the ALL world?

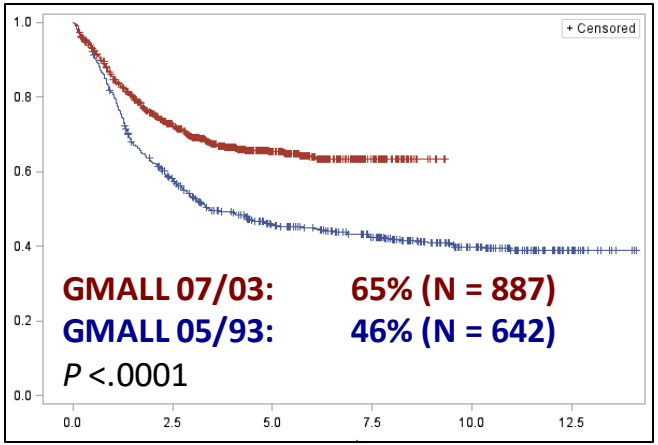


# GMALL trial 07/2003 vs 05/93

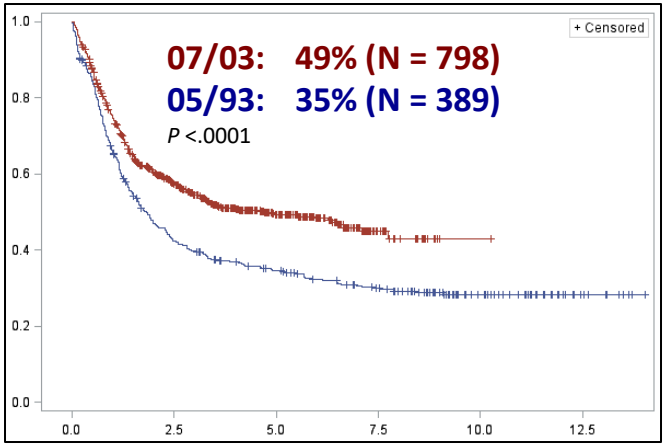
# Overall survival 07/2003 vs 05/93

Goekbuget N, et al. ASH 2014.

## 15–35 yr




## 36–55 yr




**Improved with "pediatric-based" – adult optimized approach in all age groups**

# GMALL trial 08/2013: Flow sheet

Gökbuget N, et al. ASH 2021.

- ➔ BFM-based "pediatric" regimen
- ➔ Dexa during induction/consolidation I
- ➔ 9 × PEG-asparaginase (2000–1000–500 U/m$^2$)
- ➔ 7 × HDMTX (1.5 g/m$^2$)
- ➔ Reinduction
- ➔ Risk-adapted SCT indication

Randomization I:
CNS irradiation vs i.th. prophylaxis in B-ALL/LBL

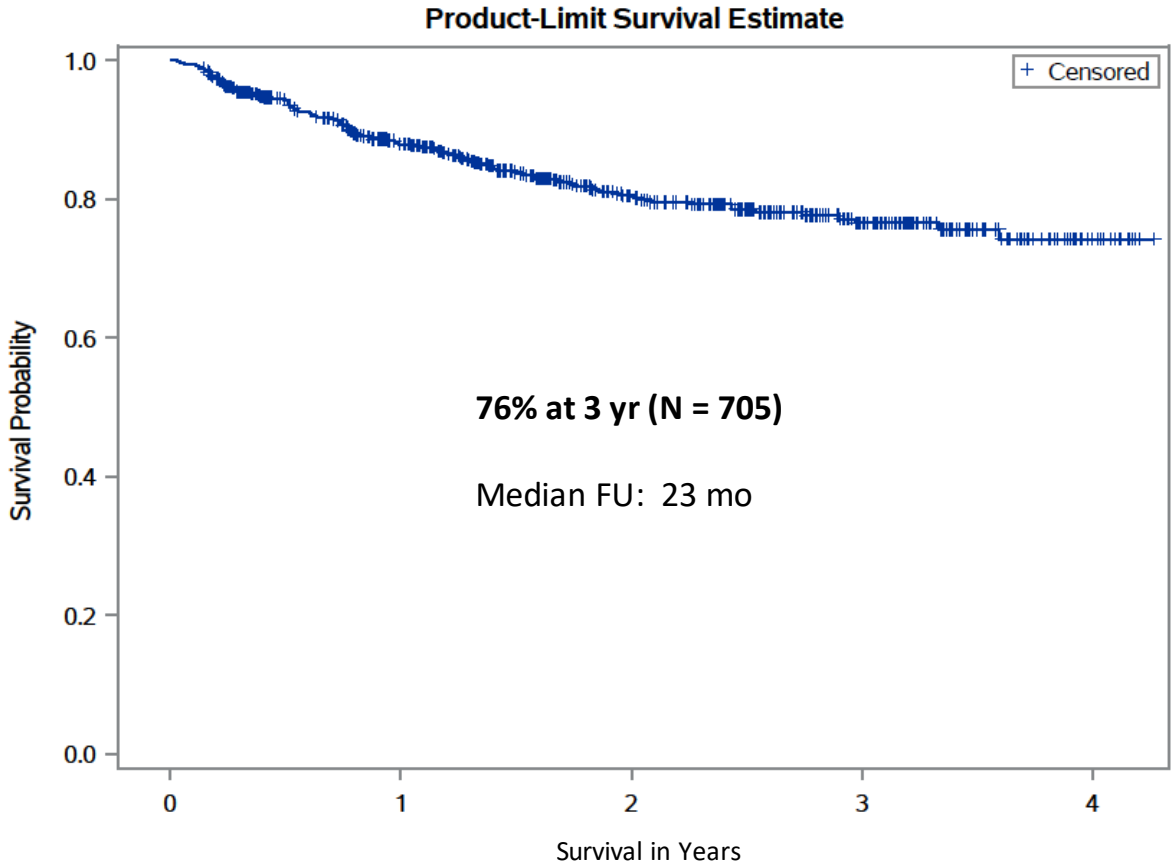
Randomization II:
SCT vs standard therapy in HR pts with MolCR after induction

**Risk stratification:** HR: ≥1 risk factor
- Pro-B-ALL and/or KMT2A
- Early/mature T
- B-precursor: WBC >30.000
- No CR after induction I

+ Molecular Failure after Consolidation I

# GMALL trial 08/2013: Overall survival

Gökbuget N, et al. ASH 2021.



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GMALL
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

# PEG-asparaginase in adults with newly diagnosed ALL (15*-55 yr)

Gökbuget N, et al. ASH 2010.

Pediatric-based regimen with 2-phase induction, reinduction, and intensive consolidation based on HDMTX, asparaginase, HDAC, and other drugs and risk-adapted SCT

Dose intensification of PEG-asparaginase:
1000 U/m$^2$ – 2000 U/m$^2$ in induction
500 U/m$^2$ – 2000 U/m$^2$ in consolidation

Patients: 1226 from 100 sites

| Asp dose | 1000/m$^2$ | 2000/m$^2$ |
|---|---|---|
| N | 826 | 400 |
| CR | 91% | 91% |
| ED | 4% | 5% |
| MRD <10-4 | 79% | 82% |
| | | |
| OS | 60% | 67% |
| RD | 61% | 74% |
| | | |
| Standard risk | | |
| OS | 68% | 80% |
| 15-45 y | 71% | 82% |
| 45-55 y | 56% | 74% |

# Thoughts about adolescents, young adults, adults, and elderly . . .

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  - **Immunotherapy**
  - **Ph+ ALL**
- Specific support for young adults

# Randomized study with rituximab in CD20-positive, Ph-negative adult ALL

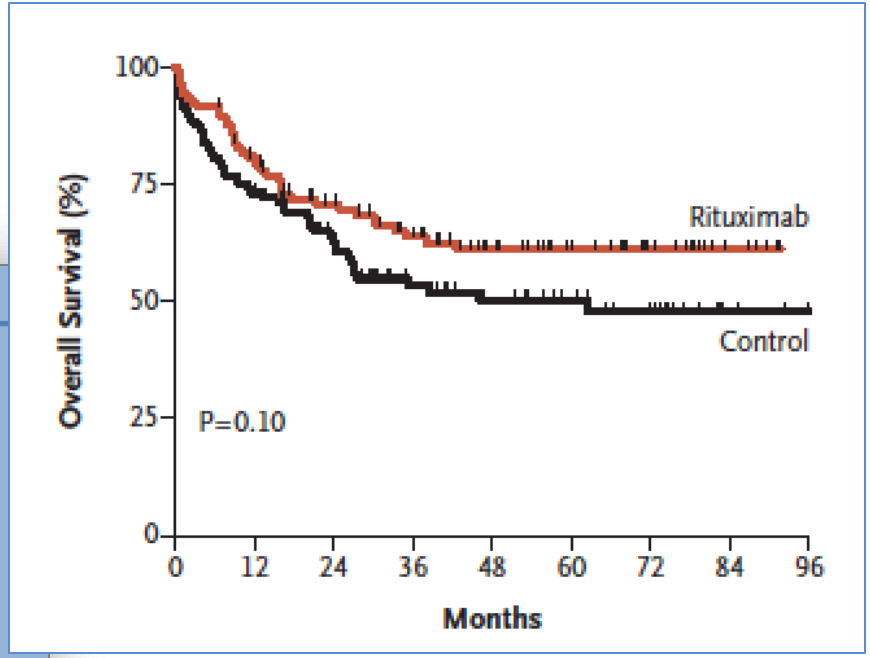
**Maury S, et al. *N Engl J Med*. 2016;375:1044-1053.**

Ph-neg, CD20-pos (>20%) B-precursor ALL
GRAALL protocol + 16-18 rituximab infusions
AlloSCT in CR1 for HR pts

N = 209 (2005-2014)
Median age: 40 (18-59) yr

| | Ritux | | No Ritux | | |
|---|---|---|---|---|---|
| **CR** | **92%** | | **91%** | | |
| MRD $<10^{-4}$ | | | | | |
| After induction | 65% | | 71% | | |
| **After cons 3** | **91%** | | **82%** | | |
| SCT rate | 34% | | 20% | | |
| **CIR 2 y** | **18%** | | **30%** | **0.02** | |
| NRM 2 y | 12% | | 12% | | |
| **EFS 2 y** | **65%** | (66%*) | **52%** | (53%*) | 0.04 (0.02*) |
| **OS 2 y** | **71%** | (74%*) | **64%** | (63%*) | 0.09 (0.02*) |

*SCT in CR1 censored.



# Selection and sequencing of immunotherapies in first-line management of adult ALL: GOALS

## Younger Patients
18–55/65 yr

- Intensify in HR subsets, avoid SCT?
- Reduce toxicity by replacing chemotherapy in low-risk subsets

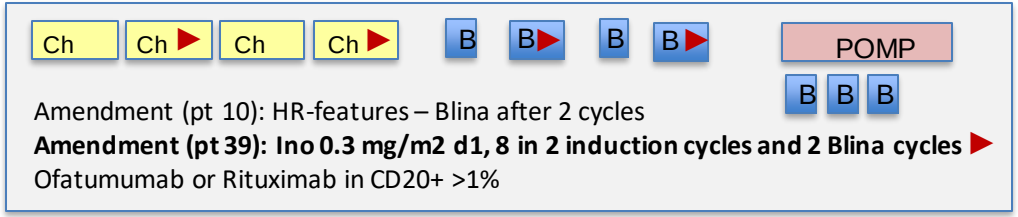
- MRD- setting
- Additional dose in induction
- Additional dose in consolidation
  - All patients
  - High-risk patients
- **Replacement of chemotherapy**

## Older Patients
>55/65 yr

- Reduce mortality in induction
- Improve efficacy in the context of dose-reduced regimens

# Hyper-CVAD + blinatumomab ± inotuzumab in younger patients Ph-neg, B-prec

**Short N, et al. EHA 2022 and *Lancet Haematol*. 2022;9:e535-e545.**



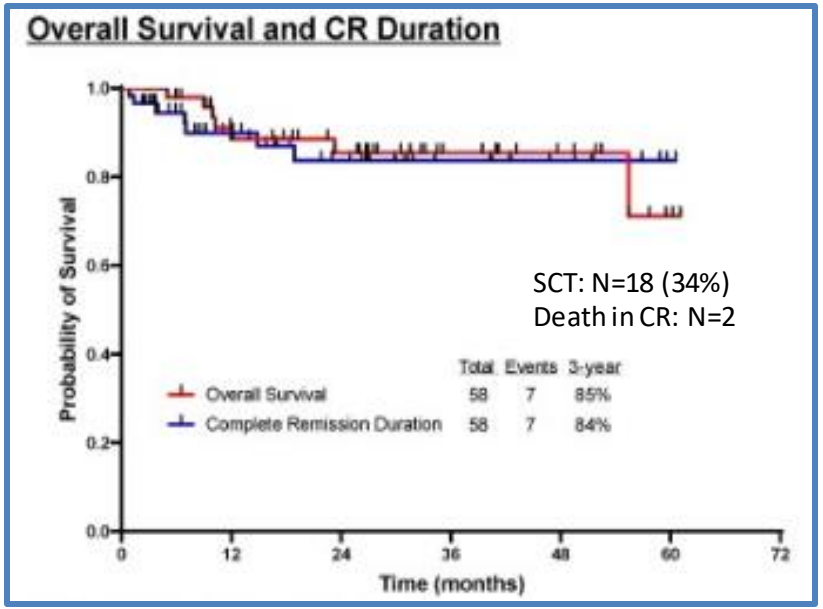

## Patient characteristics (N = 58)

| | Overall | + Blina | + Blina + Ino |
|---|---|---|---|
| N | 58 | 38 | 20 |
| Age (yr) | 34 (17-59) | 37 | 24 |

## Response (N = 45; 13 in CR at study entry)

| | Overall | + Blina | + Blina + Ino |
|---|---|---|---|
| N | 58 | 38 | 20 |
| CR after induction | 80% | 81% | 77% |
| CR at any time | 100% | 100% | 100% |
| All pts | | | |
| MRD neg ind. | 76% | 85% | 63% |
| MRD neg any | 95% | 97% | 90% |
| ED | 3% | 3% | 0% |

## Outcome (OS, CRD)



# Selection and sequencing of immunotherapies in first-line management of adult ALL: GOALS

## Younger Patients
18–55/65 yr

- Intensify in HR subsets
- Reduce toxicity by replacing chemotherapy in low-risk subsets

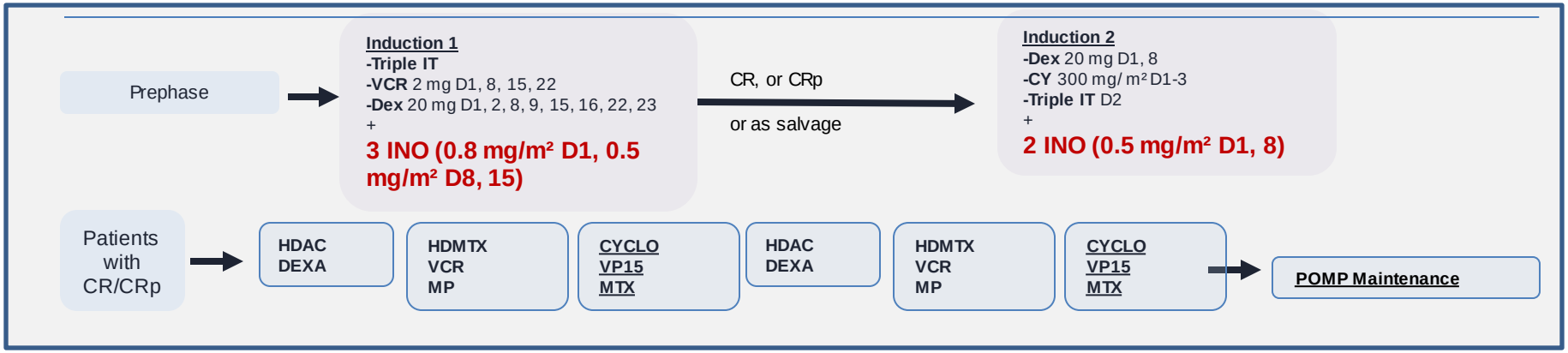
## Older Patients
>55/65 yr

- Reduce mortality in induction
- Improve efficacy in the context of dose-reduced regimens

- MRD- setting
- Replacement of induction
- Additional dose in consolidation or
- **Replacement of chemotherapy**

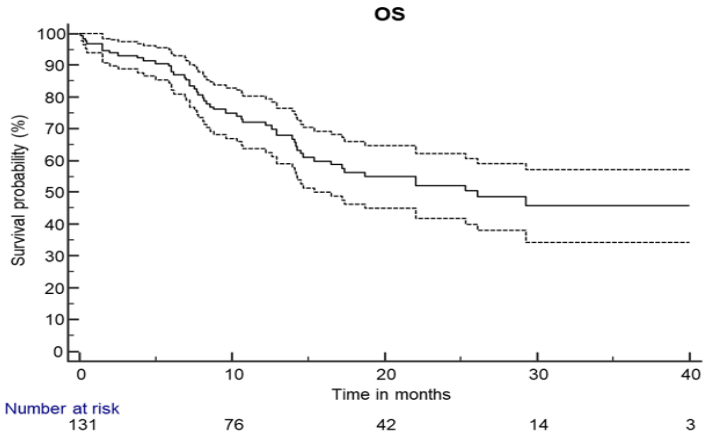
# Inotuzumab in older patients with Ph-neg ALL

**Chevallier P, et al. ASH 2022.**




| | |
|---|---|
| Patients: | 131 |
| Median age: | 68 (55-84) |

| | |
|---|---|
| CR/CRi IP1: | 88% |
| CR/CRi IP2: | 90% |
| MRD neg IP1: | 57% |
| MRD neg IP2: | 81% |

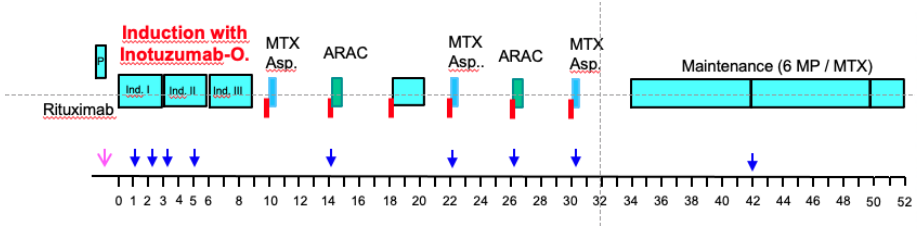



**OS (2 y): 54%**

**TRM: 18%**

# GMALL INITIAL-1: Inotuzumab induction in older patients with newly diagnosed ALL

Stelljes M, et al. *J Clin Oncol*. 2023:JCO2300546.

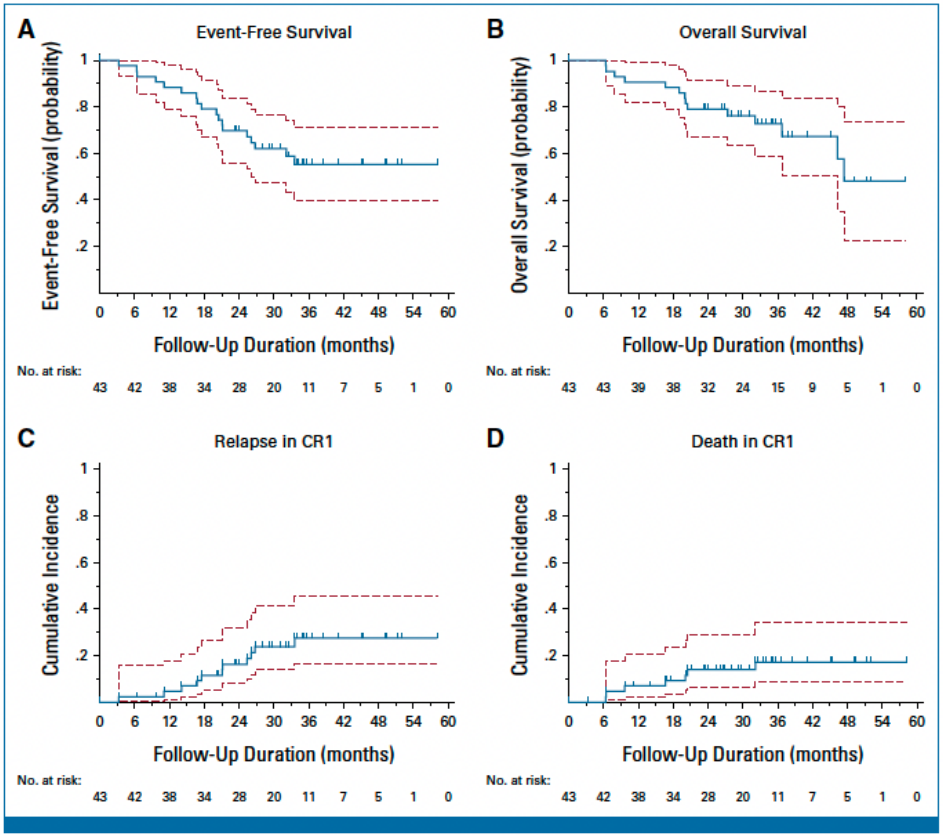



**Induction 1**
0.8 mg/m² d1
0.5 mg/m² d5
0.5 mg/m² d15

**Induction 2-3**
0.5 mg/m² d1
0.5 mg/m² d5
0.5 mg/m² d15

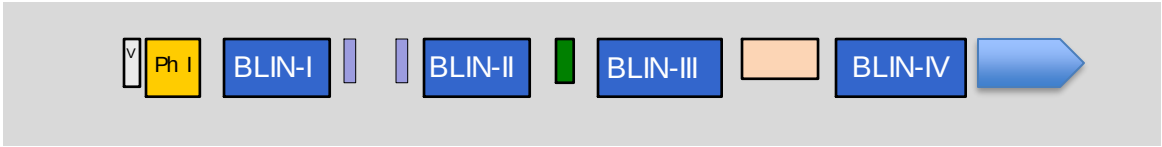
| | |
|---|---|
| Evaluable | 43 |
| **CR/CRi-rate** | **100% (74%)** |
| MRD negative | 23/43 (53%) after 2 cy<br>30/42 (71%) after 3 cy |
| **1-yr OS**<br>**3-yr OS** | **88%**<br>**73%**<br>**SCT CR1: N = 5** |

Mortality in CR: 17% at 3 y
Relapse: 27% at 3 y



# GMALL BOLD: Blinatumomab induction and consolidation in older patients with newly diagnosed ALL

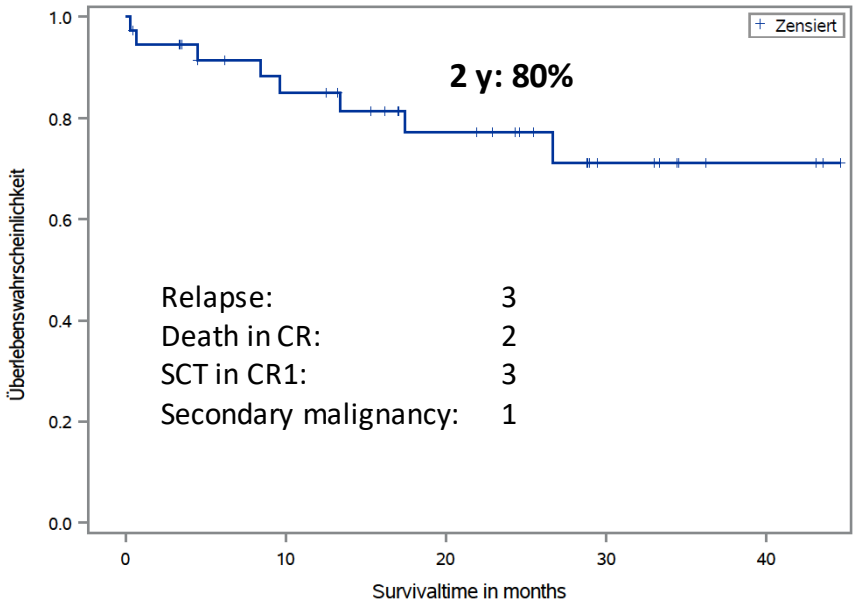
Gökbuget N, et al. ASH 2021.




## Induction I and Blina I

| | |
|---|---|
| Evaluable: | 29 |
| **Hematologic CR** | **83%** |
| Failure/Relapse | 10% |
| Early death (Ind I) | 7% |

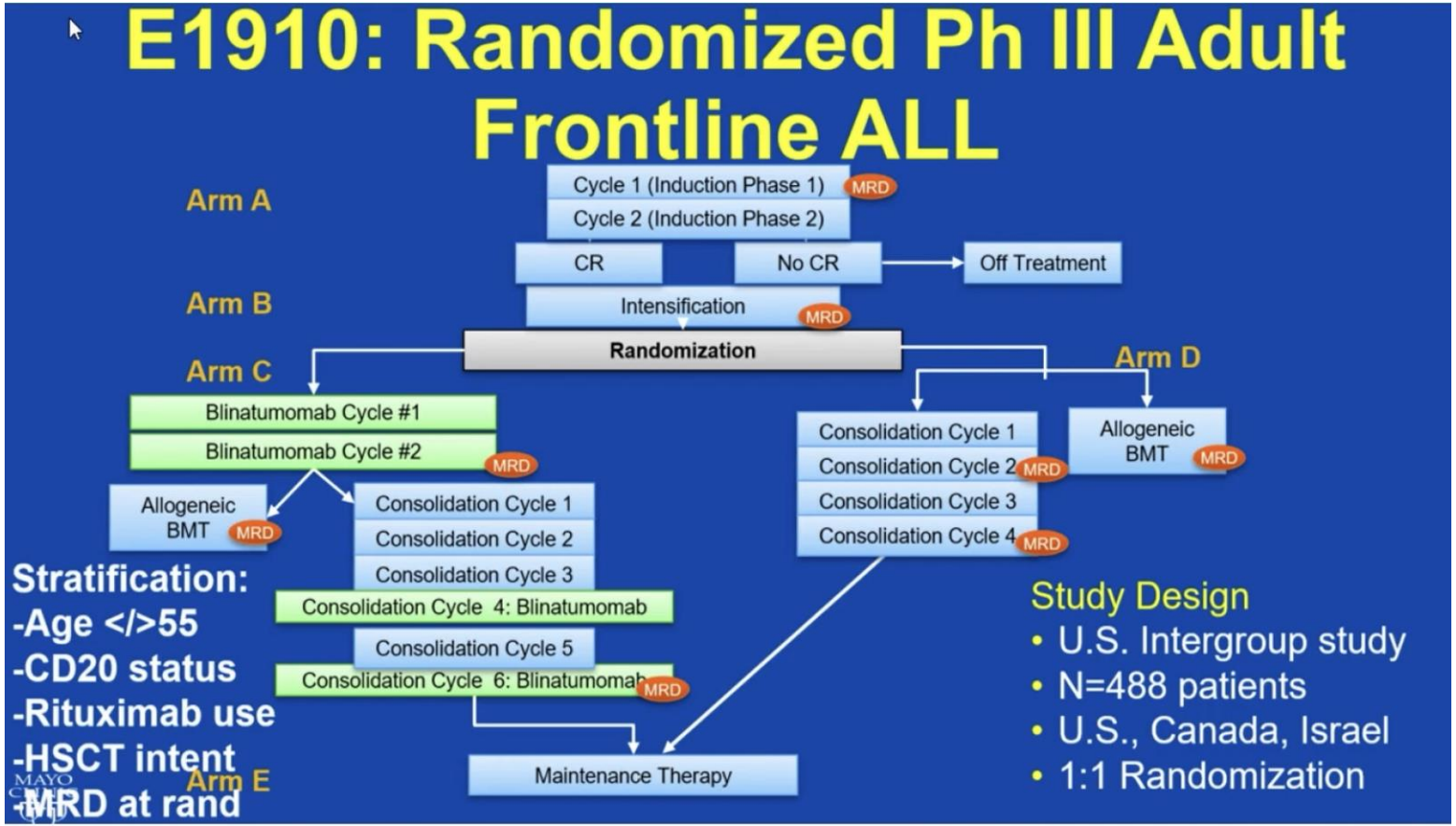
| | |
|---|---|
| CR pts/eval MRD: | 21 |
| **Molecular CR** | **76%** |
| **Molecular response** | **90%** |




Global randomized trial (Golden Gate) ongoing

# Randomized Trial with Blinatumomab Consolidation in De Novo ALL

Litzow et al, ASH 2022 (LBA-1)

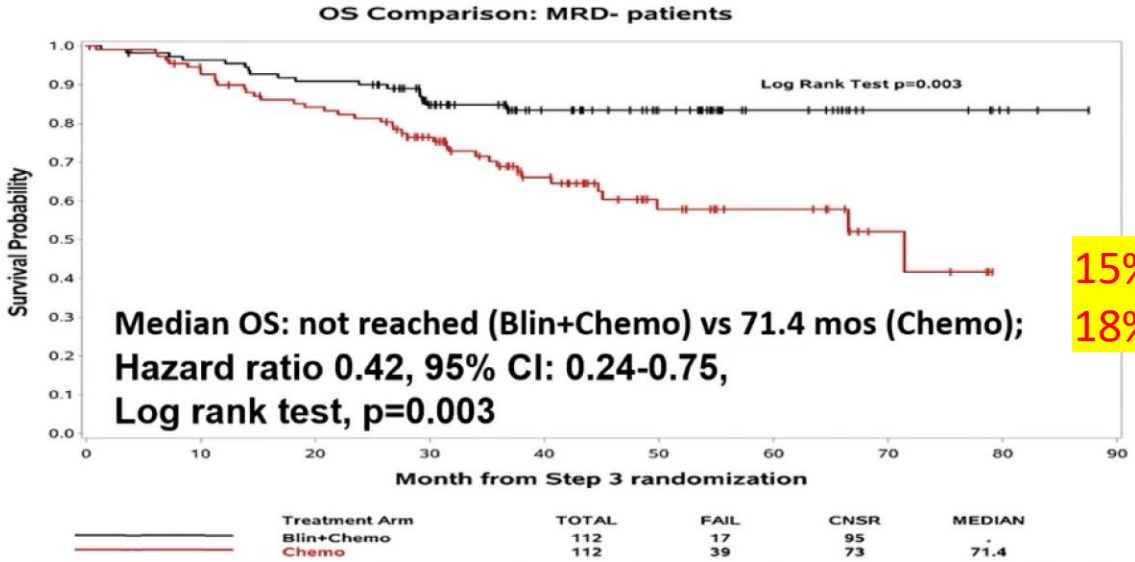


# Randomized trial with blinatumomab consolidation in de novo ALL

Litzow M, et al. ASH 2022. Abstract LBA1.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

## Overall Survival Comparison: MRD negative patients




8% NRM
7% after relapse

15% NRM
18% after relapse

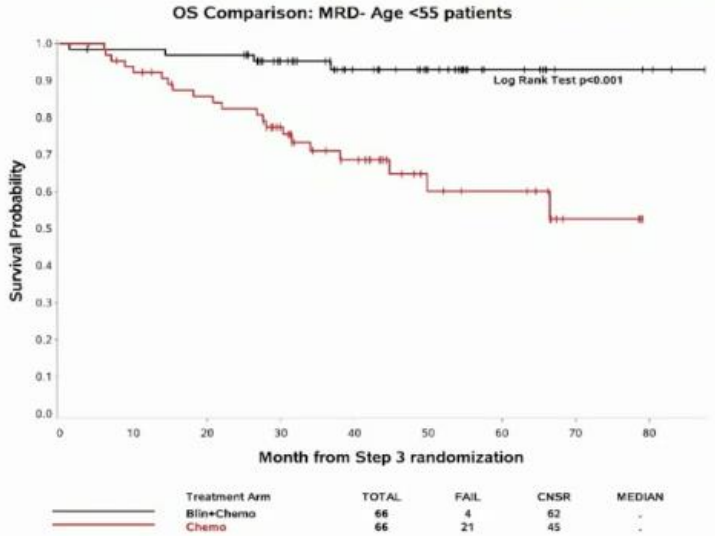
Deaths on Blin+Chemo Arm=17 (2° to ALL=8, NRM=9), Chemo Arm=39 (2° to ALL=20, NRM=17, Unknown=2)

# Randomized trial with blinatumomab consolidation in de novo ALL

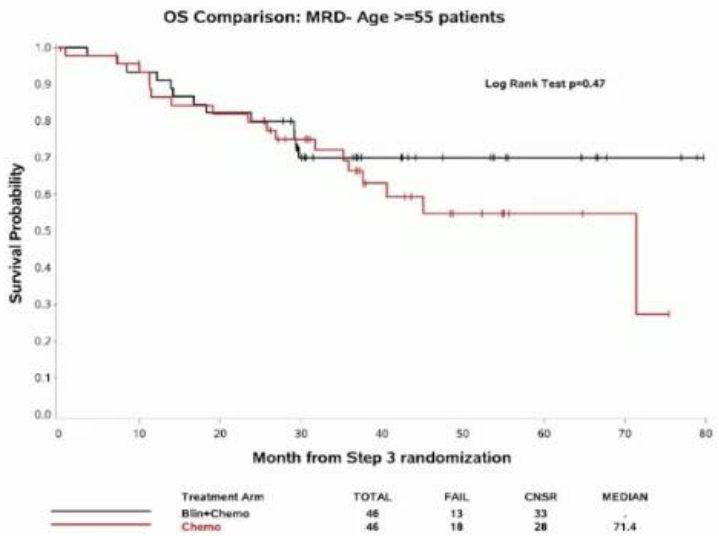
Litzow M, et al. EHA 2023.

## Results

OS for MRD-negative patients stratified by age < 55 years or >= 55 years




Median OS not reached both arms; HR 0.18, 95% CI: 0.06-0.52, p<0.001




Median OS NR vs 71.4 months, HR 0.77, 95% CI: 0.37-1.58, p=0.47

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  - **Ph+ ALL**
- Specific support for young adults

Questions
- Which TKI?
- Prognostic factors?
- Immunotherapy?
- Role of SCT?

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# Do we need AYA-specific therapy protocols?

**No**

- Current "adult" protocols are pediatric based, yield good results, and integrate immunotherapy
- Integration of several different protocols, eg, 3 age groups, yields risks and has no good rationale
- Future treatment decisions to be based on age and comorbidities

**What do we need?**

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

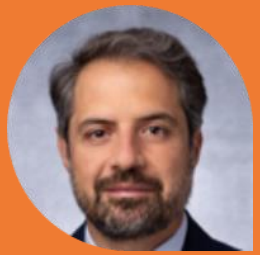
Global Leukemia Academy

# Q&A

APTITUDE HEALTH

Global Leukemia Academy

# ALL case-based panel discussion



Case 1: Jacopo Nanni on behalf of Christina Papayannidis

Case 2: Fabian Lang

Moderator: Elias Jabbour

APTITUDE HEALTH

Global Leukemia Academy

# Ph-neg elderly patient: A clinical case

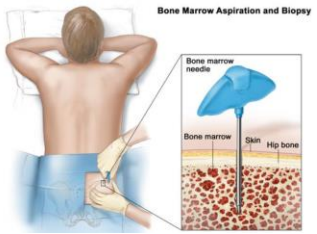
Jacopo Nanni on behalf of Christina Papayannidis
University of Bologna
Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi"
Bologna, Italy

APTITUDE HEALTH

# Past medical history

- **73-year-old** woman
- Comorbidities: hypertension, hypothyroidism, chronic bronchitis
- **March 2020:** serotonin fever unresponsive to antibacterial therapy, night sweats
- Blood tests @ Emergency Unit: **WBC 133,000/mmc** (Ly BC 90%), Hb 7.5 g/dL, Plt 15.000/mmc, LDH 991 U/L
- No signs or symptoms of CNS involvement, no lymphadenopathies
- Renal and liver function tests, coagulation tests: in range

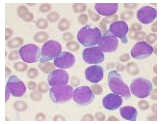
The patient was referred to our Hematology Unit



# Diagnostic workup

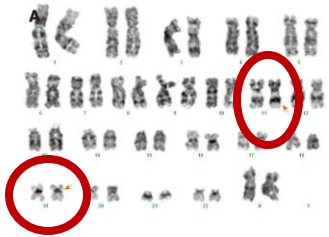
**Morphology:**

98% blast cells



**Cytogenetics:**

t(11;19)(q23;p13.3)



**Flow Cytometry:**

CD34-, CD19+, CD20-, CD10-, CD22+, CD33+, HLADR, CD38+, (pro-B ALL).

**Molecular biology:**

*KMT2A-MLLT1* fusion gene (RT-PCR)

*IgH/TCR* probe detected

- After 6 days of steroids: WBC 13000/mmc
- Abdominal ultrasound: no alterations
- Echocardiogram: E.F. 58%
- Total body PET/CT: no extramedullary disease localizations

March 2020:
very high risk
pro-B ALL (hyperleukocytosis, r-KMT2A)

# Question 1

**How would you treat this patient?**

A. Pediatric-like schedule

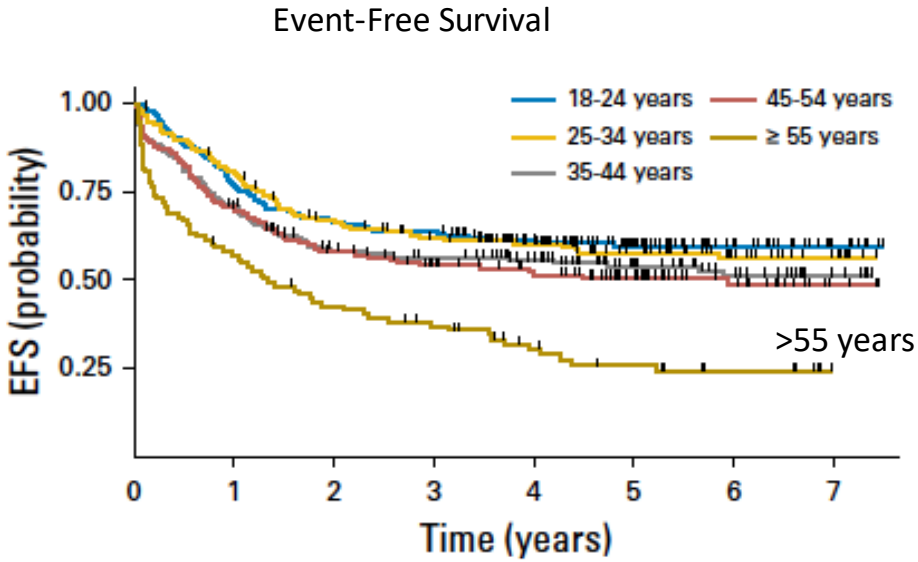
B. HyperCVAD

C. Elderly adapted regimen

D. VCR + steroids

E. Clinical trial (if available)

# Upper age limit for a pediatric-inspired therapy?




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

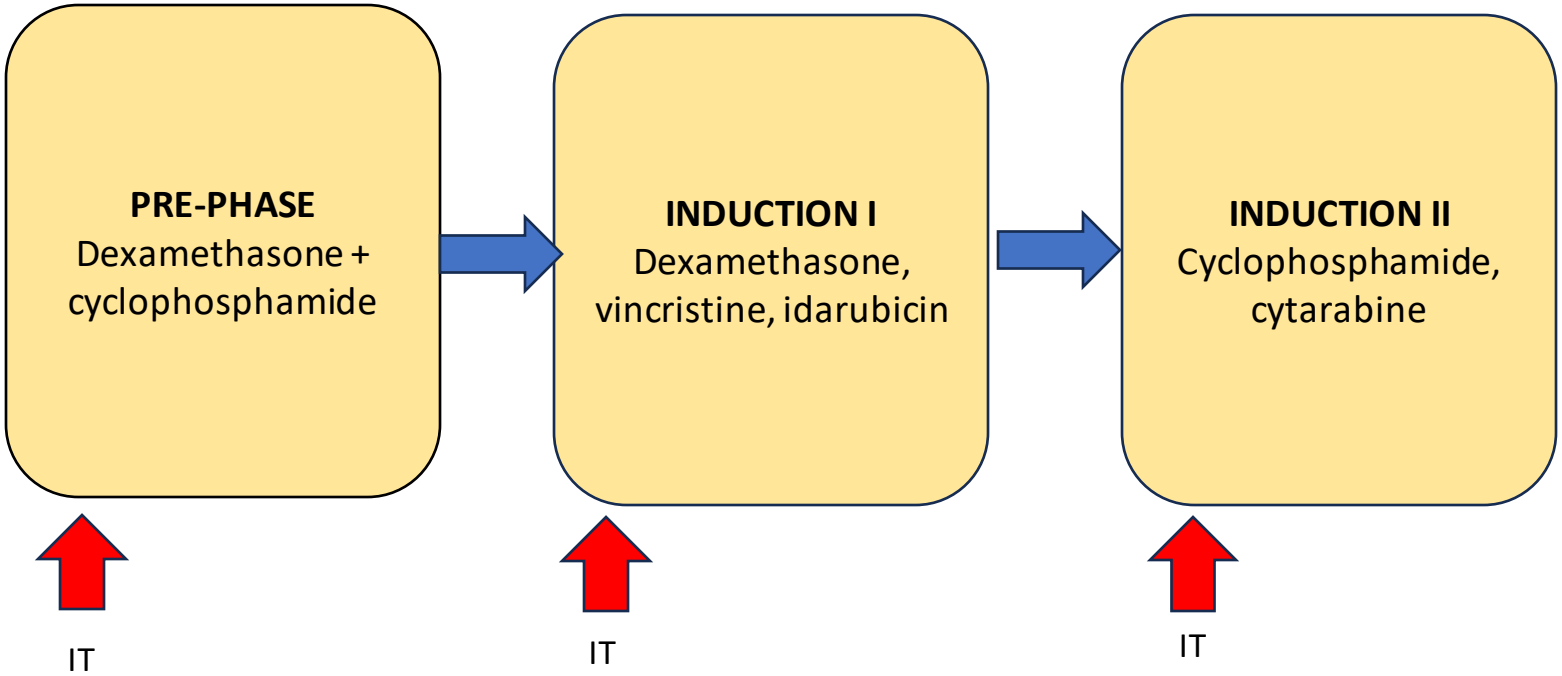
Huguet F, et al. *J Clin Oncol*. 2018;36:2514-2523.

# Poor outcome of elderly Ph-neg ALL before the incorporation of antibodies into the first line

| Studies including both Ph-positive and Ph-negative ALL | | | Age | | | OS | | |
|---|---|---|---|---|---|---|---|---|
| HyperCVAD[2] | 122 | NR | ≥ 60 | 84 | 10 | 20% at 5 years | NR | NR |
| MRC UKALL XII/ECOG E2993[3] | 100 | None | 56 (55-65) | 73 | 18 | 21% at 5 years | 5-year EFS, 19% | NR |
| Modified DFCI[19] | 30 | Imatinib | 58 (51-72) | 67 | 13 | 52% at 2 years | 2-year DFS, 52% | 16 (53) |
| Ph-negative ALL studies | | | | | | | | |
| CALGB 9111[4] | 41 | None | ≥ 60 | 77 | 17 | 17% at 3 years | 3-year DFS, 19% | NR |
| GMALL[6] | 268 | NA | 67 (55-85) | 76 | 18 | 23% at 5 years | 5-year CCR, 32% | NR |
| EWALL[7] | 59 | NA | 65 (61-83) | 76 | 7 | 24% at 3 years | 3-year DFS, 19% | NR |
| PETHEMA ALL-96[17] | 33 | NA | 65 (56-77) | 58 | 36 | 39% at 2 years | 2-year DFS, 46% | NR |
| GRAALL-SA1[34] | 60 | NA | 66 (55-80) | 82 | 8 | 24% and 35% at 2 years | 2-year EFS, 24% and 35% | NR |
| PETHEMA ALL-OLD07[20] | 56 | NA | 66 (56-79) | 74 | 11 | Median, 12.4 months | Median DFS, 8 months | NR |

Aldoss I, et al. *J Oncol Pract*. 2019;15:67-75.

# Therapy




Adverse events

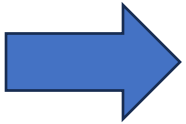
- Febrile neutropenia (FUO) during induction I, treated and resolved with empirical antibacterial therapy
- Mucositis G2

# Disease assessment after induction II

1. **Flow cytometry analysis**
   Sensitivity level: 0.01% ($10^{-4}$) → **0.09%**

2. **Molecular MRD**
   Real-time PCR – *IgH/TCR*
   Sensitivity level: $10^{-3}$ → **positive 2 × $10^{-2}$**

3. **Molecular MRD**
   Nested – RT-PCR fusion gene *KMT2A-MLLT1*
   Sensitivity level: $10^{-4}$ → **positive**



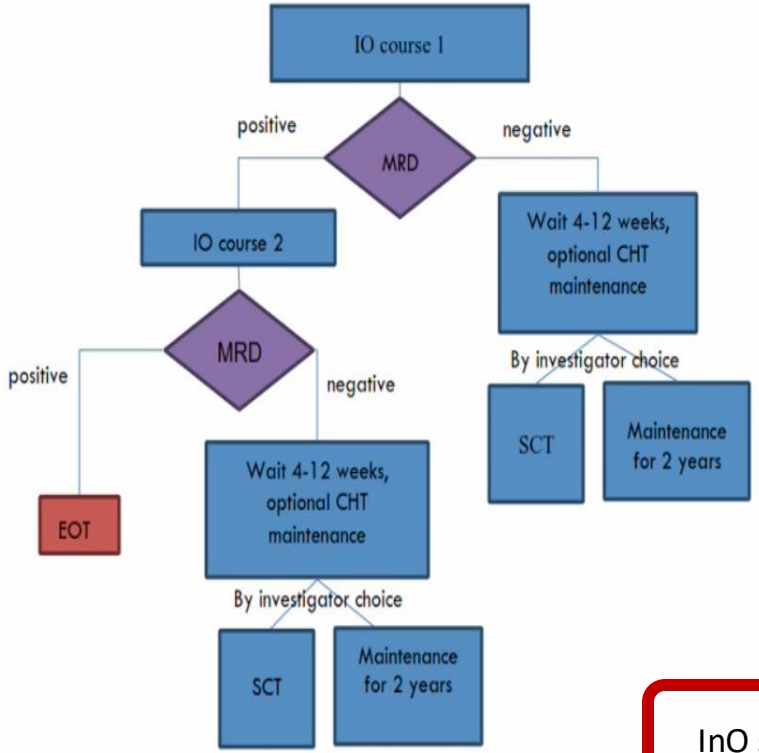
Morphologic CR, **MRD+**

# Question 2

**Which approach would you choose?**

1. Consolidation of GMALL schedule
2. Switch to another chemo schedule
3. Switch to blinatumomab
4. Clinical trial (if available)

# 2726 Gimema ALL2418: Interim Analysis of a Phase Iia Study of Feasibility and Effectiveness of Inotuzumab Ozogamicin in Adult Patients with B-Cell Acute Lymphoblastic Leukemia with Positive Minimal Residual Disease before Any Hematopoietic Stem Cell Transplantation




## Main inclusion criteria

1. ≥ 18 years old
2. Ph+ (n=38) or Ph- (n=38) ALL
3. **MRD positive** with BCR-ABL1 or V(d)J
4. ECOG performance status ≤ 2
5. **No prior HSCT**

## Main exclusion criteria

1. Severe and/or uncontrolled medical conditions or end-organ damage
2. **Bone marrow blasts >5%**
3. Active extramedullary disease
4. Active CNS disease

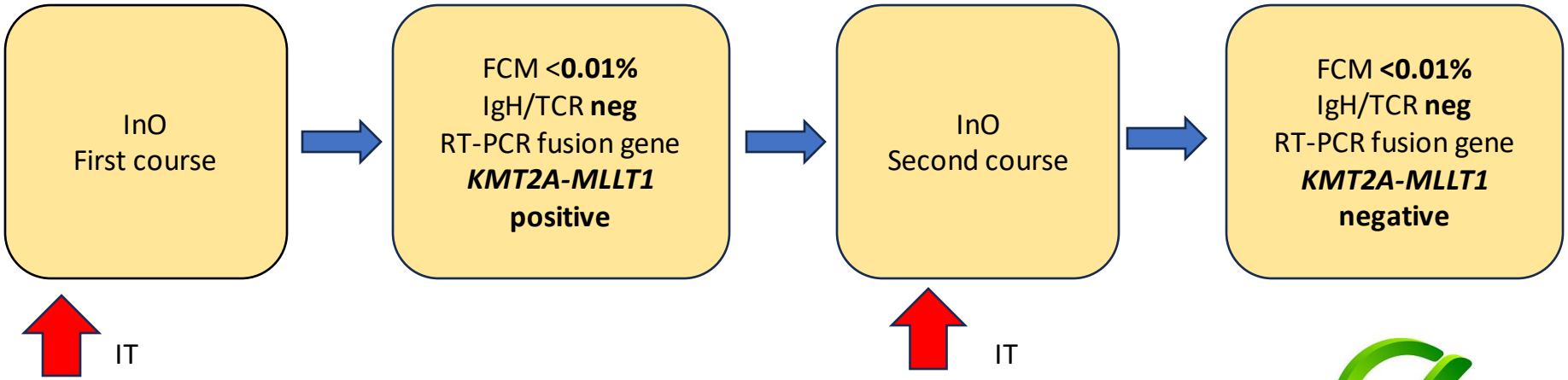
InO schedule: 0.5 mg/m$^2$ on days 1, 8, 15

Marconi G, et al. *Blood*. 2022;140(suppl 1):6119-6121.

# InO-MRD treatment

Before InO, **liver assessment**

- Abdominal ultrasound: moderate steatosis, liver stiffness assessed by FibroScan® kPa 3.5
- Liver tests all in range; ursodeoxycholic acid was given
- Peripheral counts were normal (no anemia, no thrombocytopenia)




No adverse events, no VOD, only transient G1 AST increase was observed

# Maintenance program

- **September 2020: maintenance program (as per protocol) –** 28-day cycles (6-MP, MTX + IT lumbar punctures)

- MRD monitoring @ BM every 2 months
- After 12 months:

1. **Flow cytometry analysis**
   Sensitivity level: 0.01% ($10^{-4}$) → **0.36%, CD19+, CD22+**

2. **Molecular MRD**
   Real-time PCR – *IgH/TCR*
   Sensitivity level: $10^{-3}$ → **positive 1 × $10^{-3}$**

3. **Molecular MRD**
   Nested – RT-PCR fusion gene *KMT2A-MLLT1*
   Sensitivity level: $10^{-4}$ → **positive**

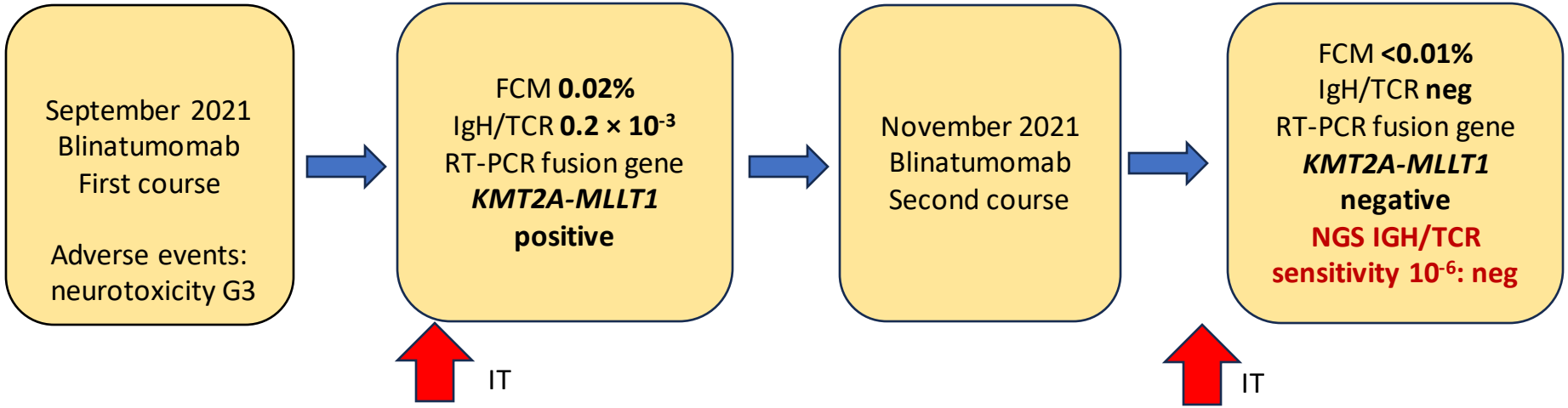
→ **MOLECULAR RELAPSE** (September 2021)

# Question 3

**Which therapy now?**

1. Switch to another chemo schedule
2. Switch to blinatumomab
3. Clinical trial (if available)
4. Palliative care

# Blinatumomab




- All 4 blinatumomab courses were given (until Feb 2022), with 15 IT, and the patient mantained neg MRD (even by NGS)
- In March 2022, low-dose chemo-based maintenance (6-MP, MTX) was started, for 12 cycles; stopped July 2023
- The patient is now 76 years old, in **MRD-neg CR @ 3 years and 8 months from diagnosis**
- **Hospitalized only for induction and first blinatumomab course (14 days); transfusion independent**

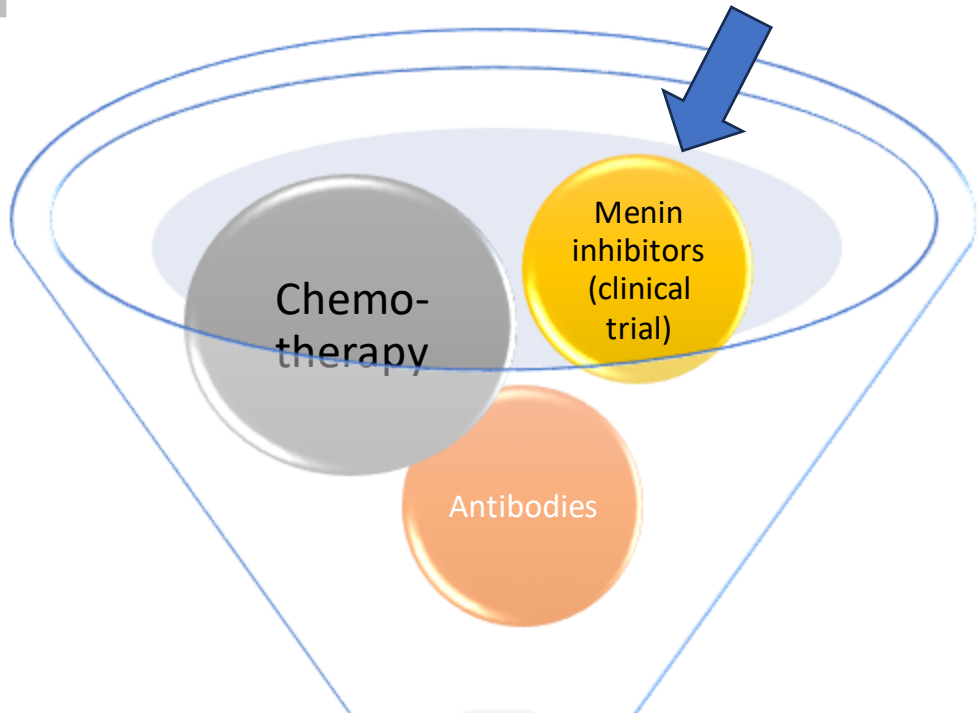
# In 2023?
# Frontline Blinatumomab and Inotuzumab combinations in newly diagnosed older ALL

| | Agent | N | Median Age (yrs, range) | % CR | % MRD negativity | % OS (x-yr) |
|---|---|---|---|---|---|---|
| ASH Mini-HCVD-inotuzumab-blinatumomab | Blinatumomab and inotuzumab | 79 | 68 (60-87) | 89 | 94 | 55 (3-yr) |
| SWOG-1318 | Blinatumomab | 31 | 73 (66-86) | 66 | 92 | 37 (3-yr) |
| ASH EWALL-INO | Inotuzumab | 131 | 69 (55-84) | 88 | 57 | 54 (2-yr) |
| GMALL Bold | Blinatumomab | 34 | 65 (56-76) | 76 | 69 | 89 (1-yr) |
| INITIAL-1 | Inotuzumab | 45 | 65 (56-80) | 100 | 74 | 81 (2-yr) |

**Phase 3 Randomized Controlled Golden Gate Study** for newly diagnosed B-ALL elderly patients (>55 years) Blinatumomab+chemotherapy vs chemotherapy (Jabbour E et al, ASH 2022)

Short NJ et al, Blood 2021; Jabbour E et al, Cancer 2018; Advani AS et al, JCO 2022; Chevallier P et al, Blood 2022; Goekbuget N et al, Blood 2021; Stelljes M et al, JCO 2023

# At a future relapse?




Issa GC, et al. *Nature*. 2023;615(7954):920-924.


# Thank you!

M. Cavo
Antonio Curti
Chiara Sartor
Gianluca Cristiano
Jacopo Nanni
Stefania Paolini
Sarah Parisi
Letizia Zannoni
Federico Zingarelli
Andrea Davide Romagnoli
Federica Ardizzoia
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Mario Arpinati

Giovanni Martinelli
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Lorenza Bandini
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Gabriella Chirumbolo
Dorian Forte
Martina Barone
Francesco Ingletto
Manuel Cella

GIMEMA
Gruppo Italiano Malattie EMatologiche dell'Adulto

cristina.papayannidis@unibo.it

Global Leukemia Academy

# Discussion
# Case 1: ALL

Christina Papayannidis, MD, PhD

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# Case report: Ph+ ALL, 25-year-old male

Fabian Lang, MD

APTITUDE HEALTH

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GOETHE-UNIVERSITÄT

# Case report:
# Ph+ ALL, 25-year-old male

Fabian Lang, MD



Goethe University Hospital, Department of Haematology/Oncology, Frankfurt/M, Germany

MED2 MED2

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# Primary diagnosis

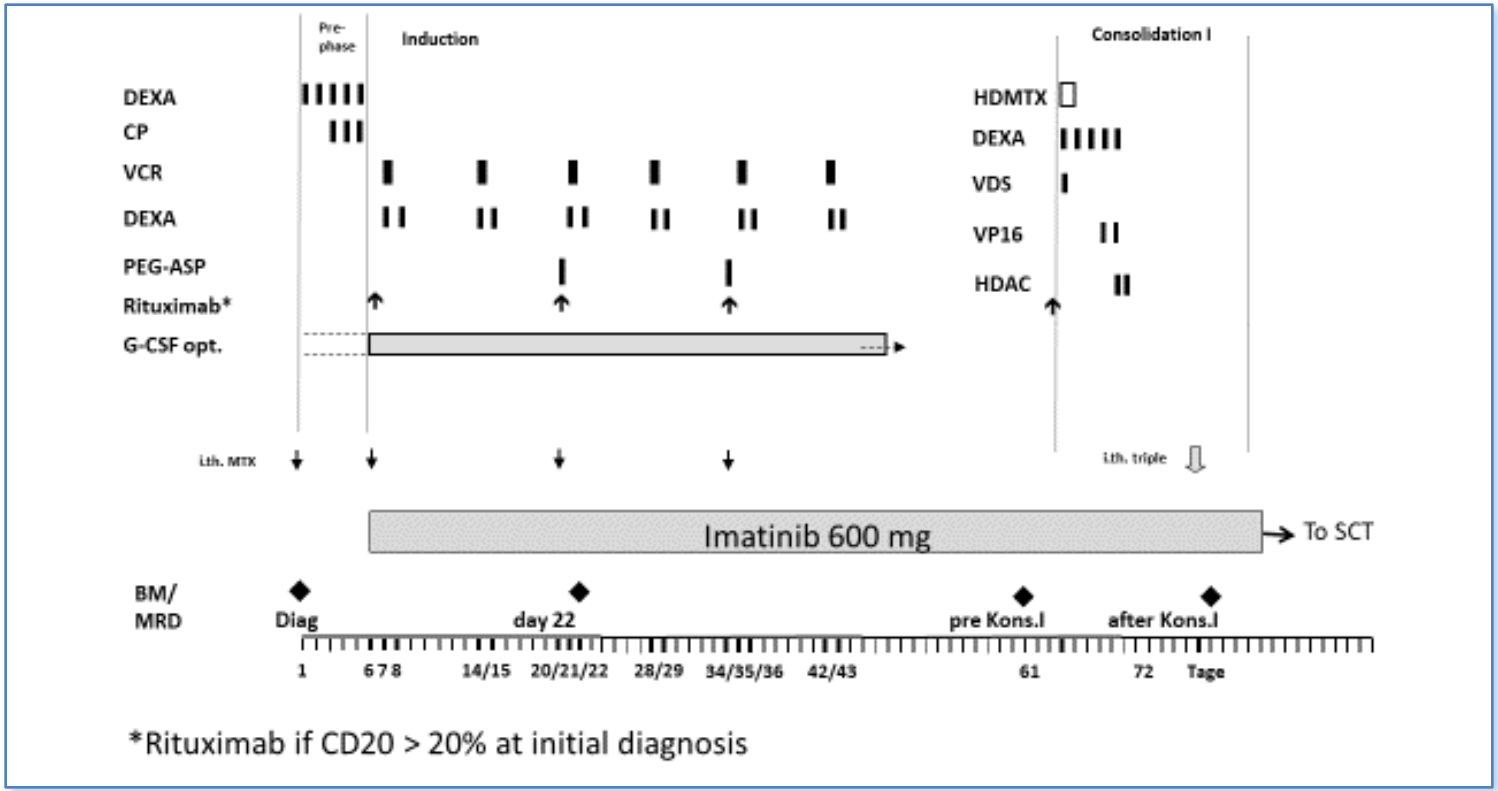
Male, age 25 years

04/2017: primary diagnosis acute lymphoblastic leukemia

| | |
|---|---|
| Initial blood count: | Leukocytes 108/nL, peripheral blasts 28% |
| Immunophenotype: | CD19 positive, CD20 negative, CD22 positive |
| Cytogenetics: | 46 XY [1], 46 XY t(9;22)(q34;q11) [3],<br>46 XY der(9)t(9;22)(q34;q11), ider(22)(q10)<br>t(9;22)(q34;q11) [16] |
| Molecular genetics: | *BCR::ABL1* positive, b3a2 |
| Comorbidities: | None |

# GMALL 08/2013

**Patients aged 18–55 years**



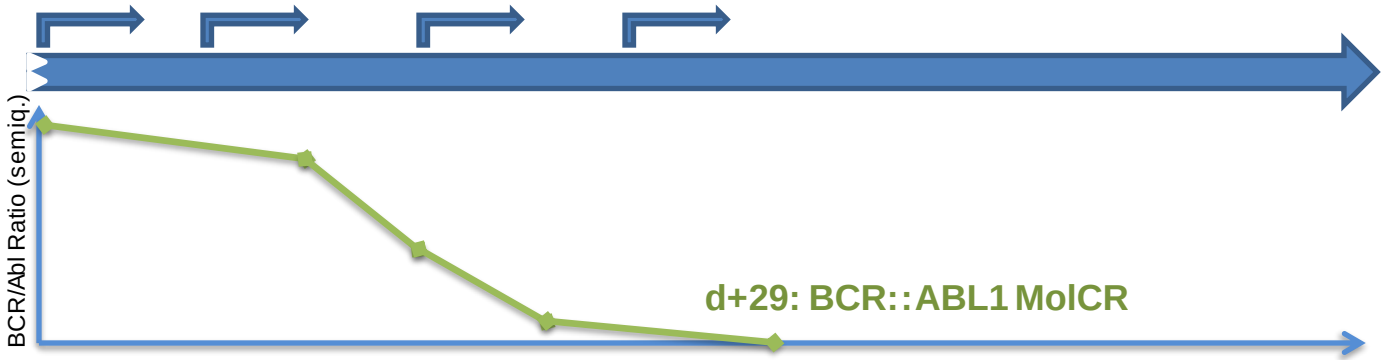

Pfeifer H, et al, EHA 2023. Abstract P355.

# Course of therapy according to GMALL 08/2013

| Prephase | Induction | Cons I |
|---|---|---|
| 04/2017: | 04-05/2017: | 06/2017: |
| Imatinib | Imatinib | Imatinib |
| Cyclo | VCR-Dexa | HDMTX |
| Dexa | Peg-Asp | Dexa-VDS |
| | | VP16-HDAraC |

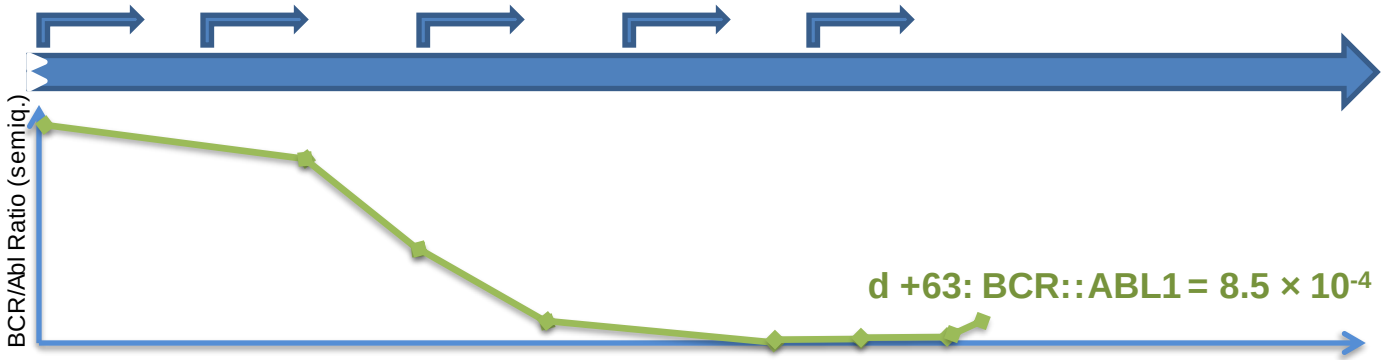
# Course of therapy according to GMALL 08/2013

| Prephase | Induction | Cons I | Allo SCT |
|---|---|---|---|
| 04/2017: | 04-05/2017: | 06/2017: | 08/2017: |
| Imatinib | Imatinib | Imatinib | 10/10 sibling |
| Cyclo | VCR-Dexa | HDMTX | donor |
| Dexa | Peg-Asp | Dexa-VDS | 12Gy-Eto |
| | | VP16-HDAraC | CsA-MTX |



# Course of therapy

| Prephase | Induction | Cons I | Allo SCT | TKI free |
|---|---|---|---|---|
| 04/2017: | 04-05/2017: | 06/2017: | 08/2017: | 09/2017: |
| Imatinib | Imatinib | Imatinib | 10/10 sibling | Post-SCT |
| Cyclo | VCR-Dexa | HDMTX | donor | surveillance |
| Dexa | Peg-Asp | Dexa-VDS | 12Gy-Eto | |
| | | VP16-HDAraC | CsA-MTX | |



# 25yo male, mol relapse after myeloablative SCT d +69

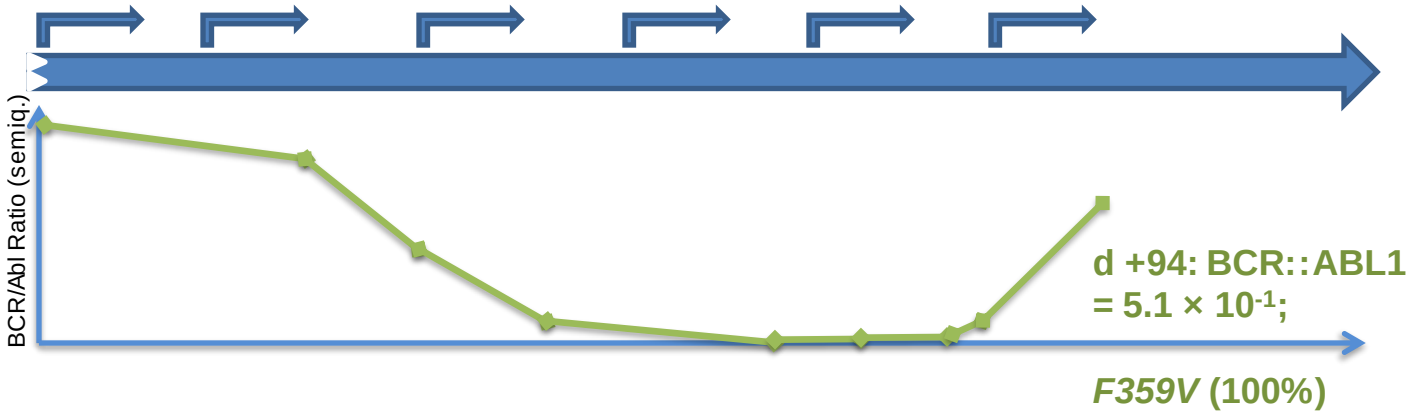
?

***Which therapeutic option would you choose?***

- Switch to ponatinib 30 mg QD
- Switch to dasatinib 70 mg QD
- **Restart imatinib 400 mg QD**
- No TKI therapy, cont. BCR::ABL1 control

# Course of therapy

| Prephase | Induction | Cons I | Allo SCT | TKI free | |
|---|---|---|---|---|---|
| 04/2017: | 04-05/2017: | 06/2017: | 08/2017: | 09/2017: | 10/2017: |
| Imatinib | Imatinib | Imatinib | 10/10 sibling | Post-SCT | Imatinib |
| Cyclo | VCR-Dexa | HDMTX | donor | surveillance | 400 mg QD |
| Dexa | Peg-Asp | Dexa-VDS | 12Gy-Eto | | |
| | | VP16-HDAraC | CsA-MTX | | |



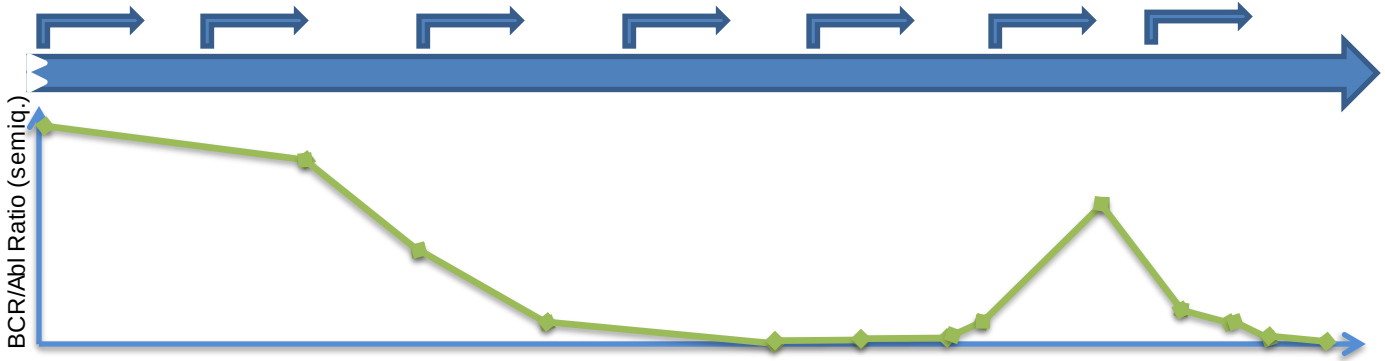
# 25yo male, rising BCR::ABL1 with *F359V* mutation and cytologic CR; d +94


***Which therapeutic option would you choose?***

- Switch to ponatinib 30 mg
- Switch to dasatinib 140 mg QD
- Start blinatumomab and switch to ponatinib
- Add DLIs to TKI treatment

# Course of therapy

| Prephase | Induction | Cons I | Allo SCT | TKI free | | |
|---|---|---|---|---|---|---|
| 04/2017: | 04-05/2017: | 06/2017: | 08/2017: | 09/2017: | 10/2017: | 11/2017: |
| Imatinib | Imatinib | Imatinib | 10/10 sibling | Post-SCT | Imatinib | Dasatinib |
| Cyclo | VCR-Dexa | HDMTX | donor | surveillance | 400 mg QD | 140 mg QD |
| Dexa | Peg-Asp | Dexa-VDS | 12Gy-Eto | | | Stop CsA |
| | | VP16-HDAraC | CsA-MTX | | | d+100 |



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# Current status 11/2023

Male, age 31 years

04/2017: Primary diagnosis acute lymphoblastic leukemia
08-12/2017: Allo SCT and successful treatment of mol relapse

→ Continuous deep molecular remission under dasatinib (70 mg QD)

12/2017: Onset liver GvHD → no DLIs; steroid responsive
07/2018: Onset severe cGvHD with deep skin sclerosis
07/18-04/19: Multiple GvHD treatments
(everolimus, ECP, ruxolitinib, prednisolone)

→ cGvHD well controlled under tacrolimus + abatacept

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# Summary and emerging questions

- Deepening of molecular response before allo SCT indicated?
- Role of TKI maintenance vs MRD-triggered TKI therapy after allo SCT?
- Risk of mol relapse given also after allo SCT
- Strict MRD monitoring incl. mutational analysis is mandatory
- Increased risk of severe GvHD in case of mol relapse and sudden stop of immunosuppression

Global Leukemia Academy

# Discussion
# Case 2: ALL AYA

Fabian Lang, MD

APTITUDE HEALTH

Global Leukemia Academy

# BREAK

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

Global Leukemia Academy

# Genetic characterization and risk stratification of AML

Stephane De Botton

APTITUDE HEALTH

ALFA
Acute Leukemia French Association

UNIVERSITÉ PARIS SUD
université PARIS-SACLAY

GUSTAVE ROUSSY

# Genetic characterization and risk stratification of AML

Stéphane
De BOTTON

# Genetic characterization and risk stratification of AML

- **To diagnose acute myeloid leukemia**
- **To constitute homogeneous groups of patients**
  - For research including drug development
  - For clinical retrospective studies
  - For clinical trial eligibility
- **To assess response to treatment**
- **To build algorithm of treatment**

# AML classification according to genetic analyses

Recurrent cytogenetic abnormality or gene rearrangement

**ELN22 favourable**
AML 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)/*CBFB::MYH11*

**ELN22 intermediate**
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*
AML with t(5;11)(q35.2;p15.4)/*NUP98::NSD1*
AML with t(11;12)(p15.4;p13.3)/*NUP98::KMD5A*
AML with other recurring translocations involving *NUP98*
AML with other rare recurring translocations
AML with t(1;22)(p13.3;q13.1)/*RBM15::MRTFA*
AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*
AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1*
AML with t(7;12)(q36.3;p13.2)/*ETV6::MNX1*
AML with t(10;11)(p12.3;q14.2)/*PICALM::MLLT10*
AML with t(16;21)(p11.2;q22.2)/*FUS::ERG*
AML with t(16;21)(q24.3;q22.1)/*RUNX1::CBFA2T3*
AML with inv(16)(p13.3q24.3)/*CBFA2T3::GUS2*

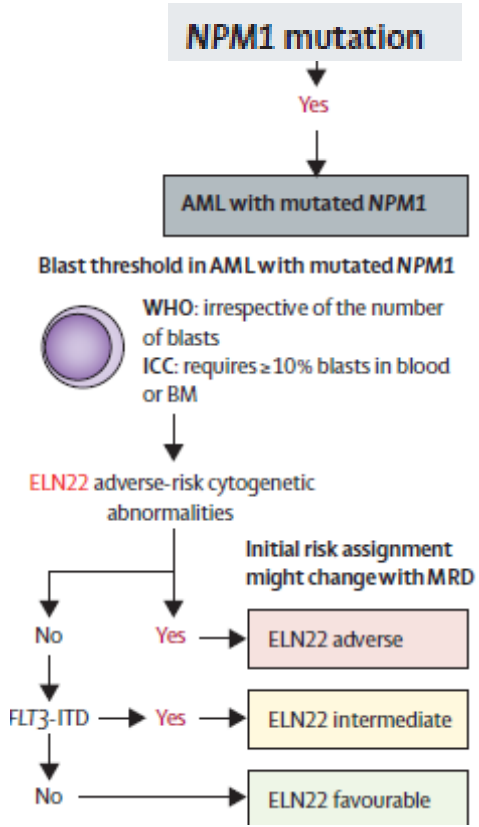
**ELN22 adverse**
AML with t(10;11)(p12.3;q23.3)/*MLLT10::KMT2A*
AML with other translocations involving *KMT2A*
AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*
AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
AML with MECOM(EVI1) rearrangement
AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1**

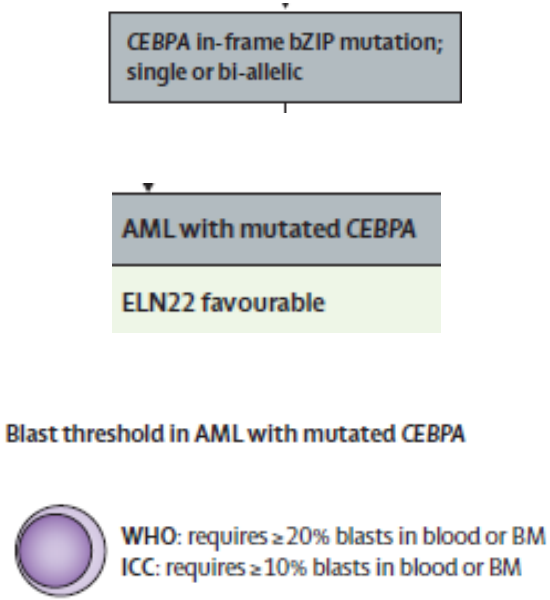
**Blast threshold in AML with a recurrent gene rearrangement**

**WHO**: irrespective of the number of blasts
**ICC**: requires ≥10% blasts in blood or BM
*Exception: AML with *BCR::ABL1* requires ≥20% blasts in blood or BM (ICC and WHO)

Shallis RM, et al. *Lancet Haematol.* 2023;10:e767–e776. doi: 10.1016/S2352-3026(23)00159-X.

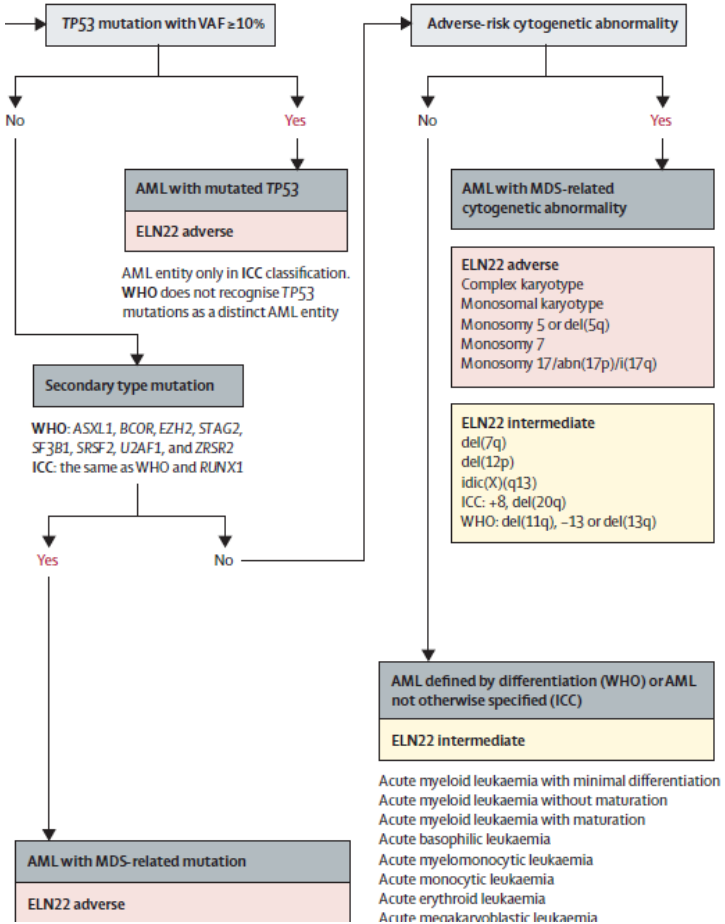
# AML classification according to genetic analyses




Shallis RM, et al. *Lancet Haematol.* 2023;10:e767-e776. doi: 10.1016/S2352-3026(23)00159-X.

# AML classification according to genetic analyses




**Blast threshold in other AML subtypes**

**WHO and ICC**: AML diagnosis requires ≥20% blasts in blood or BM
If blasts 10–19% → MDS with increased blasts (WHO) or MDS/AML (ICC)

Shallis RM, et al. *Lancet Haematol.* 2023;10:e767–e776. doi: 10.1016/S2352-3026(23)00159-X.

# ELN 2022 guidelines for the diagnosis and management of AML

## Molecular and Cytogenetic Analyses for Patients With AML

| Analysis | Results Preferably Available Within |
|---|---|
| **Cytogenetics** | **5–7 days** |
| **Screening for gene mutations required to establish the diagnosis and identify actionable therapeutic targets**<br>• *FLT3*, *IDH1*, *IDH2*, *NPM1*<br>• *CEBPA*, *DDX41*, *TP53*; *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2* | • 3–5 days<br>• First cycle |
| **Screening for gene rearrangements**<br>• *PML::RARA*, *CBFB*::*MYH11*, *RUNX1::RUNX1T1*, *KMT2A* rearrangements, *BCR::ABL1*, other fusion genes (if available) | • 3–5 days |
| **Additional genes recommended to test at diagnosis**<br>• *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1* | |

Cytogenetic analysis is mandatory for patients with AML

Molecular testing for all genetic abnormalities is recommended to

- Define disease
- Define risk categories
- Identify actionable therapeutic targets

For *NPM1*$^{mut}$ AML and CBF-AML, baseline molecular assessment by qPCR or ddPCR is recommended to facilitate MRD monitoring after treatment

Döhner H, et al. *Blood*. 2022;140:1345-1377. doi: 10.1182/blood.2022016867.

# ELN 2022 guidelines for the diagnosis and management of AML

## ELN Risk Classification by Genetics at AML Diagnosis

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

Mutations affecting the bZIP of *CEBPA* are categorized as favorable risk, irrespective of biallelic or monoallelic occurrence

Patients with *NPM1*$^{mut}$ AML are classified as favorable or intermediate risk in the absence of adverse cytogenetic abnormalities

- If adverse cytogenetic abnormalities are present, patients are classified as adverse risk

All AML with *FLT3*-ITD is categorized as intermediate risk, irrespective of allelic ratio or *NPM1* co-mutations. Reasons for this include

- Methodological issues with standardizing the assay to measure *FLT3*-ITD allelic ratio
- The modifying impact of midostaurin-based therapy on *FLT3*-ITD without *NPM1* mutation
- The increasing role of MRD in treatment decisions

Döhner H, et al. *Blood*. 2022;140:1345-1377. doi: 10.1182/blood.2022016867.

# ELN 2022 guidelines for the diagnosis and management of AML

## ELN Risk Classification by Genetics at AML Diagnosis

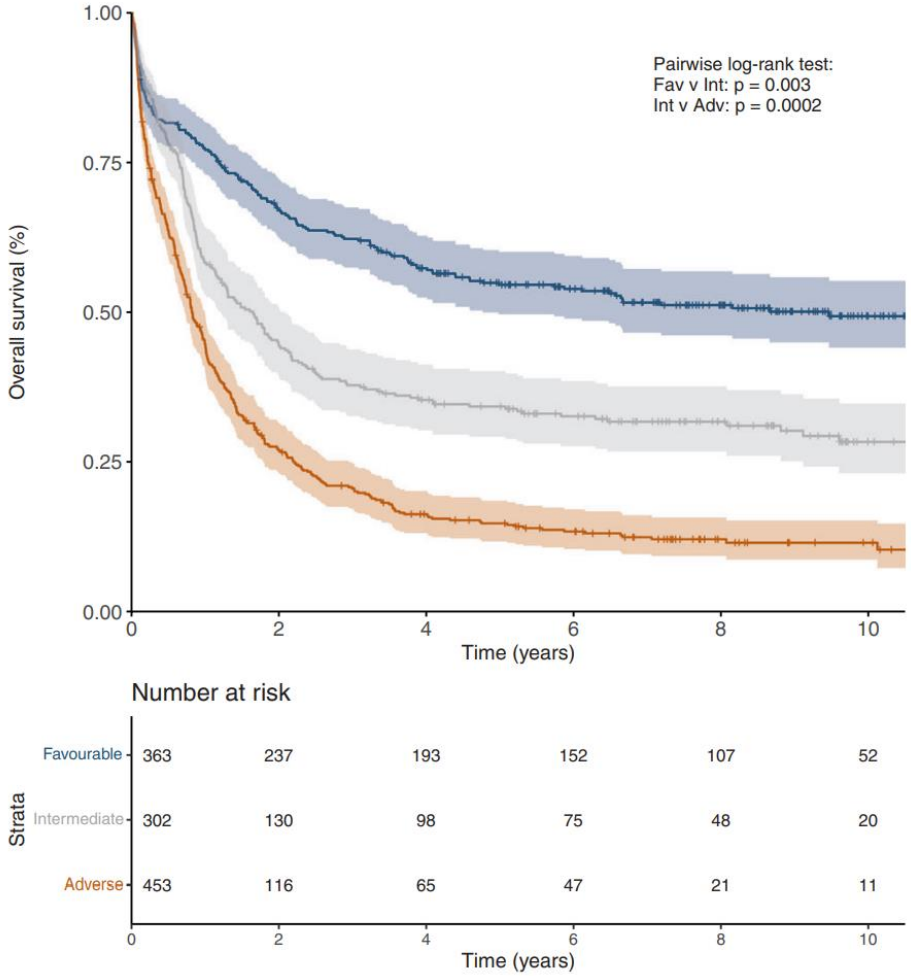
| Risk Category | Genetic Abnormality |
|---|---|
| **Favorable** | • *t(8;21)(q22;q22.1)/RUNX1::RUNX1T1*<br>• *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22)/CBFB::MYH11*<br>• Mutated *NPM1* without *FLT3*-ITD<br>• bZIP in-frame mutated *CEBPA* |
| **Intermediate** | • Mutated *NPM1* with *FLT3*-ITD<br>•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

Additional disease-defining recurring cytogenetic abnormalities are now included in the adverse-risk group

Hyperdiploid karyotypes with multiple trisomies (or polysomies) are no longer considered as complex karyotypes and as adverse risk

AML with myelodysplasia-related gene mutations are now categorized as adverse risk, and new mutations have been included in this category in addition to *ASXL1* and *RUNX1*

Döhner H, et al. *Blood.* 2022;140:1345-1377. doi: 10.1182/blood.2022016867.



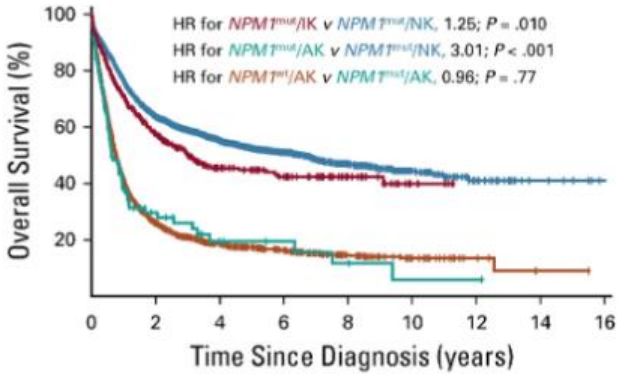

Rausch C, et al. *Leukemia*. 2023;37:1234–1244.

# *NPM1*$^{mut}$/*FLT3*-ITD $^{neg/low}$ AML and abnormal karyotypes: Pooled analysis of individual patient data

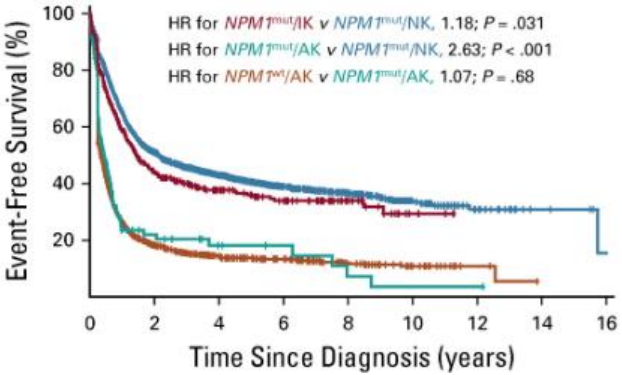
- Can we better define the impact of mutations on prognosis in intensively treated patients with *NPM1*$^{mut}$/*FLT3-ITD*$^{neg/low}$ AML?
- N = 2426 patients from 9 international cohorts
- Karyotype distribution
  - Normal: 2000 patients (82.4%)
  - Abnormal: 426 patients (17.6%)
    - Intermediate risk: 329 patients (13.6%)
    - Adverse risk: 83 patients (3.4%)

Angenendt L, et al. *J Clin Oncol.* 2019;37:2632-2642.

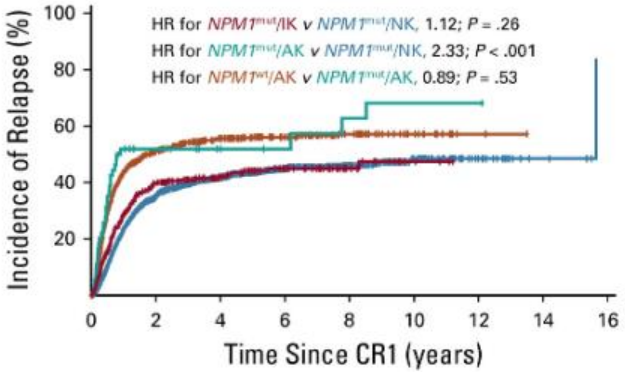
# Outcomes by cytogenetic risk: *NPM1*$^{mut}$/*FLT3*-ITD$^{neg/low}$ AML




Intermediate vs normal cytogenetics inferior OS:
HR (95% CI): 1.27 (1.07 to 1.50)
*P* = .0060




Intermediate vs normal cytogenetics inferior EFS:
HR (95% CI): 1.21 (1.04 to 1.41)
*P* = .014




Angenendt L, et al. *J Clin Oncol.* 2019;37:2632-2642.

# Impact of *NPM1*/*FLT3*-ITD genotypes defined by the 2017 European LeukemiaNet in patients with AML

Impact of *NPM1*/*FLT3*-ITD genotypes defined by the 2017 European LeukemiaNet (ELN) in patients with acute myeloid leukemia

**Figure 1: Kaplan-Meier plot of overall survival by genetic risk group**
The results from this retrospective explorative analysis of the RATIFY trial confirm the prognostic value of the 2017 ELN genetic risk classification also in patients with *FLT3*-ITD positive AML.

**Figure 2: Overall survival by 2017 ELN risk group and by treatment arm (midostaurin [red curves] *versus* placebo [black curves])**
In a multivariate Cox model for OS there is a consistent beneficial effect of midostaurin across the three 2017 ELN risk groups.

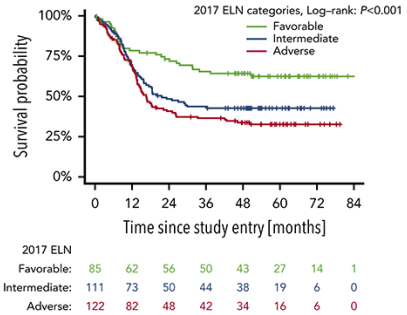



Figure 1

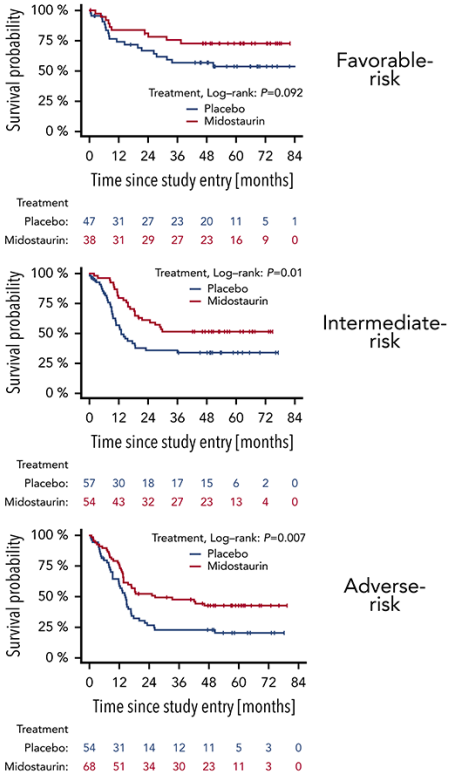
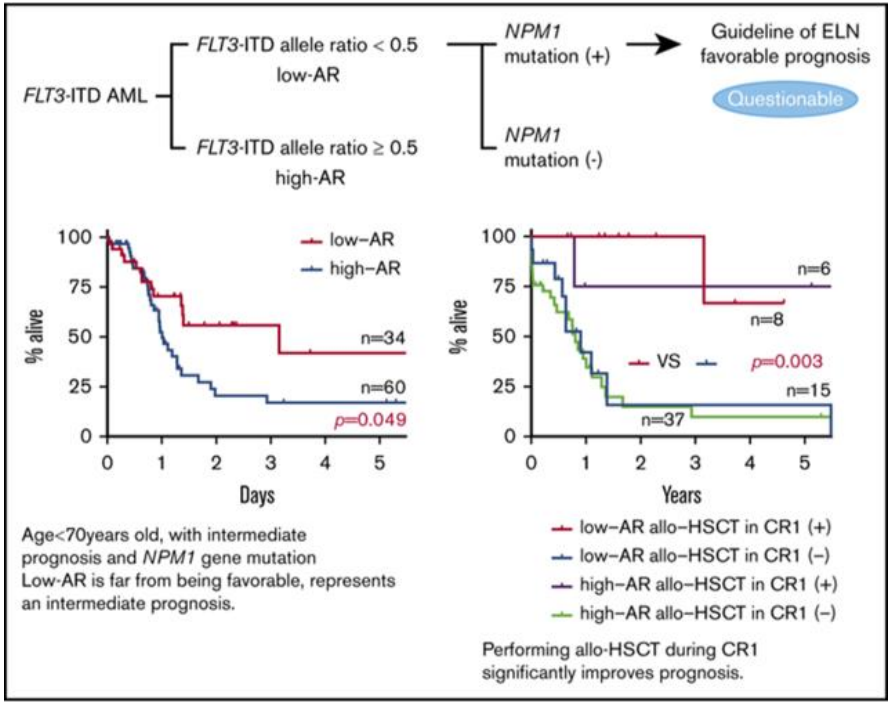



Figure 2



Döhner K, et al. *Blood.* 2020;135:371-380. https://doi.org/10.1182/blood.2019002697

# Prognostic impact of low allelic ratio *FLT3*-ITD and *NPM1* mutation in AML



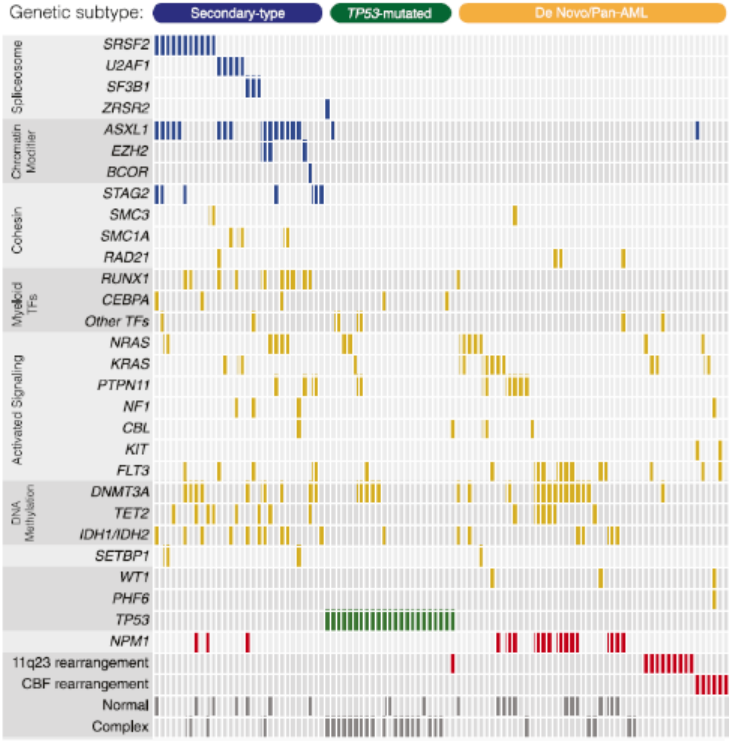



Sakaguchi M, et al. *Blood Adv.* 2018;2:2744–2754.

# Secondary AML: Spectrum of somatic genetic mutations

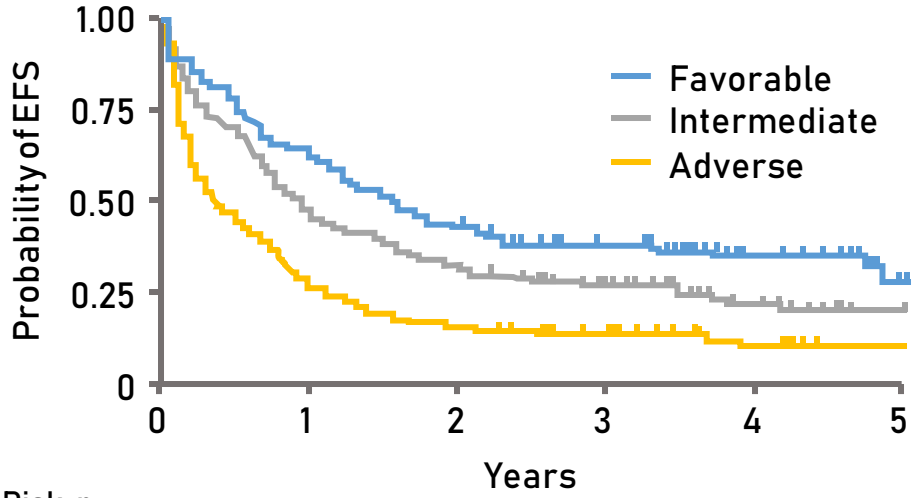
- Targeted mutation analysis in patients with rigorously defined s-AML (n = 93)
- Mutations in key genes were >95% specific for s-AML diagnosis

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




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

# ALFA-1200: EFS according to ELN 2017 risk subgroup (>60 y and IC)

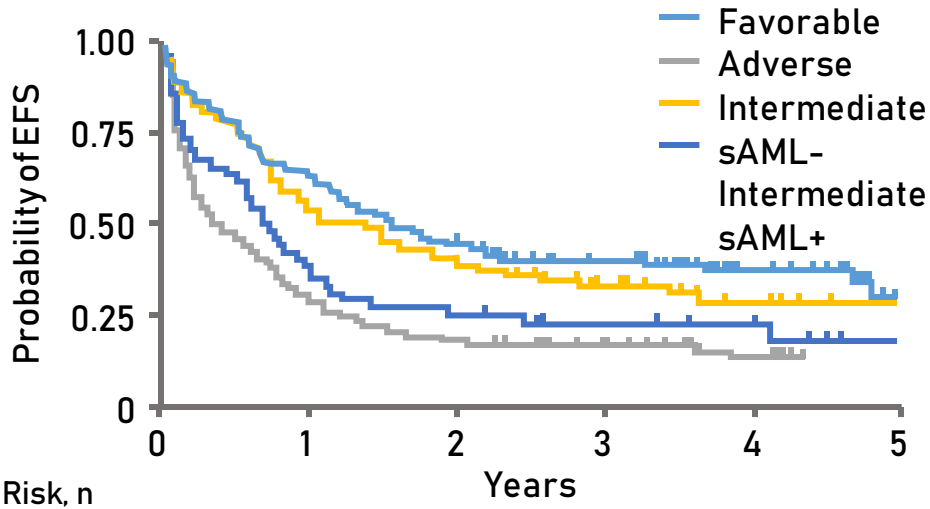



| Patients at Risk, n | | | | | | |
|---|---|---|---|---|---|---|
| Favorable | 136 | 86 | 58 | 42 | 19 | 6 |
| Intermediate | 157 | 73 | 50 | 32 | 16 | 4 |
| Adverse | 200 | 53 | 30 | 19 | 6 | 1 |

| Risk Subgroup | Median EFS (95% CI), mo |
|---|---|
| Favorable | 18.8 (14.3-25.8) |
| Intermediate | 11.2 (8.7-14.0) |
| Adverse | 4.1 (2.8-6.7) |

Gardin C, et al. *Blood Adv.* 2020;4:1942-1949.

# ALFA-1200: EFS according to ELN 2017 risk subgroup – sAML-like mutations (>60 y and IC)



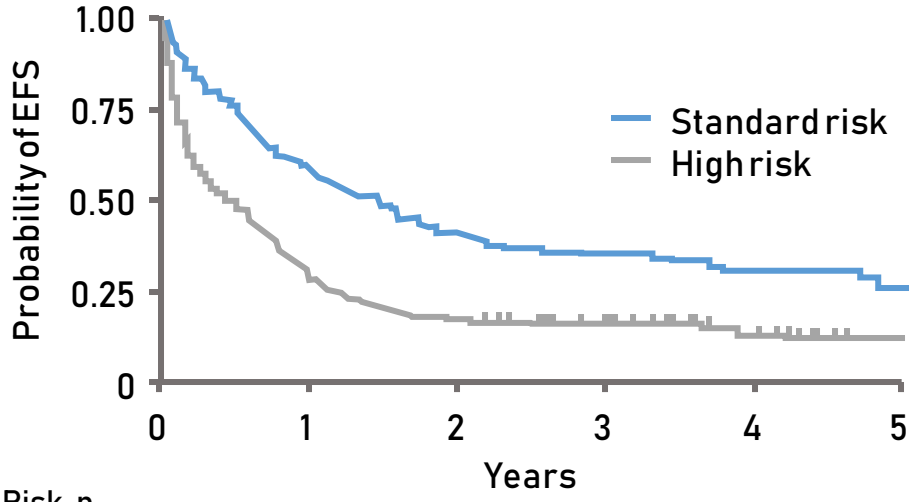

| Patients at Risk, n | | | | | | |
|---|---|---|---|---|---|---|
| Favorable | 136 | 86 | 58 | 42 | 19 | 6 |
| Intermediate | 80 | 41 | 31 | 19 | 9 | 3 |
| sAML- | 200 | 53 | 30 | 19 | 6 | 1 |
| Adverse | 49 | 19 | 11 | 7 | 5 | 0 |
| Intermediate | | | | | | |
| sAML+ | | | | | | |

| Risk Subgroup | Median EFS (95% CI), mo |
|---|---|
| Intermediate sAML-like neg | 13.0 (9.3-22.5) |
| Intermediate sAML-like pos | 8.5 (5.4-12.0) |

HR (95% CI): 1.52 (1.01-2.28)
*P* = .044

Gardin C, et al. *Blood Adv.* 2020;4:1942-1949.

# ALFA-1200: EFS according to newly defined risk subgroups (>60 y and IC)




| Patients at Risk, n | | | | | | |
|---|---|---|---|---|---|---|
| Standard risk | 246 | 141 | 98 | 68 | 30 | 10 |
| High risk | 247 | 71 | 40 | 25 | 11 | 1 |

| Risk Subgroup | Median EFS (95% CI), mo |
|---|---|
| Standard | 17.8 (13.0-21.6) |
| High | 5.4 (3.6-7.4) |

HR (95% CI): 2.09 (1.69-2.59)
*P* <.001

Gardin C, et al. *Blood Adv.* 2020;4:1942-1949.

# Context = second cytogenetic subset of AML

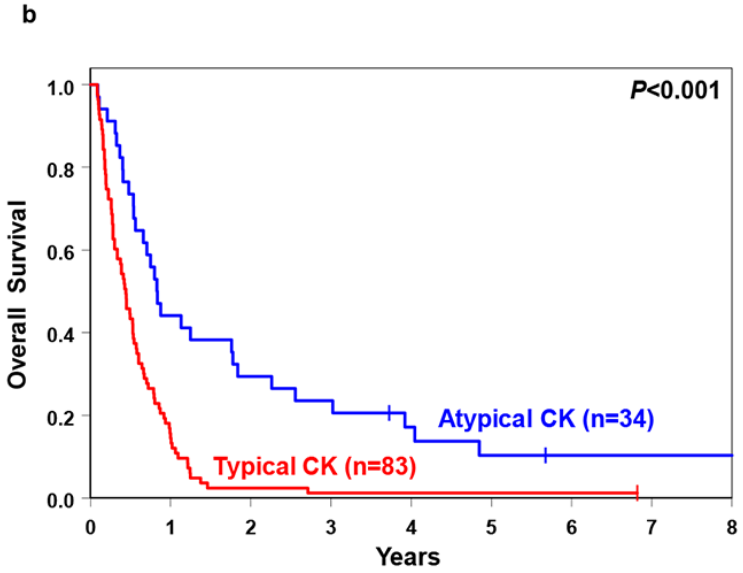
- Included in adverse-CG risk group
- Complex karyotype (CK) ≥3 chromosome abnormalities

- Unbalanced abnormalities predominate
- Abnormalities of 5q, 7q, and 17p often occur together, and ~85% of all patients with CK-AML harbor at least 1 of these abnormalities

- 10%-12% of all patients with AML

Mrózek K, et al. *Leukemia*. 2019;33:1620-1634.

# Can we further refine CK?




CK with ≥3 abnormalities that include 5q, 7q, and/or 17p loss

CK with ≥3 abnormalities other than the aforementioned ones

- Higher CR rates (59 vs 35%; *P* = .02)
- Longer OS (*P* <.001; 3-year rates, 24 vs 1%)

Mrózek K, et al. *Leukemia*. 2019;33:1620-1634.

# Exclusion of « 3+7 »
# CK + TP53 = 5-year RFS and OS of 0%

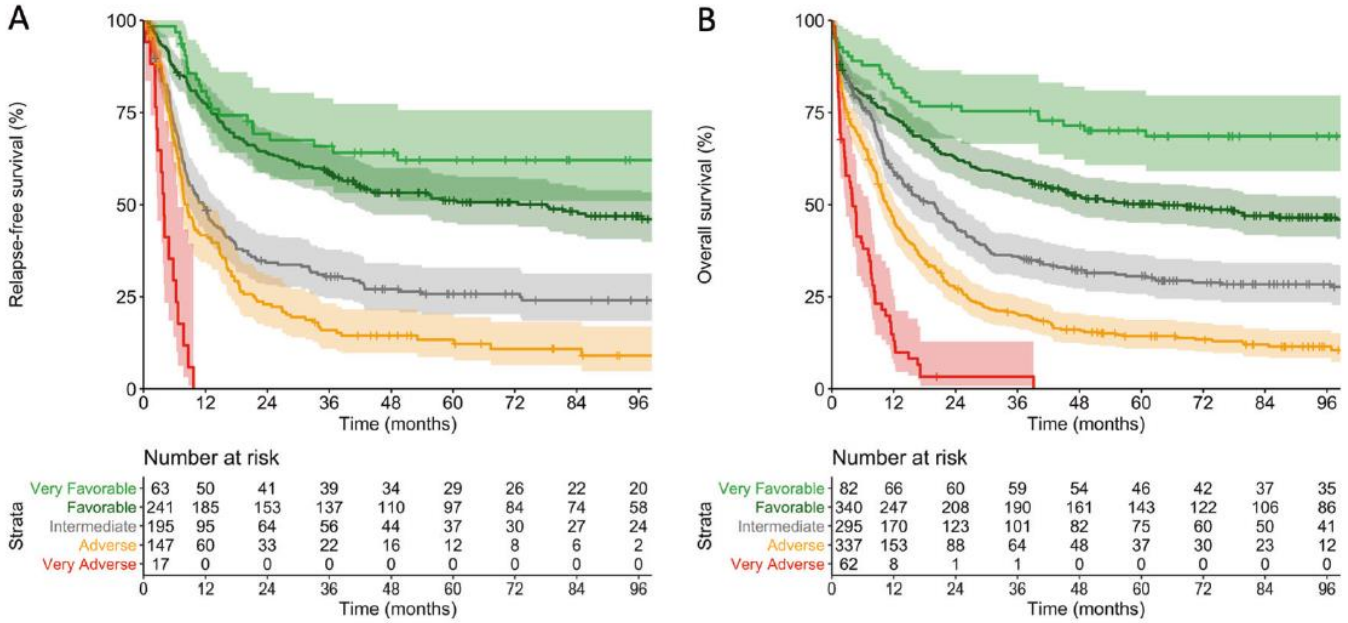


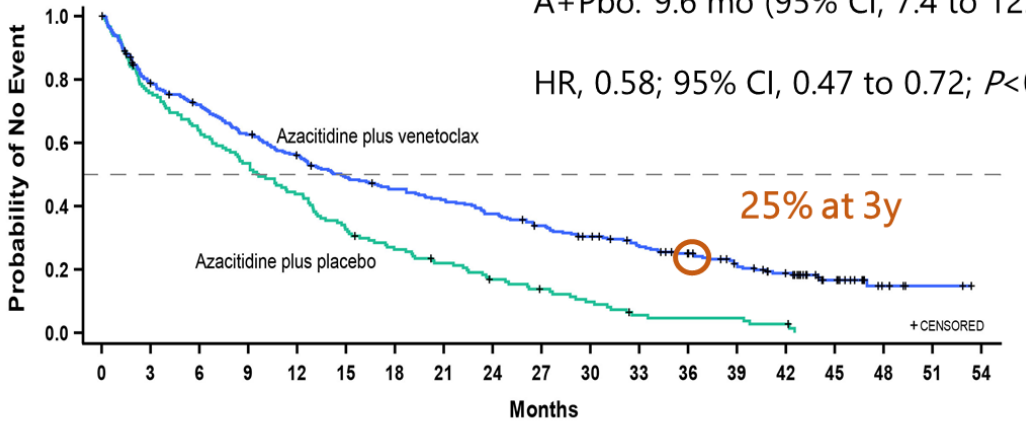

**Fig. 6 Outcomes of patients according to the proposed refinement of the ELN-2017 genetic risk groups. a** Relapse-free survival and **b** overall survival in the entire cohort of 1116 patients (age range, 18–86 years).

Herold T, et al. *Leukemia*. 2020;34:3161-3172. doi: 10.1038/s41375-020-0806-0.

# 5-AZA + VENETOCLAX

## Median FU: 43.2 months

**Figure 1. Overall Survival**




**Patients at Risk**

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

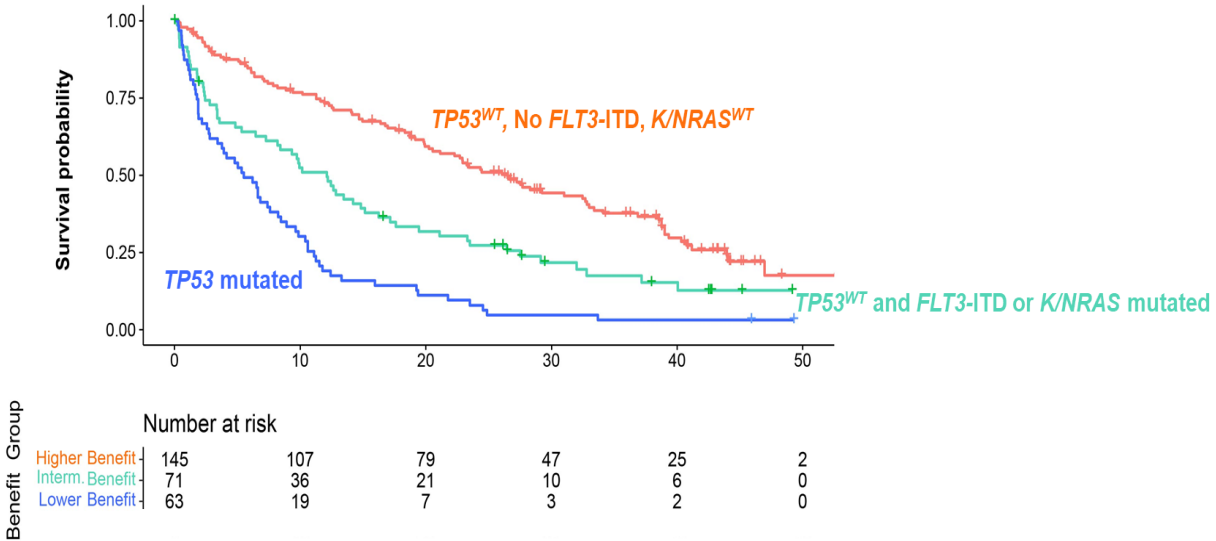
Median OS
A+V: 14.7 mo (95% CI, 12.1 to 18.7)
A+Pbo: 9.6 mo (95% CI, 7.4 to 12.7)

HR, 0.58; 95% CI, 0.47 to 0.72; *P*<0.001

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

# 5-AZA + VENETOCLAX

| Ven + Aza (N = 279) | n | Events | Median OS, months (95% CI) |
|---|---|---|---|
| Higher Benefit | 145 | 96 | 26.51 (20.24, 32.69) |
| Intermediate Benefit | 71 | 57 | 12.12 (7.26 – 15.15) |
| Lower Benefit | 63 | 61 | 5.52 (2.79 – 7.59) |




Döhner H, et al. *Blood*. 2022;140(suppl1):1441-1444. https://doi.org/10.1182/blood-2022-169509

Global Leukemia Academy

# Q&A

APTITUDE HEALTH

Global Leukemia Academy

# Therapeutic approaches in high-risk and frail AML patients

Naval Daver

APTITUDE HEALTH


# Therapeutic Approaches in High-Risk and Older AML Patients

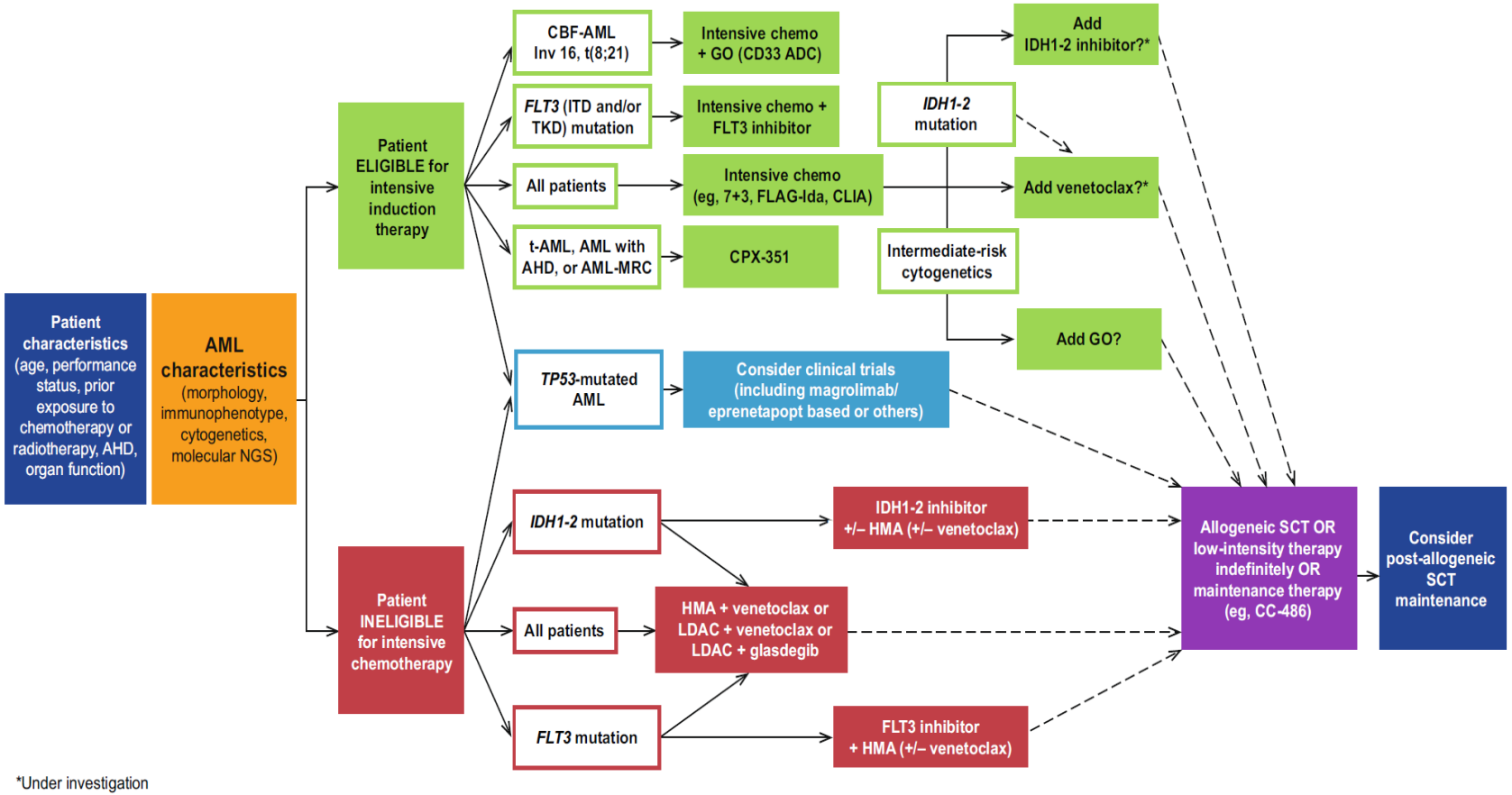
## Global Leukemia Academy

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

# Nearly a decade of progress in AML has resulted in multiple regulatory approvals

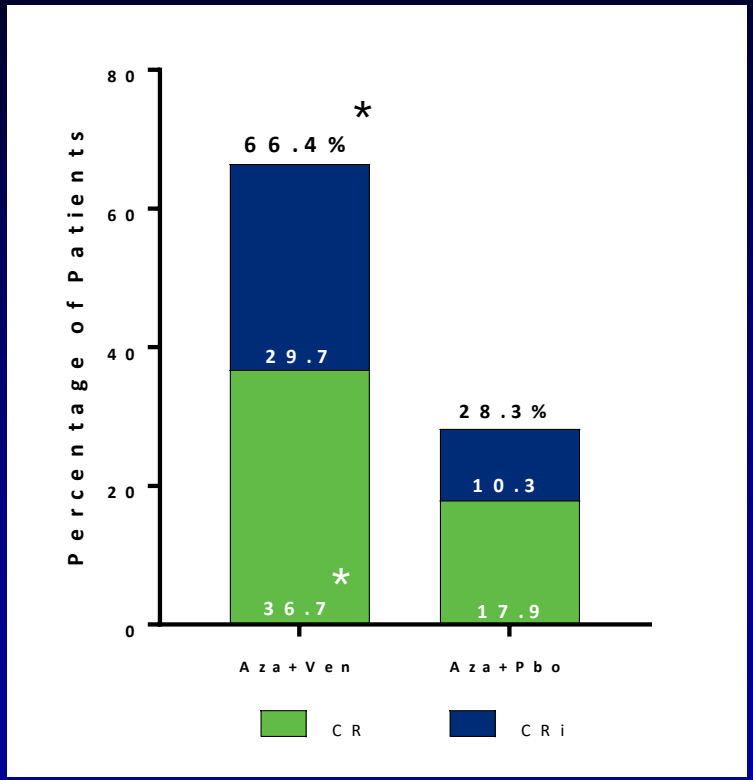
| Drug | Target/MOA | Regulatory Status in the United States |
|---|---|---|
| Midostaurin | FLT3 | Approved (2017) |
| CPX-351 (tAML, AML-MR) | Coformulation of daunorubicin and cytarabine | Approved (2017) |
| Enasidenib | IDH2 | Approved (2017) |
| Gemtuzumab ozogamicin | CD33 | Approved (2017) |
| Glasdegib | Sonic hedgehog pathway | Approved in combination with LDAC (2018) |
| Gilteritinib | FLT3 | Approved (2018) |
| Venetoclax | BCL2 | Approved in combination with azacitidine, decitabine, or LDAC (2020) |
| Oral azacitidine | Hypomethylation of DNA | Approved (2020) |
| Ivosidenib | IDH1 | Approved (2022) |
| Olutasidenib | IDH1 | Approved (2022) |
| Quizartinib | FLT3 | Approved (2023) |

# Evolving diagnostic and treatment paradigm for newly Dx AML




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

# Aza +/– Ven in AML: Composite Response Rate (CR + CRi)

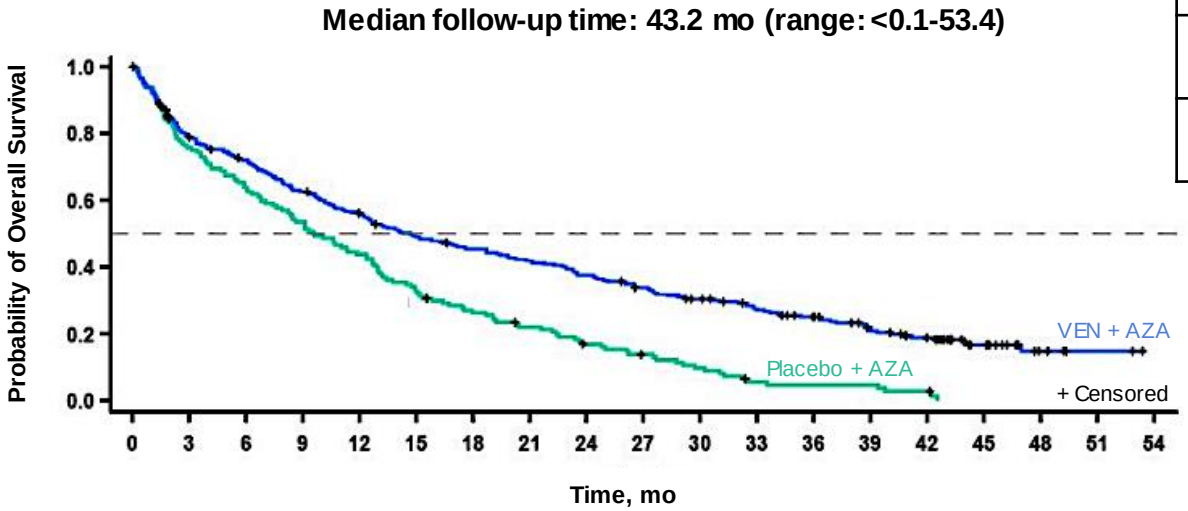



| | No of treatment cycles, median (range) | Median time to CR/CRi, Months (range) | *CR + CRi by initiation of Cycle 2, n (%) |
|---|---|---|---|
| Aza + Ven (n = 286) | 7.0 (1.0–30.0) | 1.3 (.6–9.9) | 124 (43.4) |
| Aza + Pbo (n = 145) | 4.5 (1.0–26.0) | 2.8 (.8–13.2) | 11 (7.6) |

*CR + CRi rate, CR rate, and CR + CRi by initiation of cycle 2 are statistically significant with *P* <.001 by CMH test.

DiNardo CD, et al. EHA 2020. Abstract LB2601.

# AZA + VEN improved survival, but we want to do better




| No. at Risk | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VEN + AZA | 286 | 220 | 199 | 173 | 153 | 133 | 122 | 113 | 101 | 89 | 78 | 67 | 57 | 45 | 34 | 18 | 6 | 2 | 0 |
| Placebo + AZA | 145 | 109 | 92 | 77 | 63 | 47 | 37 | 30 | 22 | 17 | 12 | 6 | 5 | 5 | 3 | 0 | 0 | 0 | 0 |

| | Events/ Patients, n (%) | OS Median, mo (95% CI) |
|---|---|---|
| VEN + AZA | 222/286 (77.6) | 14.7 (12.1-18.7) |
| Placebo + AZA | 138/145 (95.2) | 9.6 (7.4-12.7) |

**HR = 0.58 (95% CI, 0.465-0.723)**
***P* <.001**

HR reduction from 0.66 (95% CI, 0.52-0.85) at 75% OS analysis

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

# Pratz 1944: Cytopenia management in patients with newly diagnosed AML treated with venetoclax + azacitidine in the VIALE-A study

**Protocol (VIALE-A – NCT02993523)**
- Phase III, double-blind, placebo-controlled, 2:1 randomization of VEN + AZA vs PBO + AZA
- Analysis of frequency and management of cytopenia in patients with CR or CRh

**Population**
- Patients with newly diagnosed AML ineligible for intensive chemotherapy due to age ≥75 years or comorbidities

**Authors' conclusions**
- The majority of VEN + AZA responders required dosing modifications to manage cytopenia, particularly delays between cycles or within-cycle reductions of VEN dosing days
- Post-remission cytopenia and dosing modifications were more frequent with VEN + AZA vs PBO + AZA

CR/CRh rate: **66%** (VEN + AZA) vs **23%** (PBO + AZA)

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

AZA, azacitidine; CRh, CR with partial hematologic recovery; PBO, placebo; VEN, venetoclax.

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

# MDACC-recommended dosing schema

- VEN D1–21 in cycle 1
- Bone marrow EOC1 (D21–D28) for all patients: if BM blasts <5% or <10% cellularity/acellular (majority of patients) – hold VEN 10–14 days for count recovery
- If needed, use G-CSF (usually if no spontaneous recovery after 14 days of VEN interruption)
- Cycle 2 onward: VEN D1–21 (or VEN D1–14) for most (subsequently may be further reduced to 7–10 days if cumulative myelosuppression observed)
- Cycles every 4–6 weeks on the basis of count recovery
- Continue second-generation azole prophylaxis, antibiotic, and antiviral until ANC >1.0 without fluctuations (usually after 4–5 cycles)

KEY: Reducing VEN duration does not seem to impact efficacy, but significantly improves neutropenia; more CR/CRh

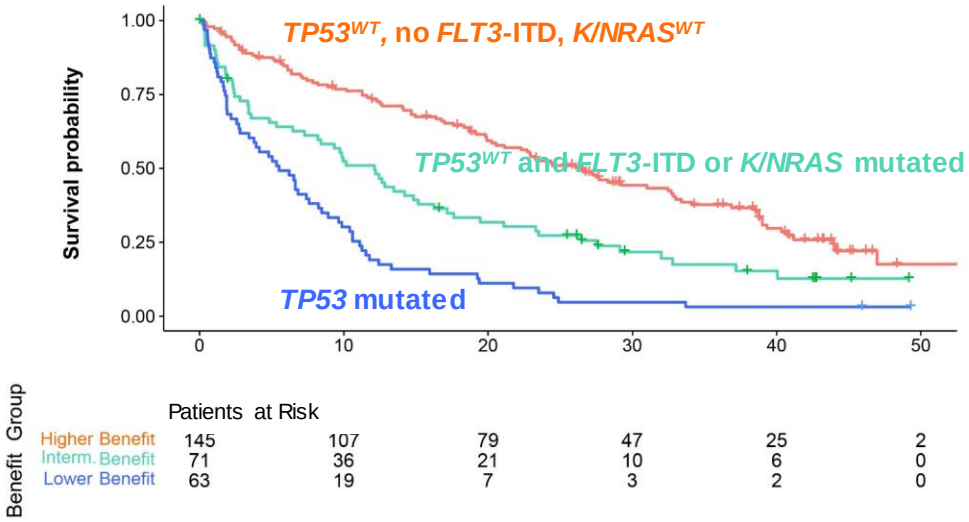
# Recommended venetoclax dose adjustments with azoles

| Antifungal | Package Insert Recommendation (VEN mg/d) | MDACC Dose Adjustment (VEN mg/d) |
|---|---|---|
| Posaconazole | 70 | 50–100 |
| Voriconazole | 100 | 100 |
| Isavuconazole | 200 | 200 |
| Caspofungin, echinocandins | 400 | 400 |

# 1. What are the most urgent populations in need of improvement?

## Patients receiving VEN + AZA distinguishable into 3 subgroups by OS benefit

- First, a higher-benefit group was identified, with a median OS >24 months
- Subsequently, a lower-benefit group was determined, with a median OS <6 months
- Patients fitting neither criteria were categorized as the intermediate-benefit group, with a median OS of 12 months



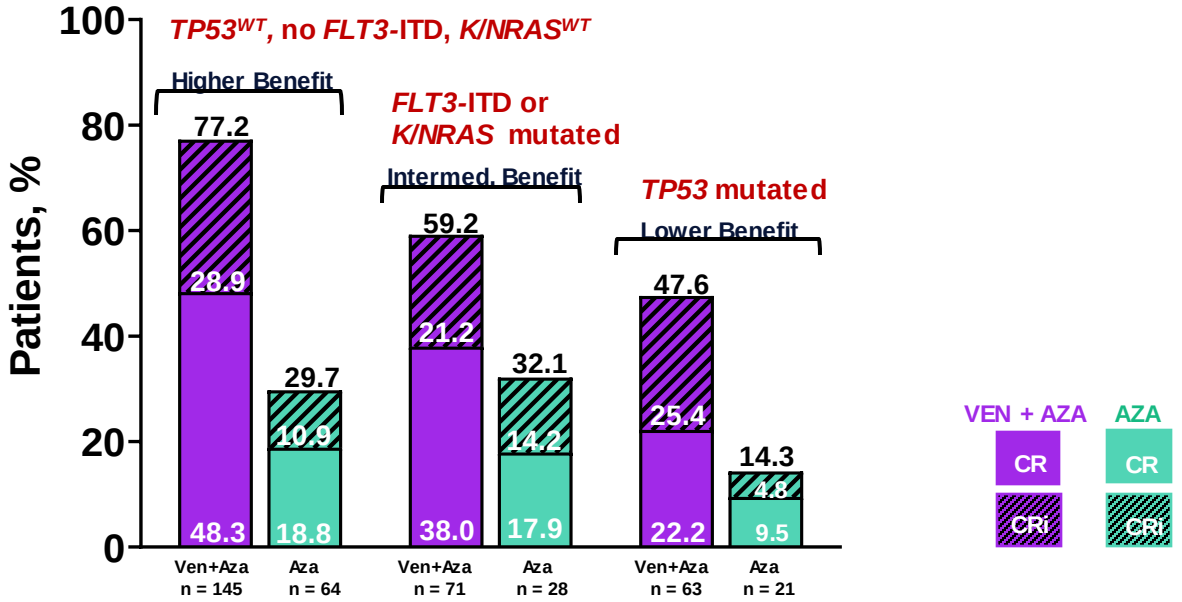

| VEN + AZA (N = 279) | n | Events | Median OS, months (95% CI) |
|---|---|---|---|
| Higher benefit | 145 | 96 | **26.51** (20.24, 32.69) |
| Intermediate benefit | 71 | 57 | **12.12** (7.26 – 15.15) |
| Lower benefit | 63 | 61 | **5.52** (2.79 – 7.59) |

- **The majority of patients in the VEN + AZA arm are in the higher-benefit group: 52% (145/279)**
- The remainder of the patients are distributed equally between the intermediate- and lower-benefit groups: 25.4% (71/279) and 22.6% (63/279), respectively

Dohner H et al, ASH 2022

## 2. Why use HMA + VEN as the backbone for a triplet? Why not a new doublet without VEN?

**Remission rates were higher with VEN + AZA than with AZA monotherapy across all 3 groups**

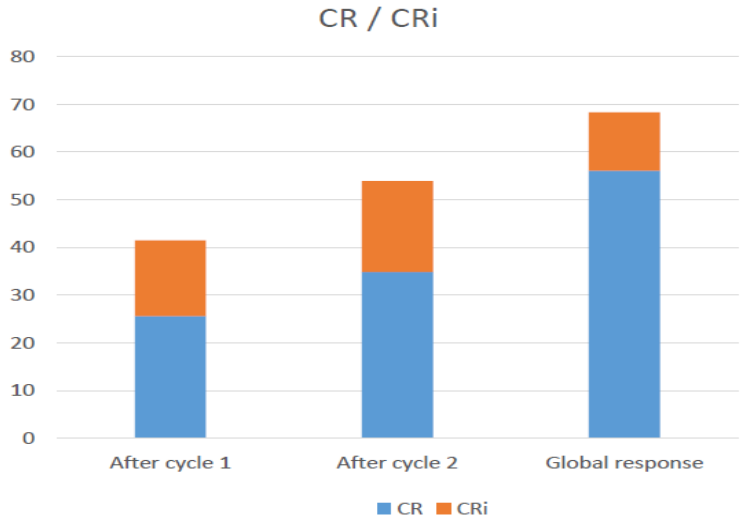



- CR and CR/CRi rates were highest in the higher-benefit group
- Higher MRD-negativity rates were achieved with VEN + AZA than with AZA monotherapy across all 3 groups

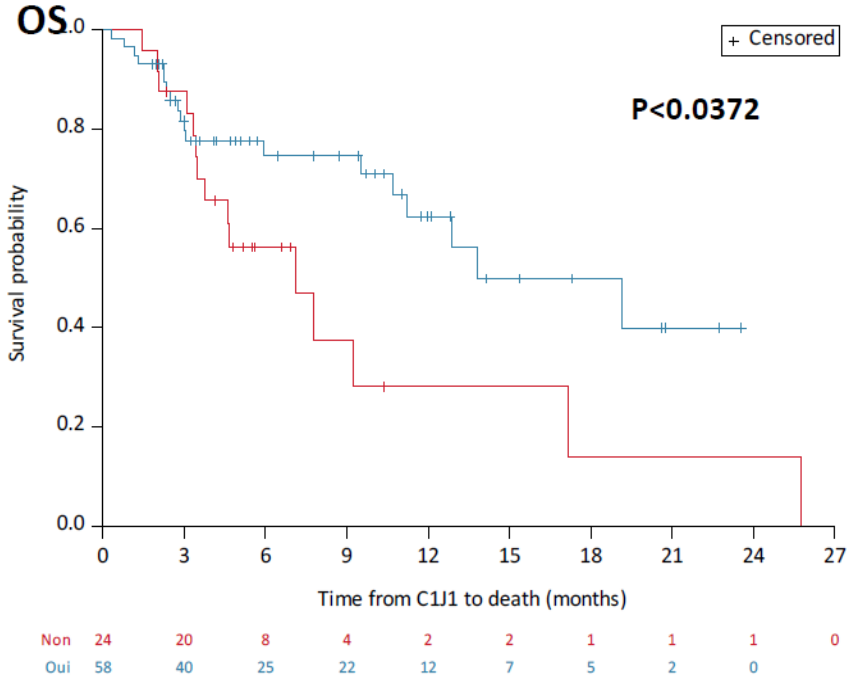
AZA, azacitidine; CR, complete remission; CRi, CR with incomplete count recovery; Intermed., intermediate; MRD, minimal residual disease; VEN, venetoclax.

# 3. How much VEN do we really need? I don't know.
# A recent poll of KOLs (EHA 2023): 14, 21, 17, 19, 22, 24 days

AZA 7 + VEN 7
French retrospective experience ASH 2022
N = 82; CR + CRi 68%




| Phenotypic MRD in CR/CRi patients | |
|---|---|
| After 1 cycle | 12/22 (54.5%) |
| After 2 cycles | 12/16 (75.0%) |
| Global<br>(median number of 1 cycle; range 1-10) | 29/38 (76.3%) |

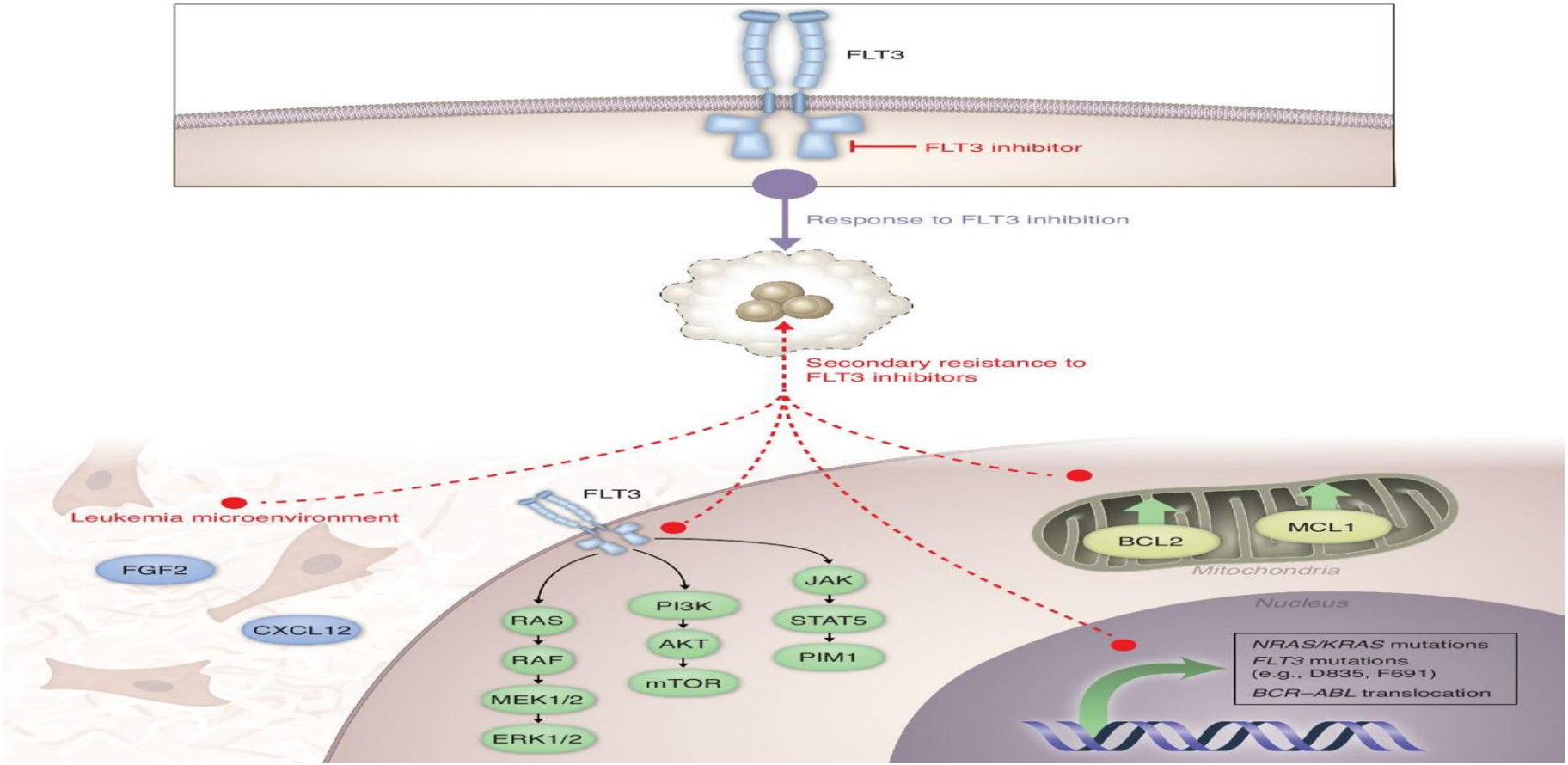



Median OS:
- Exclusion criteria (N=24) 7.10 months (IC95: 3.48-17.15)
- No exclusion criteria (N=58) **13.80 months** (IC95: 10.68-NR)

Willekens C et al, ASH 2022

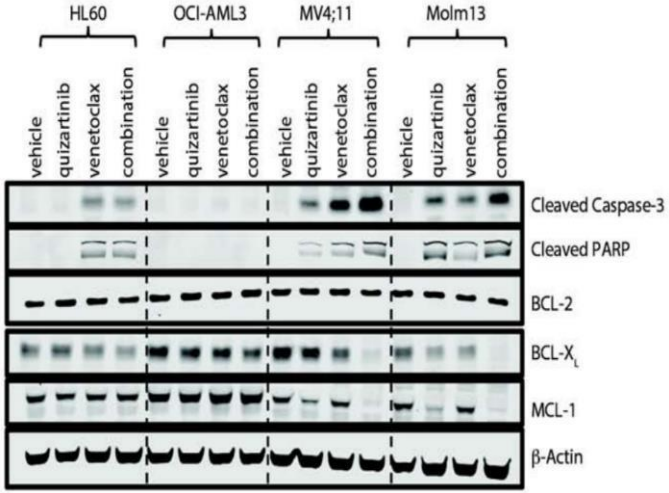
# 1. Targeting *FLT3* mutations (major unmet need, effective targeted therapy options: highly suitable for combinations)

# Combination approaches may help overcome heterogeneous mechanisms of resistance: Many *FLT3* relapses are *FLT3*wt, so better FLT3is unlikely to be the full solution

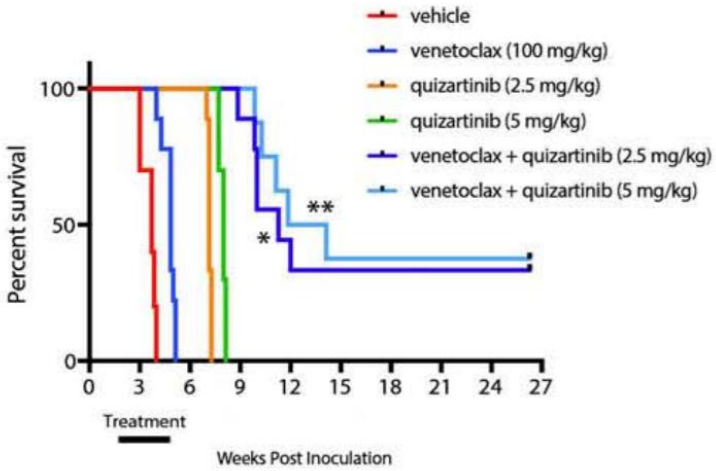


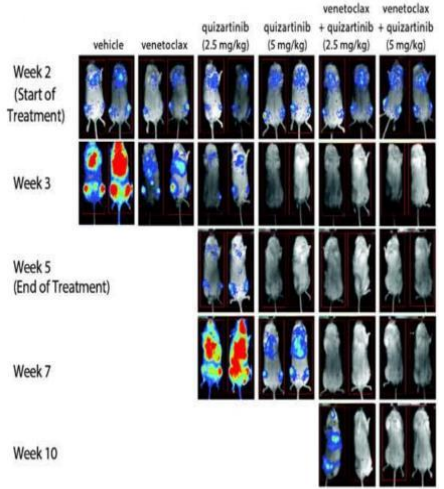

Short N et al, Cancer Discov. 2020 Apr;10(4):506-525

# Venetoclax combines synergistically with quizartinib and other FLT3is




Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-$X_L$




Venetoclax combined with quizartinib prolonged survival and reduced tumor burden in *FLT3*-ITD+ xenograft models

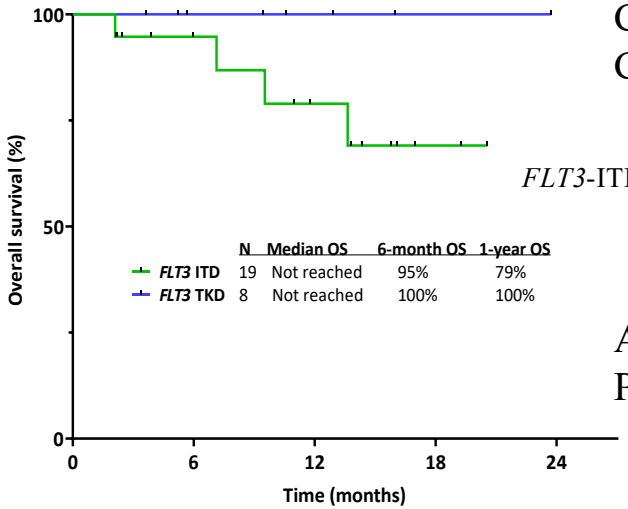
Singh Mali R, et al. Haematologica. 2021;106:1034-1046.

# AZA + VEN + gilteritinib in frontline *FLT3*-mutated AML

## Induction

**Azacitidine**
**75 mg/m² IV/SC on D1-7**

**Venetoclax R/U then 400 mg D3-28**
**→ Gilteritinib**
**120 mg on D1-28**
**(if blasts <5% on D14, hold both GV)**




CR 92%
CRi 4%

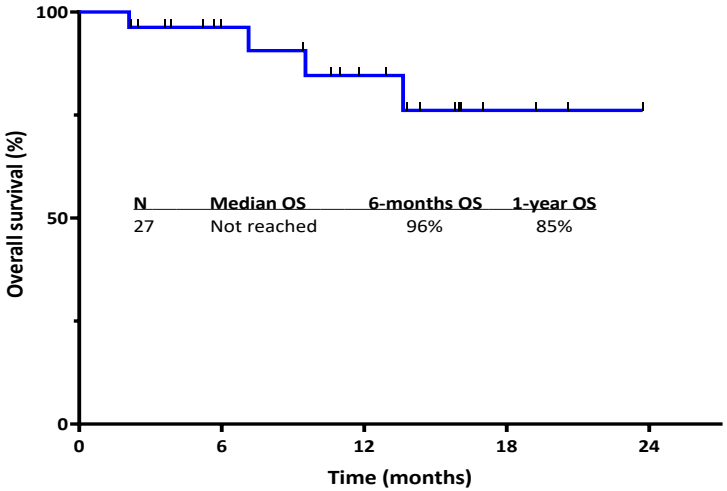
ANC ≥0.5 37 d
Plt ≥50 25 d

## Consolidation (up to 24 cycles)

**Azacitidine 75 mg/m² IV/SC on D1-5**

**Venetoclax 400 mg on D1-7**

**Gilteritinib 80 mg on D1-28**

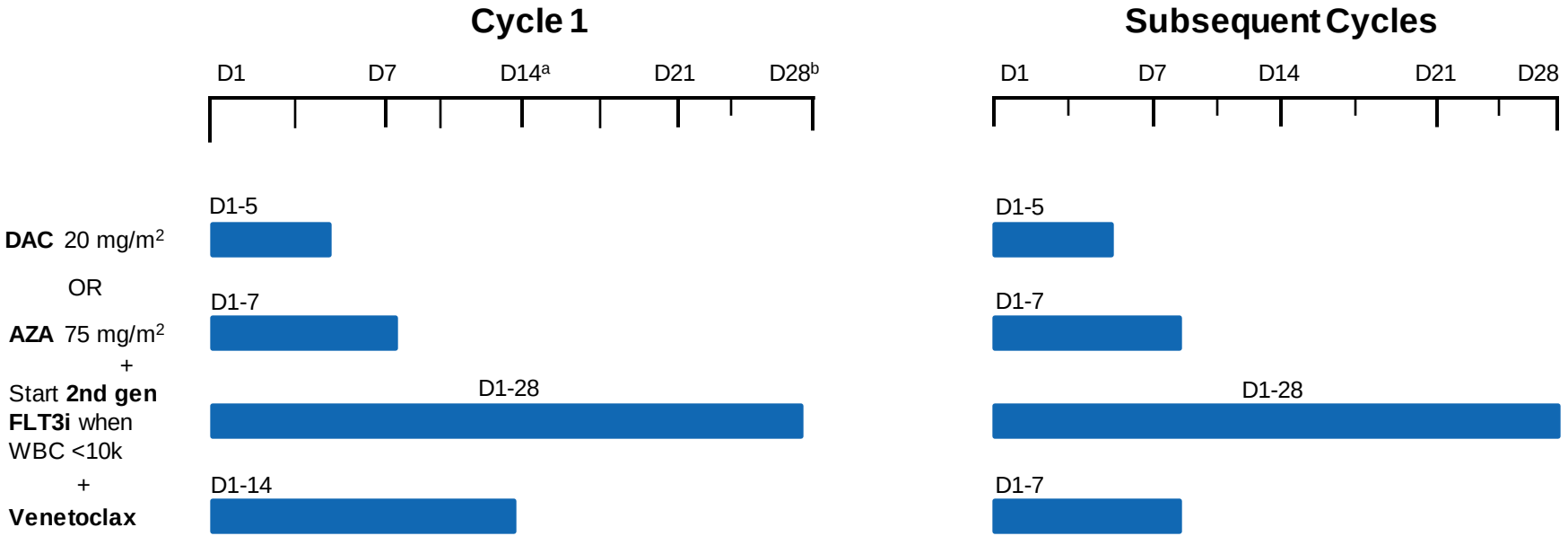



Short N et al, ASH 2022

# So, can we deliver triplets to be effective BUT still safe/deliverable??

## Dosing, duration, and response evaluation timing with FLT3 triplets (dose optimization critical and ongoing) – time, thought, and logistic support . . .

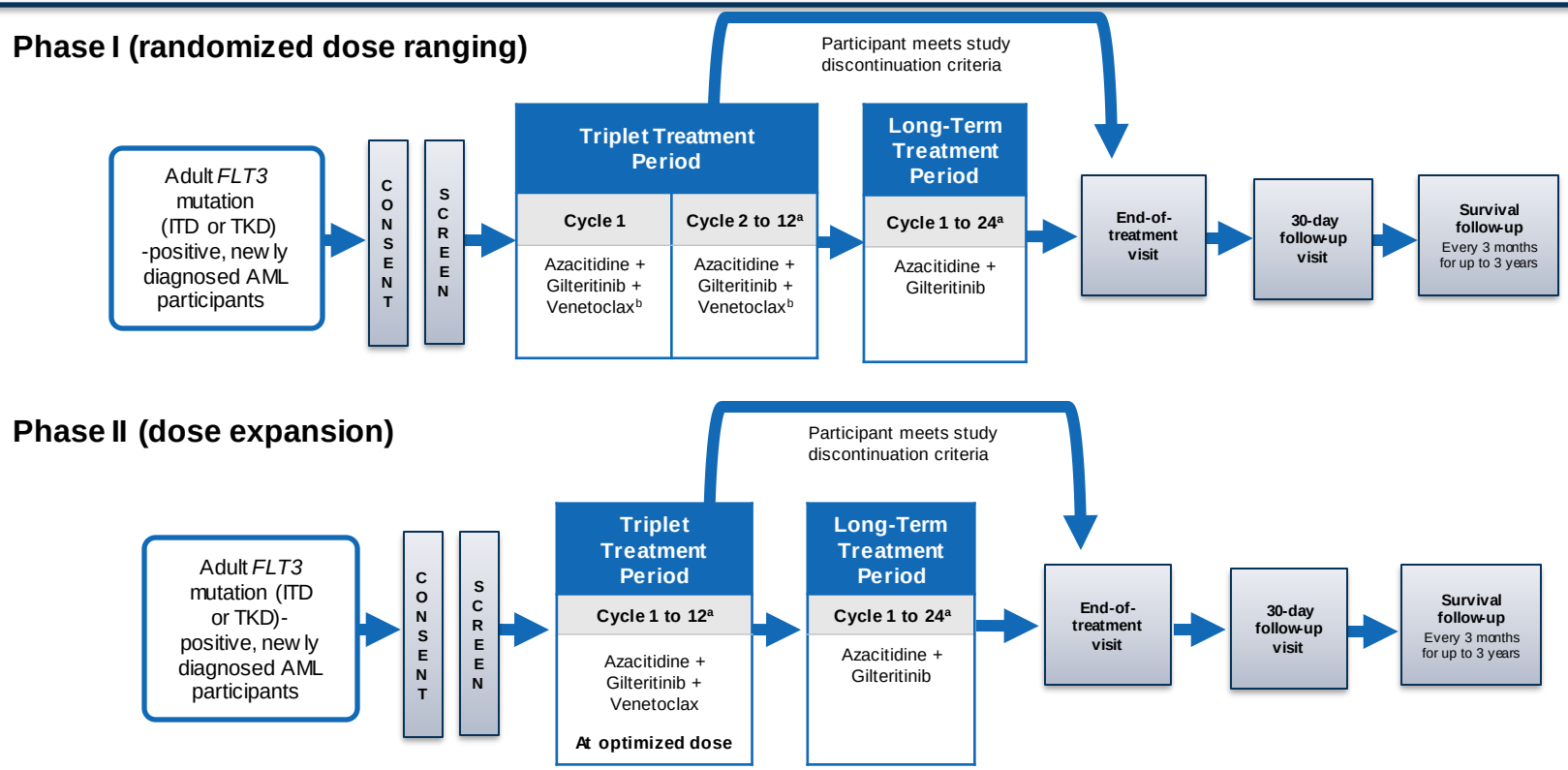
### Ongoing Prospective Trial Dosing: AZA + VEN + GILT; PI: Nick Short; DAC + VEN + Quiz; PI: Musa Yilmaz




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

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

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



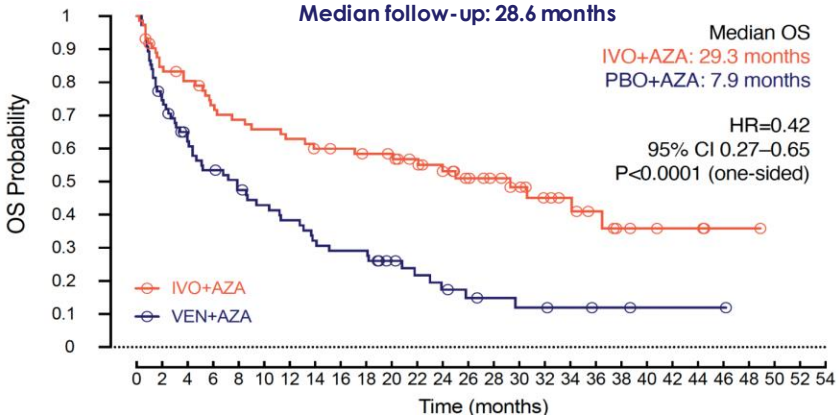

[a]Participants enrolled in phase I or phase II and receiving clinical benefit can continue treatment under the triplet treatment period beyond 12 cycles and under long-term treatment beyond 24 cycles. [b]The dose/duration of gilteritinib and venetoclax administration will depend on the dose level evaluated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

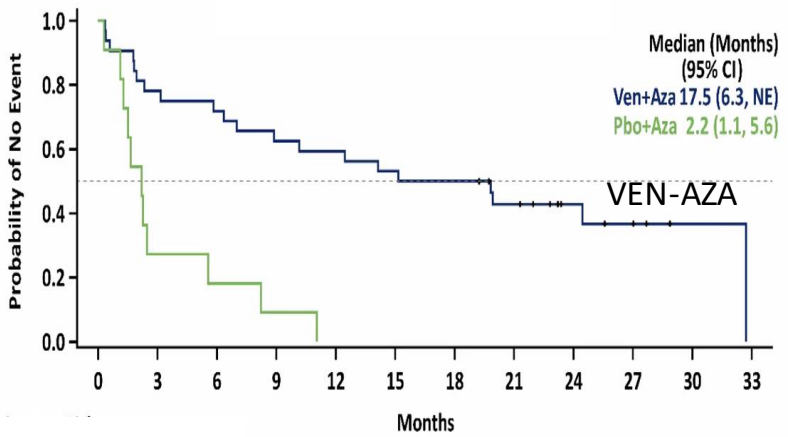
PIs: J. Altman and N. Daver

**2. Targeting *IDH1* and *IDH2* mutations (less myelosuppression, bar is higher, as outcomes not as inferior: but can get better)**

# IVO-AZA or VEN-AZA for *IDH1*-mut AML?

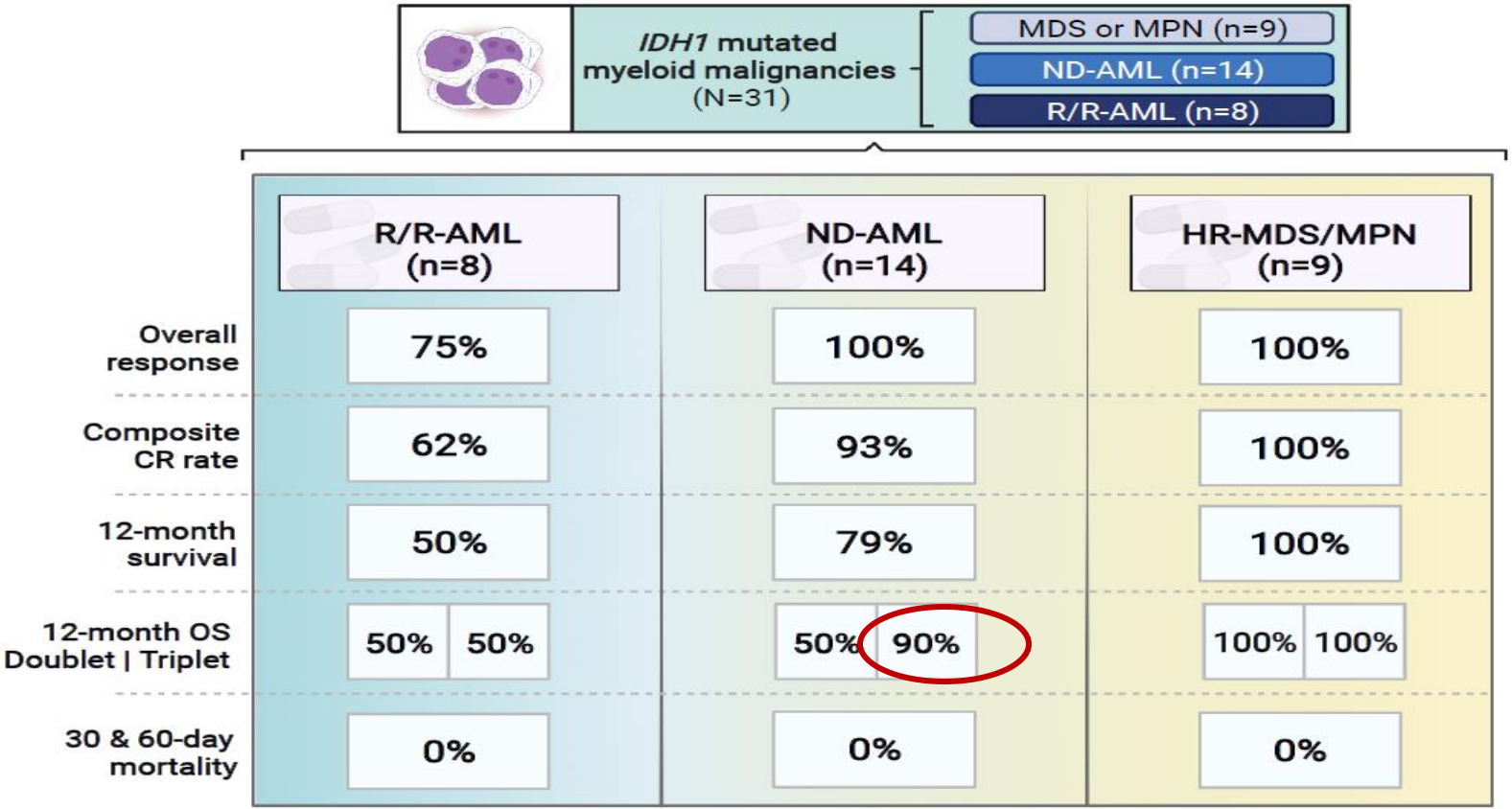
| *IDH1*m | IVO-AZA | AZA | VEN-AZA | AZA |
|---|---|---|---|---|
| N | 72 | 74 | 32 | 11 |
| Median age | 76 | 76 | 76 | 76 |
| ORR (CR/CRi) | 54% | 16% | 66% | 9% |
| CR | 47% | 15% | 28% | 0% |
| Median time to CR/CRi | 4.3 mo | 3.8 mo | 1.1 mo | 3.4 mo |
| Median OS | 29.3 mo | 7.9 mo | 17.5 mo (in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




Montesinos et al, NEJM 2022, 386; 1519-31; De Botton et al. P142, ASCO 2023; Pollyea, et al, *Clin Cancer Res 2022;28:2753–61.*

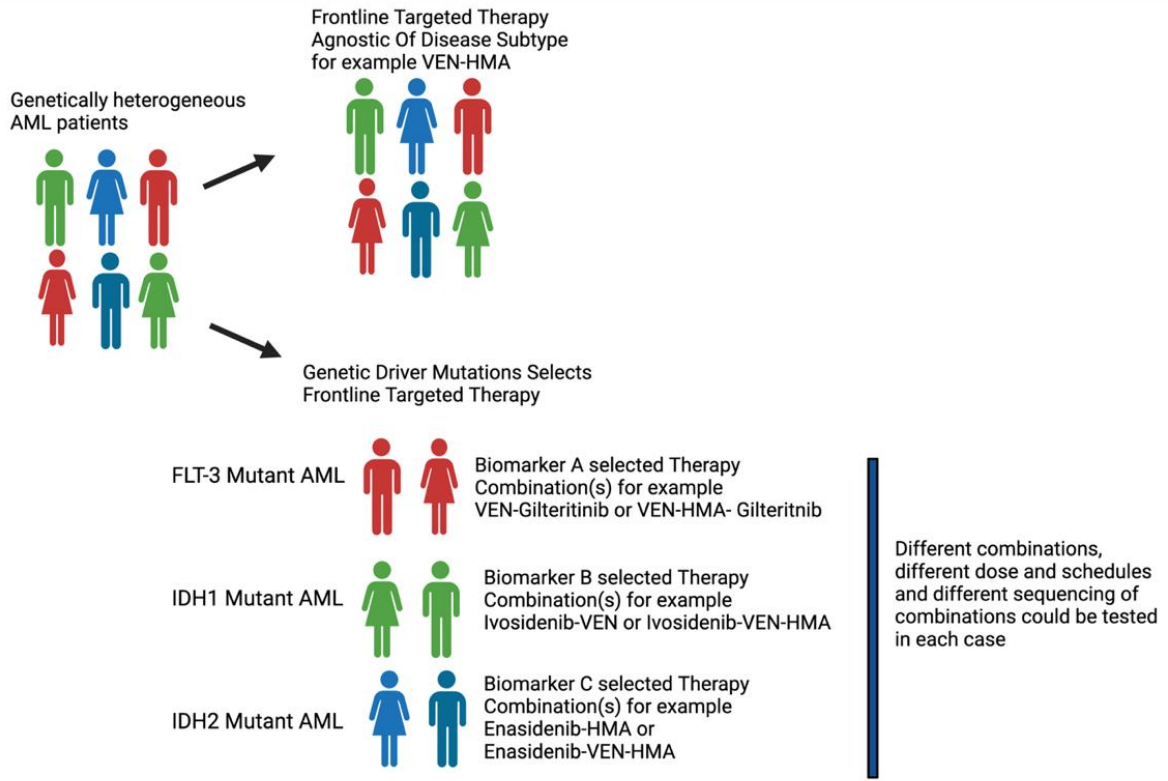
# Overview of IVO + VEN ± AZA efficacy




Lachowiez C et al, ASCO 2022

# Should we combine or sequence?

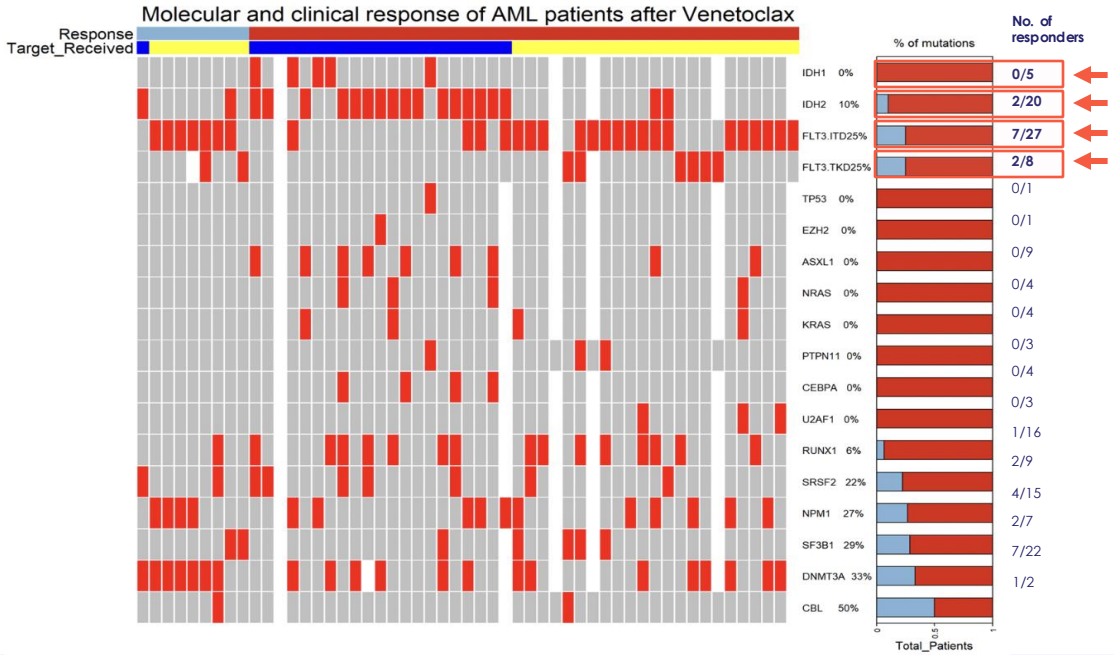
# Is sequential therapy another option? Possibly, but no prospective data to date – concern that the unique synergies at play in the triplet combos may be lost




*Perl AE, Vyas P. Clin Cancer Res. 2022 Jul 1;28(13):2719-2721*

# Sequential therapies: Retrospective comparison

OncoPrint of molecular predictors of response to **targeted therapy after prior venetoclax treatment**[1]




**Mutations**
- Present
- Absent

**Target Received**

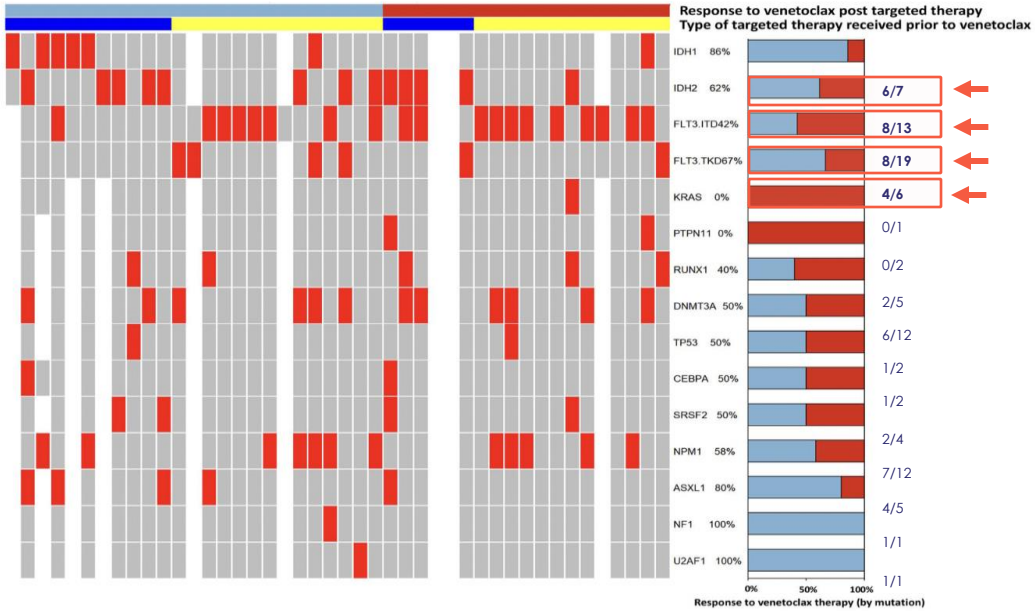
- **FLT3 inh after VEN-based Rx: 9/35 (26%)**
- **IDH inh after VEN-based Rx: 2/25 (8%)**


1. *Bewersdorf JP et al. Leukemia Research. 2022 Nov, 122:106942.*


**CR**, complete remission; **CRi,** complete remission with incomplete hematologic recovery; **CI**, confidence interval; **MLFS**: morphologic leukemia-free state; **OS:** overall survival; **PD**: persistent disease.

# Sequential therapies: Retrospective comparison

OncoPrint of molecular predictors of response to **venetoclax-based combinations after targeted therapies**[1]




**Mutations**
- Present
- Absent

**Target Received**

- **FLT3 inhib followed by VEN based: 14/20 (70%)**
- **IDH inhib followed by VEN based: 12/25 (48%)**

1. *Bewersdorf JP et al. Leukemia & Lymphoma. 2022 Dec, 9:1-9.*

**CR**, complete remission; **Cri,** complete remission with incomplete hematologic recovery; **CI,** confidence interval; **MLFS**: morphologic leukemia-free state; **OS:** overall survival; **PD**: persistent disease.

# IDH1i or VEN-based regimen as first-line therapy?

| | IDH Inhibitor First (n = 8) | VEN + AZA First (n = 18) |
|---|---|---|
| Salvage response | IDHi → VEN-AZA (4/4)<br>IDHi + AZA → VEN-AZA (3/3)<br>IDHi + IC → VEN-AZA (0/1) | VEN + AZA → IDHi (2/4)<br>VEN + AZA → IDHi + AZA or VEN (2/7)<br>VEN + AZA → IDHi + AZA + VEN (6/7) |
| Overall response | 7/8 (88%) | 10/18 (56%) |
| Median survival from first therapy | 47 mo | 20 mo |

*Hammond D et al, BCJ*

| | IDH Inhibitor First (n = 17) | VEN + AZA First (n = 22) |
|---|---|---|
| Salvage response | IDHi → VEN-based therapy | VEN-based therapy → IDHi based |
| Overall response | 11/17 (CR, CRi MLFS) [65%] | 1/22 |
| Median survival from salvage | 12.8 mo | 3.6 mo |

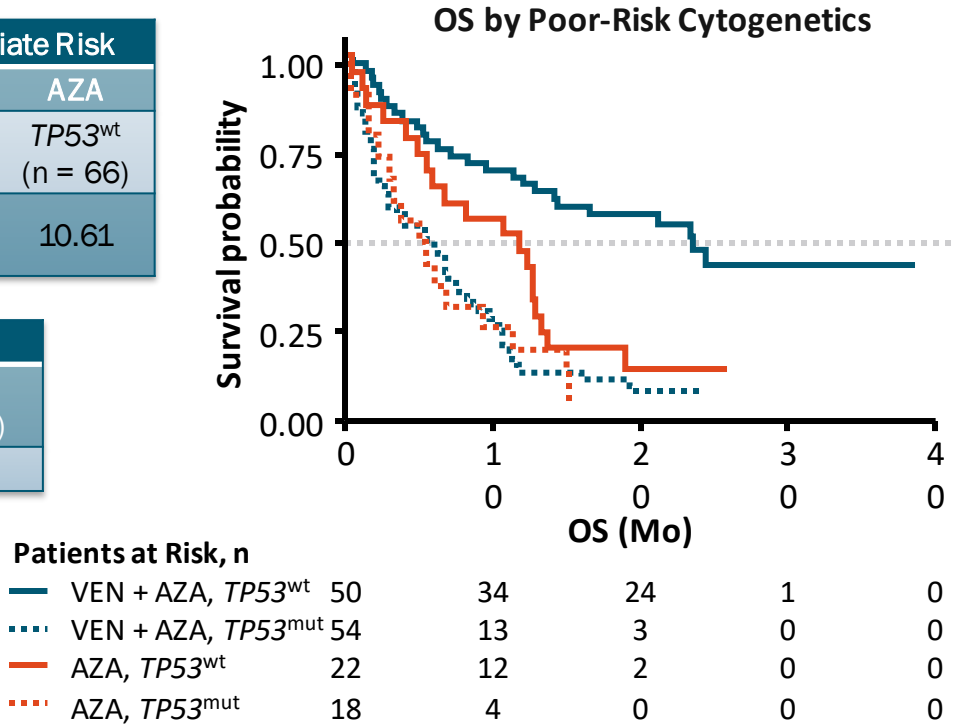
*Bewersdorf JP et al. Leukemia Research. 2022 Nov, 122:106942.*
*Bewersdorf JP et al. Leukemia & Lymphoma. 2022 Dec, 9:1-9.*

# 3. *TP53*-mutated AML (will triplet be better than doublet? Can anything move the needle forward??)

# Efficacy of VEN-AZA in patients with poor-risk cytogenetics ± *TP53*-mutant ND AML

| | Poor Risk | | | | Intermediate Risk | |
|---|---|---|---|---|---|---|
| | VEN-AZA | | AZA | | VEN-AZA | AZA |
| | *TP53*$^{mut}$ (n = 54) | *TP53*$^{wt}$ (n = 50) | *TP53*$^{mut}$ (n = 18) | *TP53*$^{wt}$ (n = 22) | *TP53*$^{wt}$ (n = 166) | *TP53*$^{wt}$ (n = 66) |
| mOS, mo | 5.17 | 23.43 | 4.90 | 11.29 | 19.15 | 10.61 |

| OS by VAF of *TP53* for Patients Who Received VEN-AZA | | | | |
|---|---|---|---|---|
| | VAF <20% (n = 6) | VAF 20%-40% (n = 5) | VAF >40% (n = 42) | wt (n = 50) |
| mOS, mo | 6.18 | 1.22 | 5.17 | 23.43 |




*Pollyea D et al. Clin Cancer Res 2022*

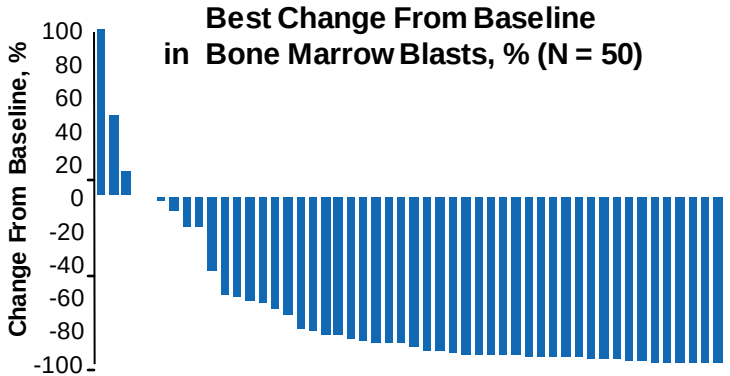
# Magrolimab + azacitidine appears to be efficacious against *TP53* AML

**Magrolimab + azacitidine:**
**49% ORR and 33% CR in *TP53* AML**

- No significant cytopenias, infections, or immune-related AEs were observed; on-target anemia
- Median OS was 10.8 months
- Patients moving to alloHCT on therapy had encouraging 1-year OS (63%) with median NR

**Magrolimab + azacitidine is being studied in patients with frontline *TP53*-mutated AML in the phase III ENHANCE-2 trial (currently recruiting; NCT04778397)**

| Outcome | Patients With *TP53* AML (N = 72) |
|---|---|
| **ORR, % (95% CI)** | **48.6 (36.7-60.7)** |
| **CR, % (95% CI)** | **33.3 (22.7-45.4)** (n = 24/72) |
| MRD- CR[a], % (95% CI) | 50 (29.1-70.9) (n = 12/24) |
| **CRi/CRh, n (%)** | 6 (8.3) |
| **PR, n (%)** | 4 (5.6) |
| **MLFS, n (%)** | 1 (1.4) |
| **DOR, median (95% CI), mo** | **8.7 (6.5-10.4)** |




[a]MRD was assessed in bone marrow samples by a central laboratory using multiparameter flow cytometry with a lower limit detection of 0.02%.

*Daver N et al. JCO July 2023 (in press)*

# Survival comparison: AZA-VEN-magrolimab vs HMA-VEN *TP53*-mutated arm

- Comparator datasets from phase Ib/II AZA + VEN and Dac10 + VEN F/L studies from MDACC (N = 150)*

**Comparison of Baseline Characteristics Among *TP53*m Patients Only**

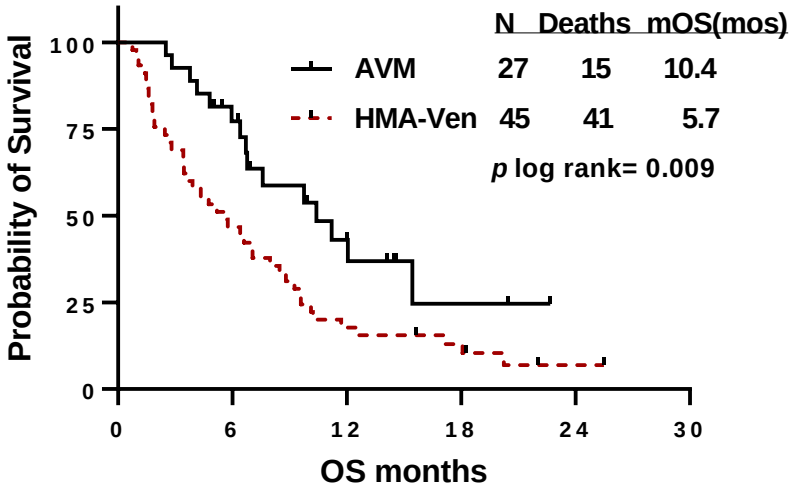
| Parameters | A-V-M (N = 27) | HMA-Ven (N = 45) |
|---|---|---|
| Age, years | 66 [58 to 84] | 74 [61 to 86] |
| t-AML | 12 (44) | 17 (38) |
| CTG- HR<br>CTG-CK | 22 (82)<br>21 (78) | 43 (96)<br>41 (91) |
| ASXL1 | 2 (7) | 2 (4) |
| RUNX1 | 2 (7) | 2 (4) |

**MV Cox Regression Analysis**

| Variable | HR | 95% CI |
|---|---|---|
| Age | 0.9865 | 0.9522 to 1.025 |
| t-AML[Y] | 1.213 | 0.6974 to 2.074 |
| CTG HR[Y] | 1.202 | 0.4719 to 3.700 |
| Rx arm [AVM] | 0.4091 | 0.1781 to 0.8811 |

**Adjusted HR for AVM arm for death = 0.41, 95% CI = 0.18-0.88**

**Comparison of Overall Survival (unmatched groups)**

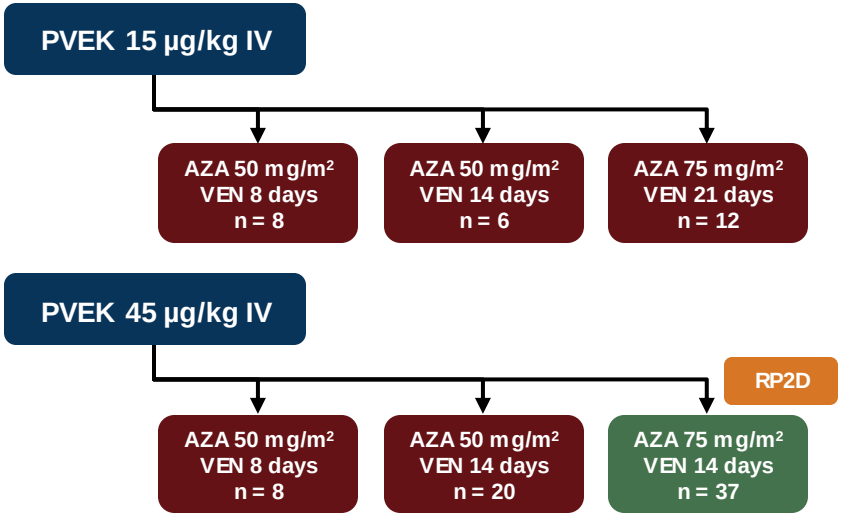



*Daver N, et al. Blood. 2022;140: Abstract 61.*

**Courtesy DiNardo, Maiti and Konopleva.*

# 4. Non-mutationally–directed combos: PVEK + VEN + AZA demonstrated activity in R/R AML; frontline cohort ongoing

- Compelling CR/CRh rates were observed in several R/R AML subgroups; including VEN naive, first relapse, and those with *IDH2* and *FLT3* mutations
- RP2D (using 14+ days of VEN) was not associated with excessive myelosuppression and was well tolerated




| | N | ORR, % | CCR, % | CR, % | CRh, % | CRp or CRi, % | MLFS, % |
|---|---|---|---|---|---|---|---|
| ITT population | 91 | 45 | 25 | 13 | 9 | 3 | 20 |
| RP2D cohort | 37 | 38 | 22 | 14 | 5 | 3 | 16 |

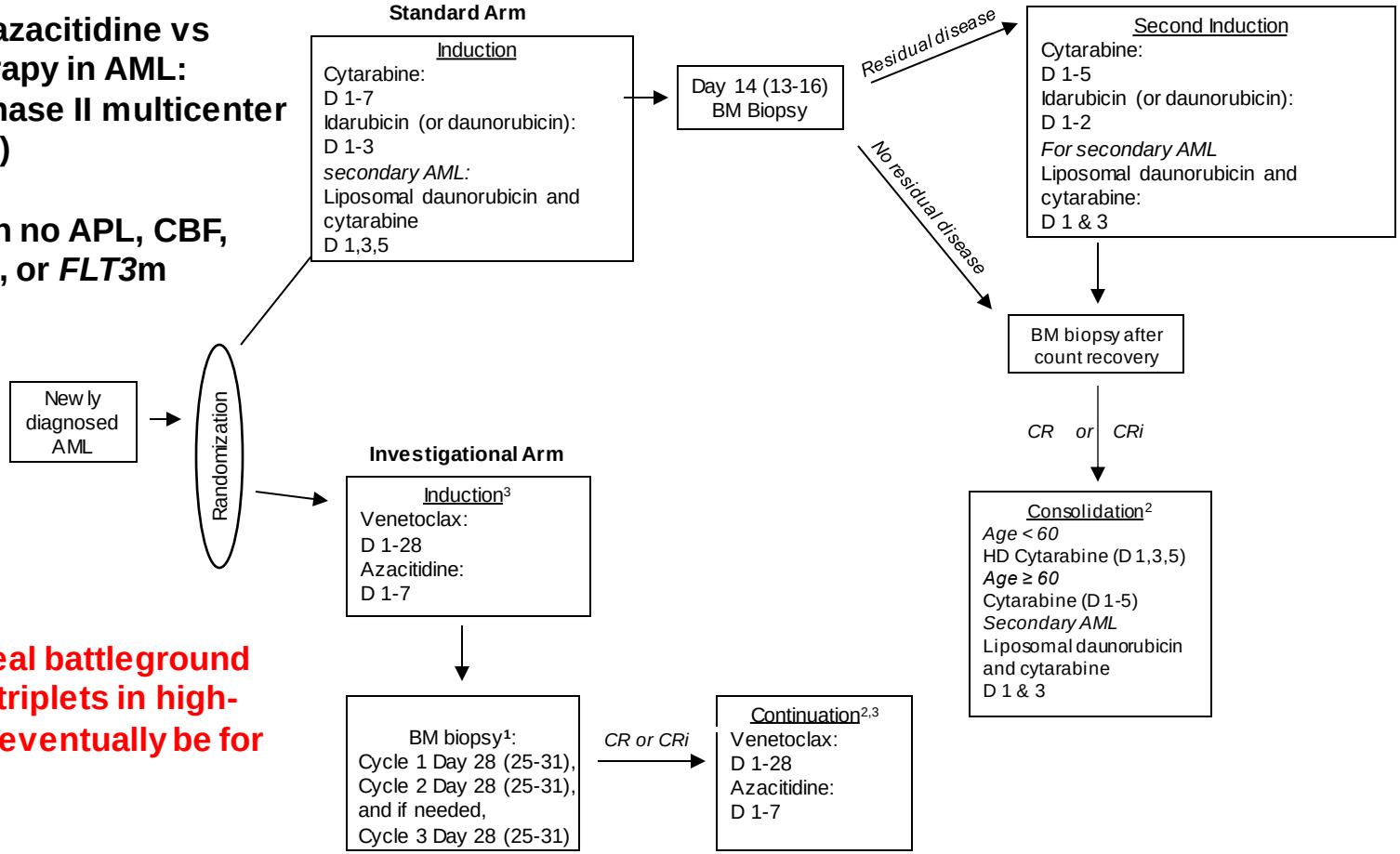
*Daver N et al. ASH 2022. Abstract 62.*

# Are we focusing on the correct population to develop these "not so non-intense regimens"?

**Venetoclax + azacitidine vs induction therapy in AML: Open-label, phase II multicenter study (n = 172)**

**Pts ≥18 yr with no APL, CBF, NPM1 (<60 yr), or *FLT3*m**

**PI: Amir Fathi**

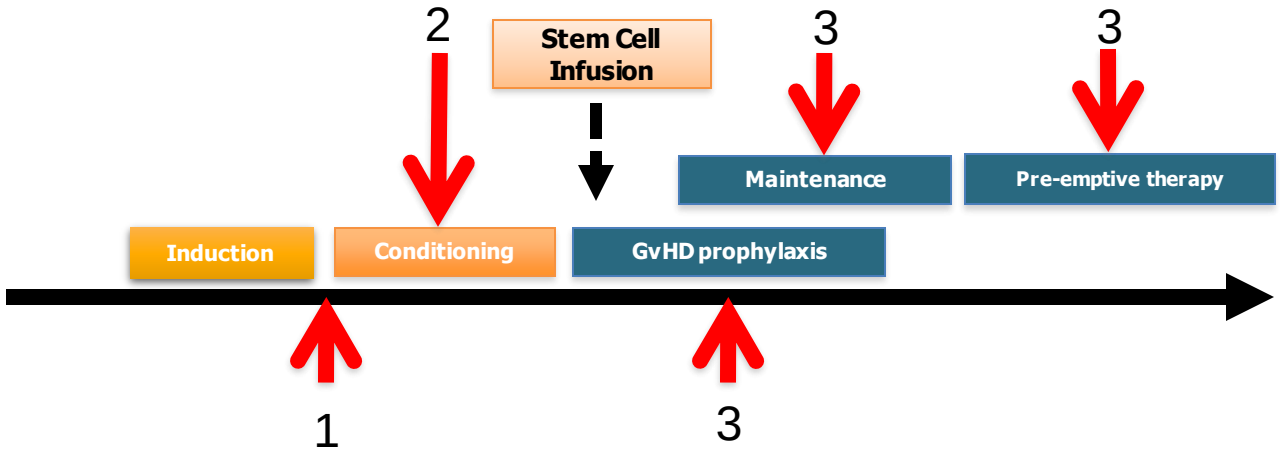



**Maybe the ideal battleground for the novel triplets in high-risk AML will eventually be for younger AML**

Slide courtesy Amir Fathi.
https://clinicaltrials.gov/ct2/show/NCT04801797

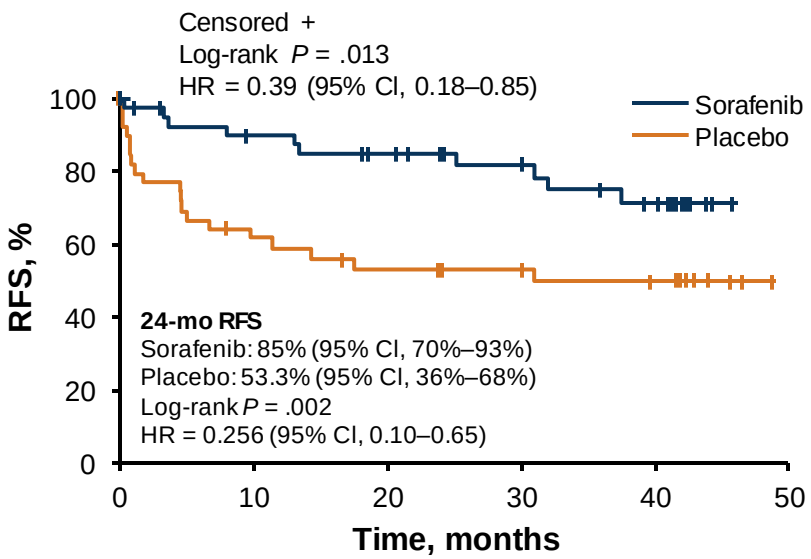
# Strategies to reduce relapse in patients allografted for AML: Choosing the best conditioning regimen – is getting to allo-SCT safely a key strategy for AML at this time?

1) Minimize pretransplant disease burden
2) Optimize cytotoxic properties of the conditioning regimen
3) Maintenance drug or cellular therapies that
   - Target residual leukemic stem/progenitors
   - Optimize a GvL effect

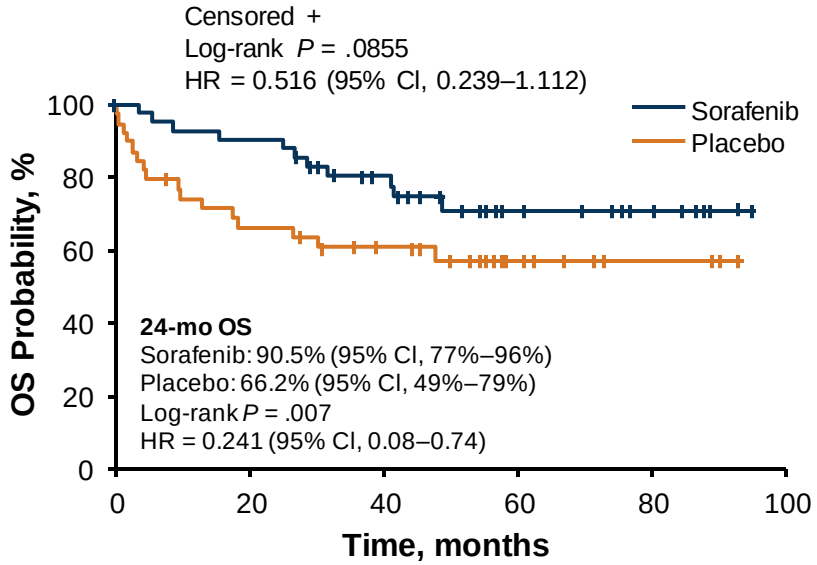



Craddock, et al. Bone Marrow Transplant. 2019

# FLT3i maintenance post-SCT: RFS and OS in *FLT3*+ AML in CR after HSCT treated with sorafenib vs placebo (SORMAIN)



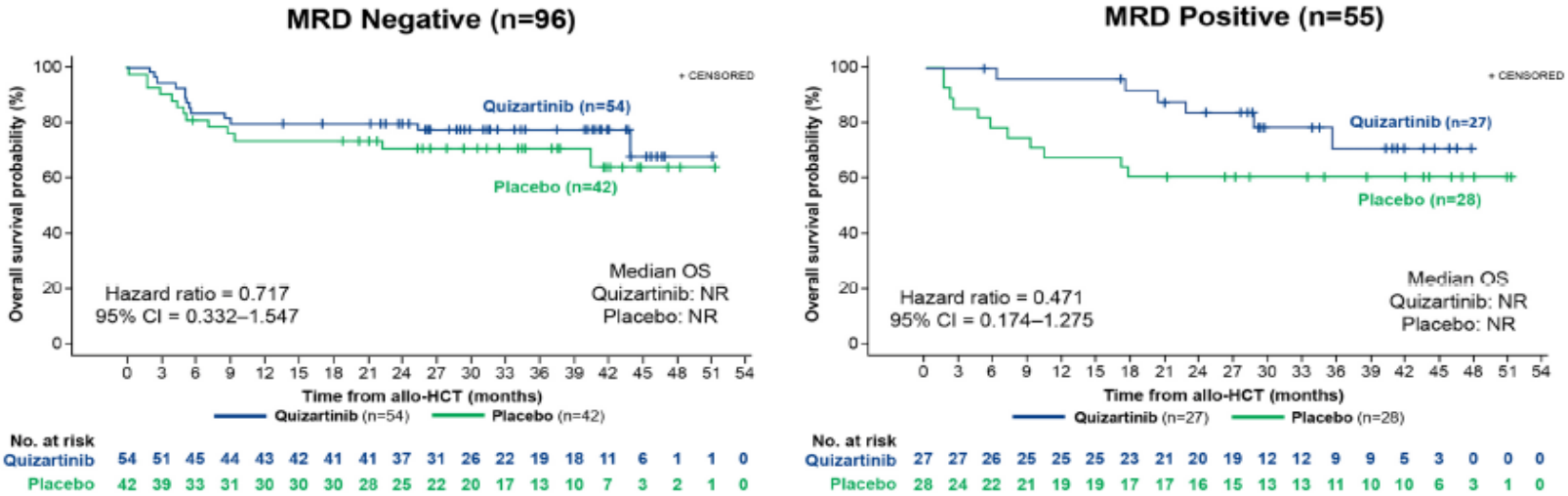

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 40 | 24 | 19 | 17 | 14 | 0 |
| Sorafenib | 43 | 35 | 31 | 25 | 18 | 0 |



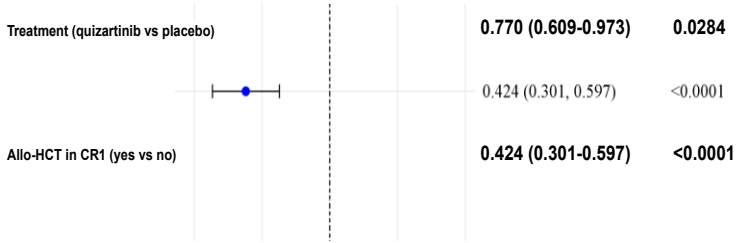

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 40 | 25 | 19 | 9 | 3 | 0 |
| Sorafenib | 43 | 38 | 28 | 12 | 7 | 0 |

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]

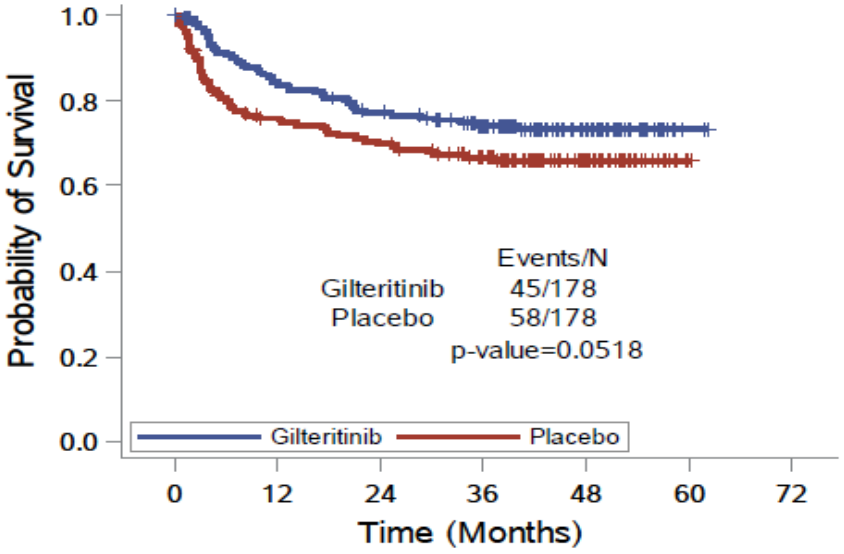



Analysis using Kaplan-Meier plots.
Note that of the 157 patients (84 in the quizartinib arm and 73 in the placebo arm) who underwent allo-HCT in CR1, 151 with MRD data were analyzed (81 in the quizartinib arm and 70 in the placebo arm).

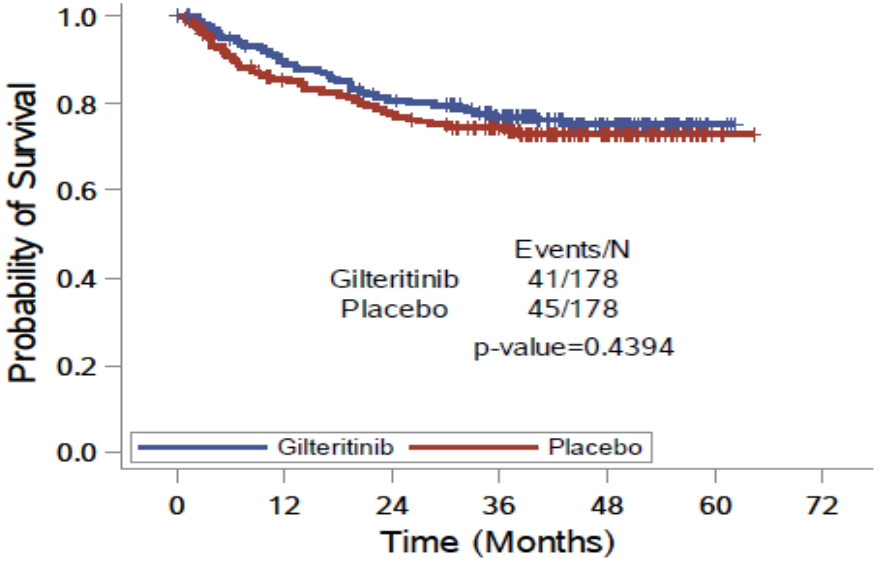


# BMT CTN 1506 (MORPHO): Efficacy outcome

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

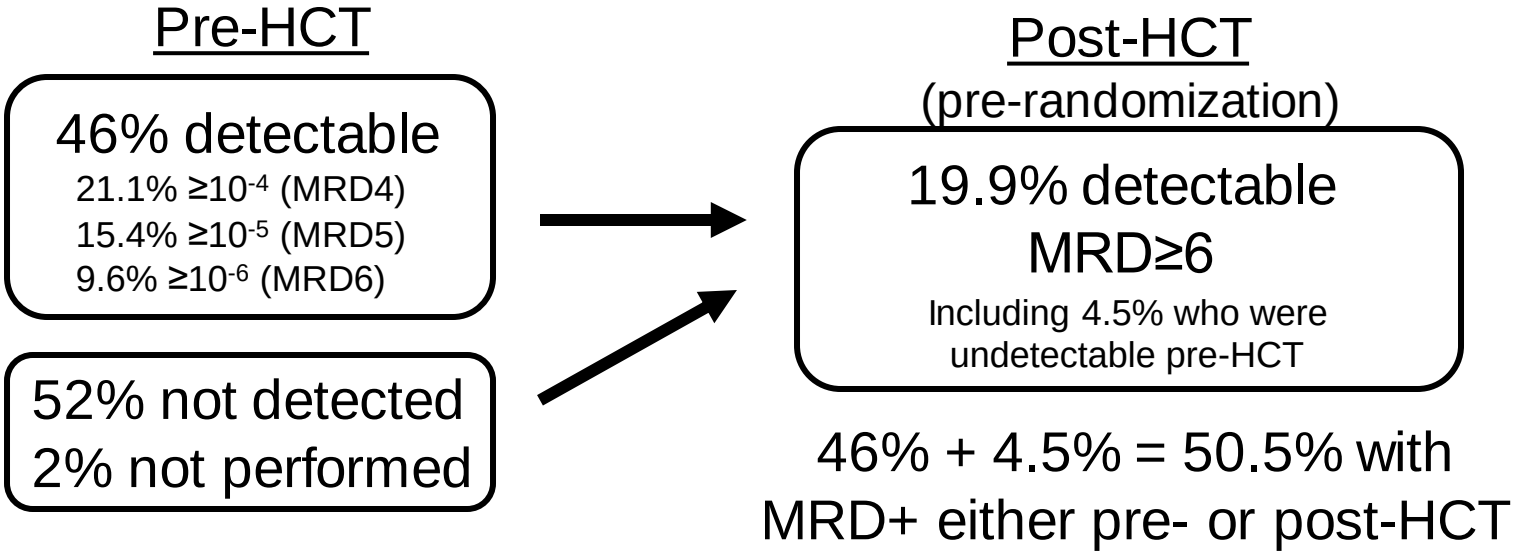



Key secondary objective:
Overall survival
HR = 0.846 (0.554–1.293)
*P* = .4394

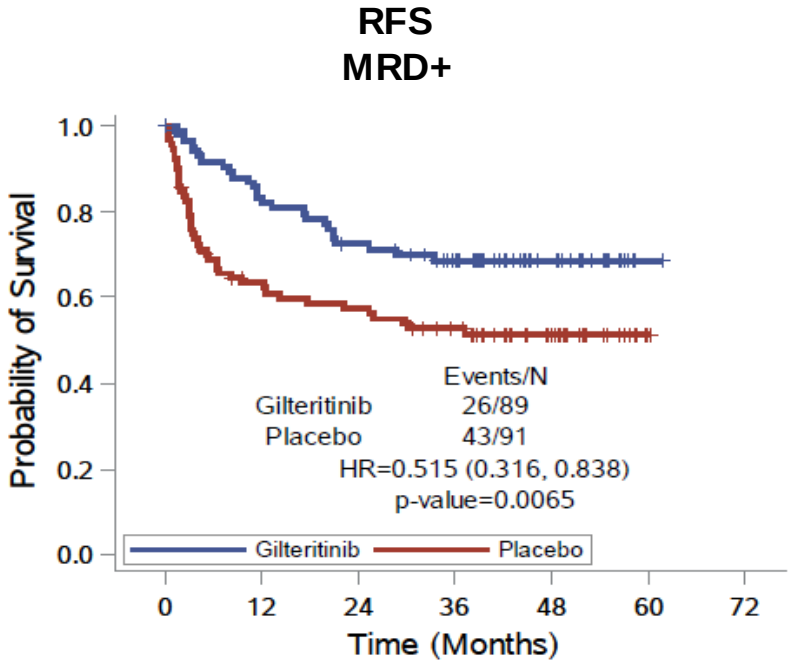


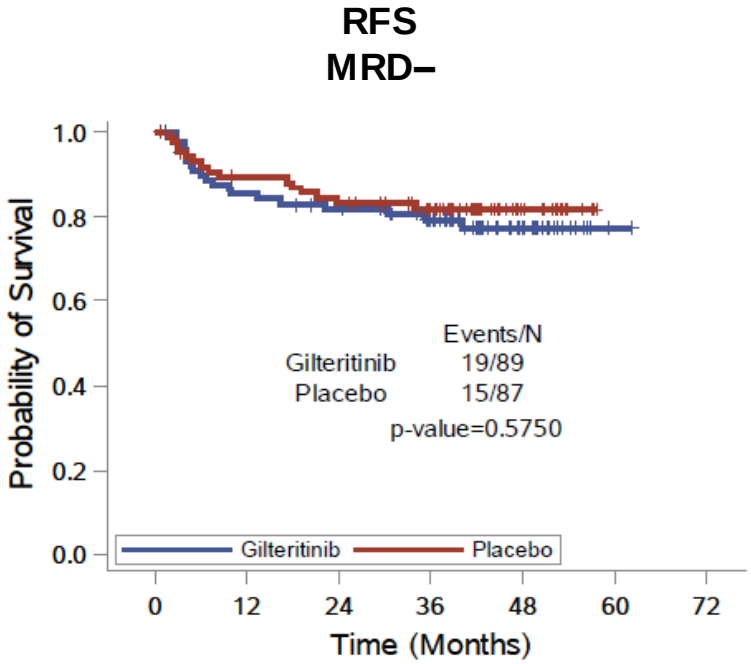
# Measurable residual disease (MRD)

- 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.

# Leukemia Questions?


- Email: ndaver@mdanderson.org
- Cell: 832-573-7080
- Office: 713-794-4392

Global Leukemia Academy

# Q&A

APTITUDE HEALTH

Instituto de Investigación CONTRA LA LEUCEMIA Josep Carreras

FUNDACIÓN PETHEMA Para el tratamiento de la Leucemia y el Linfoma

ICO Institut Català d'Oncologia Hospital Germans Trias i Pujol

Global Leukemia Academy

# Maintenance and time-limited treatment strategies in leukemias (focusing on ALL)

Josep-Maria Ribera

APTITUDE HEALTH

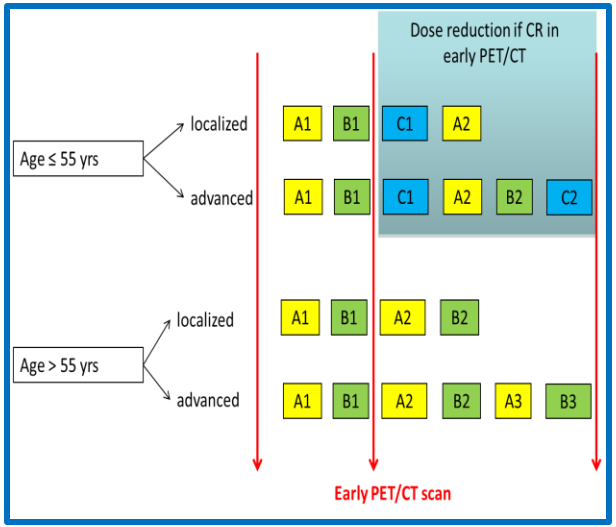
# Disclosures

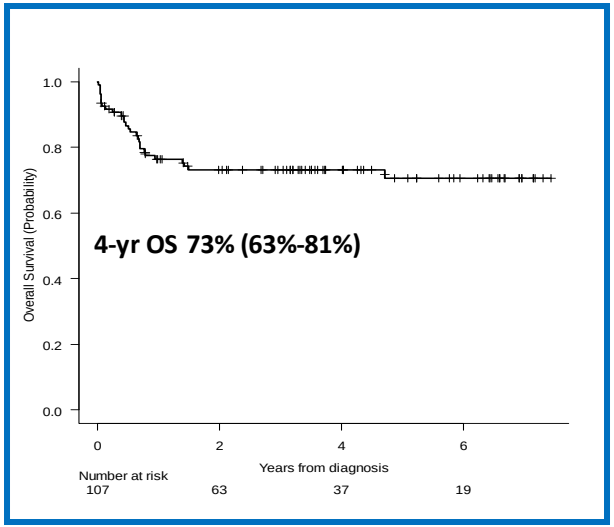
- Pfizer: speaker and advisory boards honoraria, clinical trials
- AMGEN: speaker and advisory boards honoraria, research support, clinical trials
- Shire: speaker and advisory boards honoraria
- Ariad: speaker and advisory boards honoraria, clinical trials
- Takeda: speaker and advisory boards honoraria,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

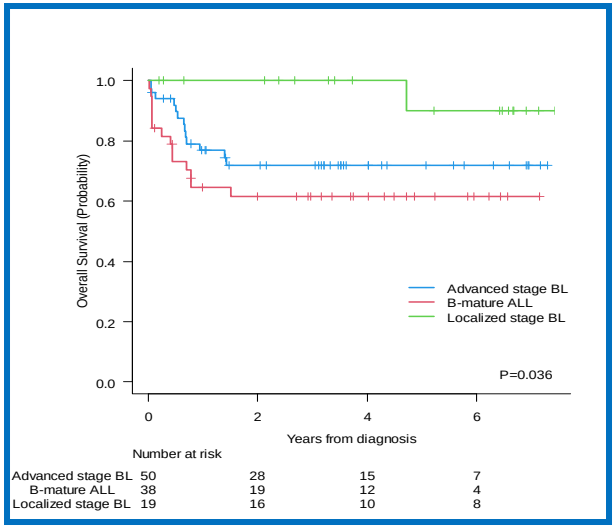
# Maintenance therapy in ALL

- **Definitively not needed**
  - **Mature B-ALL (Burkitt) under chemoimmunotherapy (dose-intensive or infusional)**
- **Under discussion**
  - Ph+ ALL after HSCT
  - Cortical T-ALL in CR1 (reduction of the duration)
  - Maintenance duration according to the ALL risk
  - Maintenance after alloHSCT
- **Future issue**
  - BCP-ALL with sustained deep MRD negativity achieved with chemoimmunotherapy (including CAR T)

# Dose-intensive chemoimmunotherapy in mature B-ALL: BURKIMAB-14 (PETHEMA + GELTAMO)




N: 107
Age (median): 51 yr (18–80)
Mature B-ALL: 38 pts (35%)
CR: 80%

Ribera JM, et al. *Haematologica*. 2023. doi: 10.3324/haematol.2023.283342.

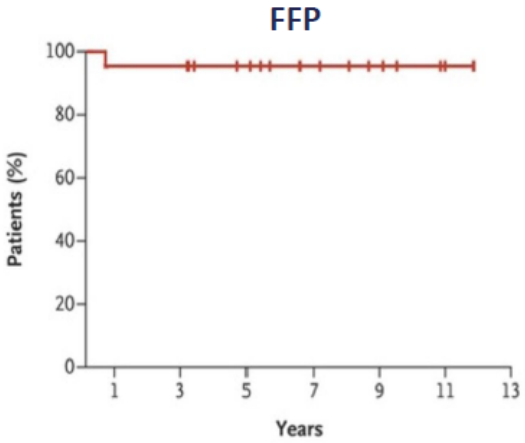
# Low-intensity therapy in BL

2013 → 2022

ALL included HIV positive BL

## Single-center

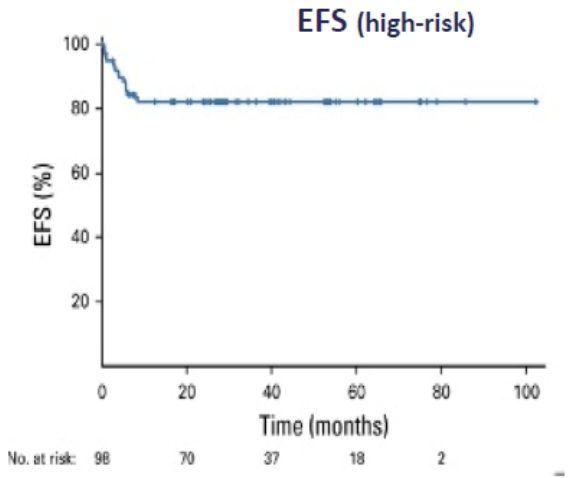
DA-EPOCH-R




*Dunleavy et al. NEJM 2013*

## Multi-center

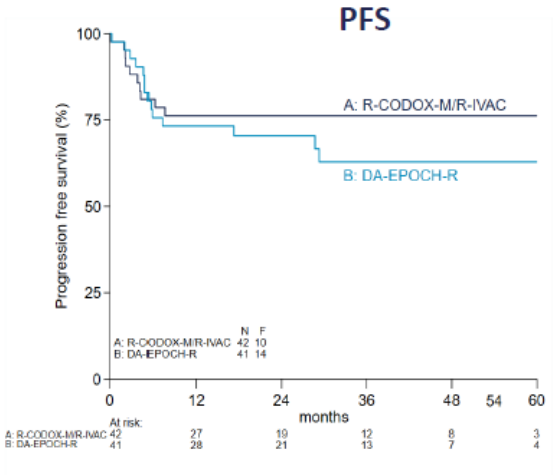
DA-EPOCH-R




*Roschewski, Dunleavy et al JCO 2020*

## Randomized

R-CODOX-M/IVAC vs DA-EPOCH-R




*Chumuleau et al. EHA 2022*

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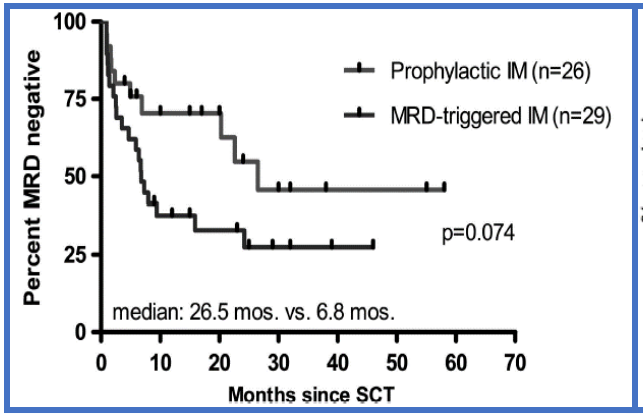
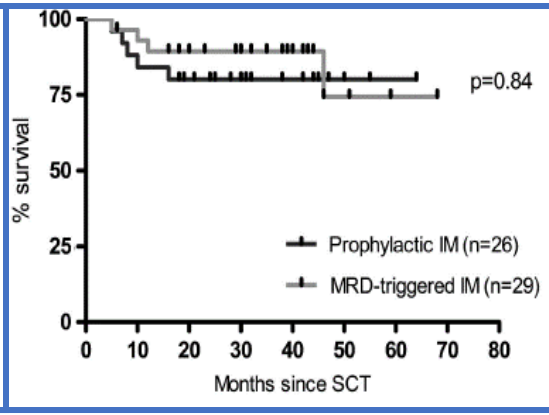
- **Future issue**
  - BCP-ALL with sustained deep MRD negativity achieved with chemoimmunotherapy (including CAR T)

# Prophylactic vs MRD-triggered imatinib after allogeneic HSCT

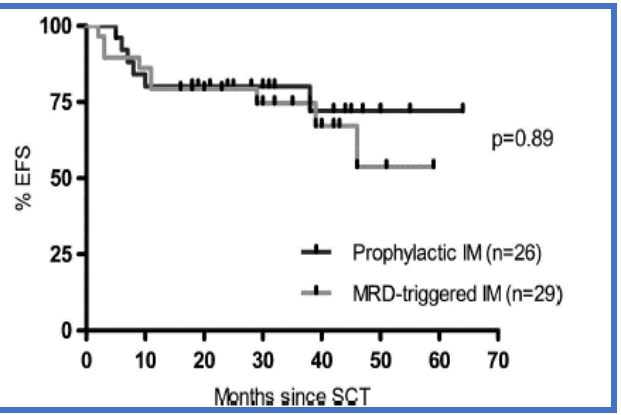
**Duration of Molecular Remission by Treatment Arm**




**Survival After HSCT by Treatment Cohort**

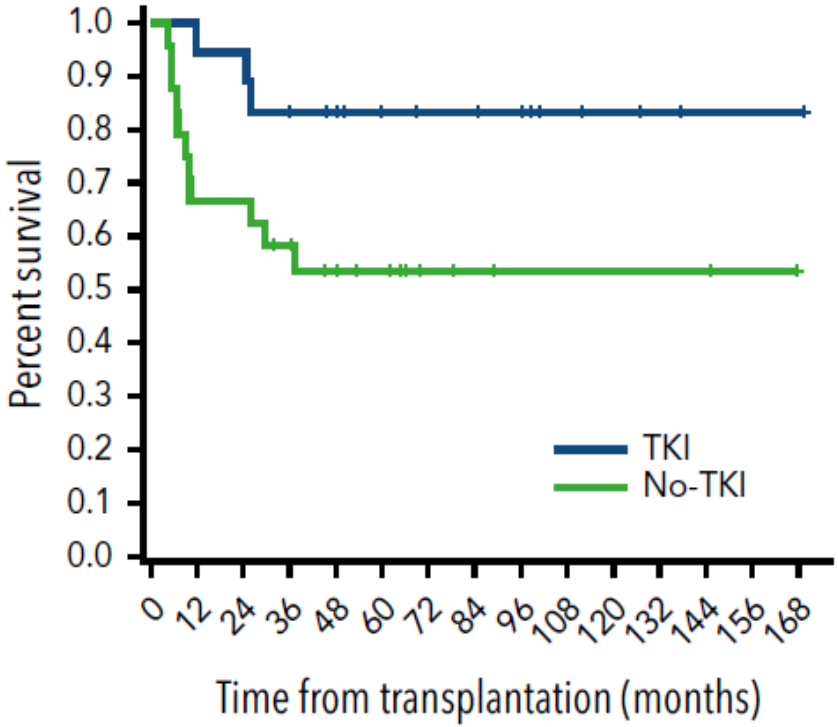


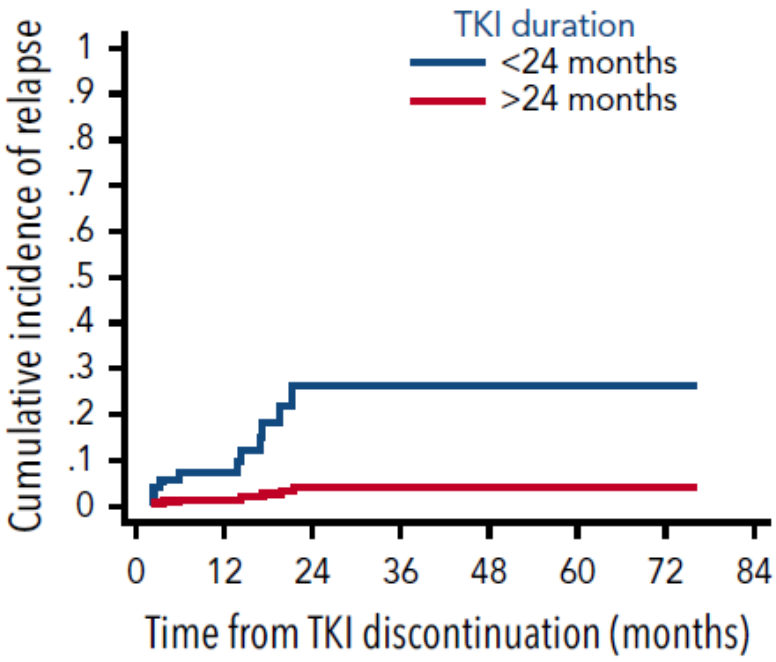

**EFS After HSCT by Treatment Cohort**




Pfeifer H, et al. *Leukemia*. 2013;27:1254-1262.

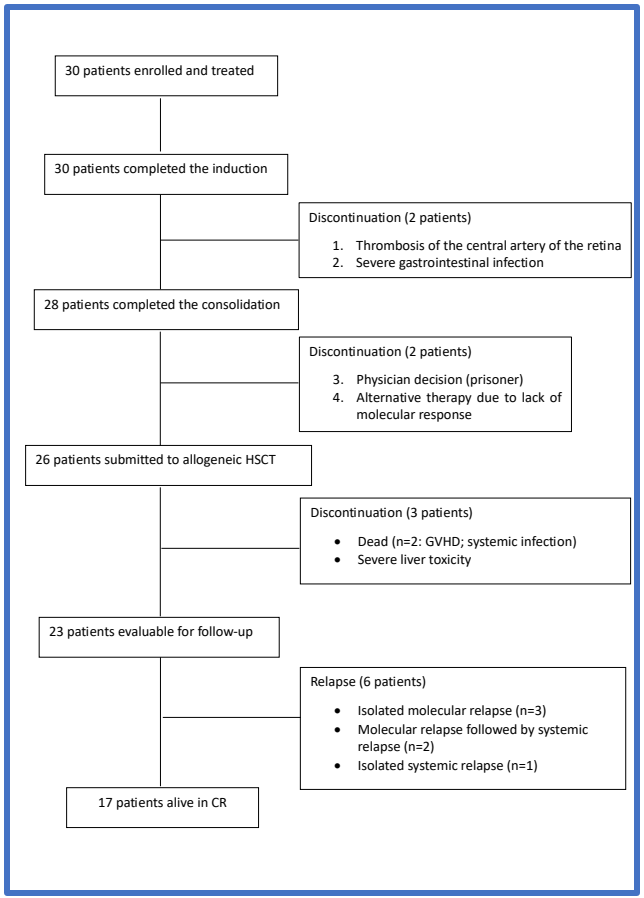
# Prophylactic TKI after alloHSCT: MDACC experience



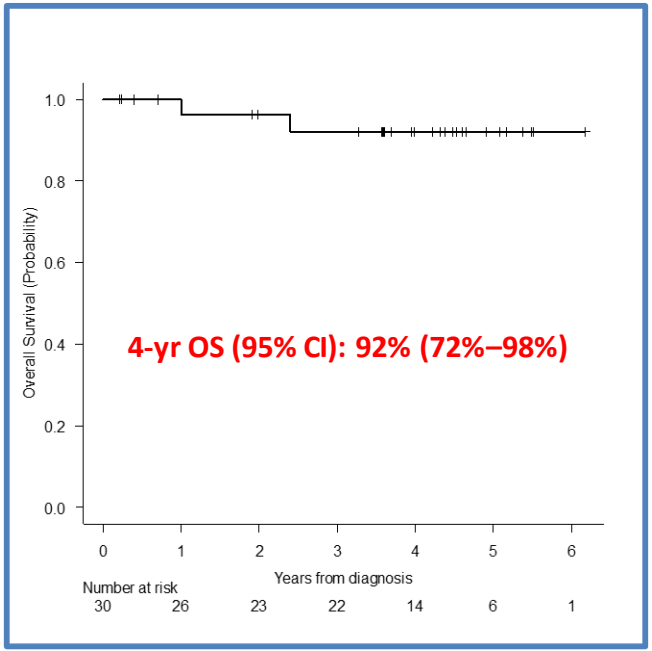




Saini N, et al. *Blood*. 2020;136:1786-1789.

# PONALFIL trial




**Median FU: 4 yr**




**Pre-emptive maintenance strategy allowed to avoid TKI after HSCT in 17/23 pts (74%)**

Ribera JM, et al. Manuscript in preparation.

# Maintenance TKI: EBMT and ASTCT recommendations

1. All Ph-positive ALL patients are candidates for post-transplant use of TKIs. Unclear for patients in CR1 at HSCT with CMR and use of TKI.
2. Patients with **undetectable MRD after HSCT may be treated prophylactically or as a pre-emptive strategy (if monitoring is possible).**
3. **MRD monitoring should start 4 weeks after HCST: monitoring BCR::ABL1 every 6–8 weeks in BM and every 3–4 weeks PB (first year).**
4. Patients with detectable MRD after HSCT should be started on TKI as soon as possible.
5. Imatinib at initial dose of 400 mg/d is the first choice of TKI (or the last TKI used).
6. Switching to a second-generation TKI is recommended if BCR::ABL1 transcript levels remain detectable after 6–8 weeks of post-transplant imatinib.
7. For patients transplanted in CR1, TKI treatment should be given for 12 months of continuous MRD negativity. For ≥CR2, treatment should be given indefinitely.

Giebel S, et al. *Cancer*. 2016;122:2941-2951; DeFilipp Z, et al. *Biol Blood Marrow Transplant*. 2019;25:2113-2123.

# Maintenance therapy in ALL

- **Definitively not needed**
  - Mature B-ALL (Burkitt) under chemoimmunotherapy (dose-intensive or infusional)
- **Under discussion**
  - Ph+ ALL after HSCT
  - **Standard-risk T-ALL in CR1 (reduction of the duration)**
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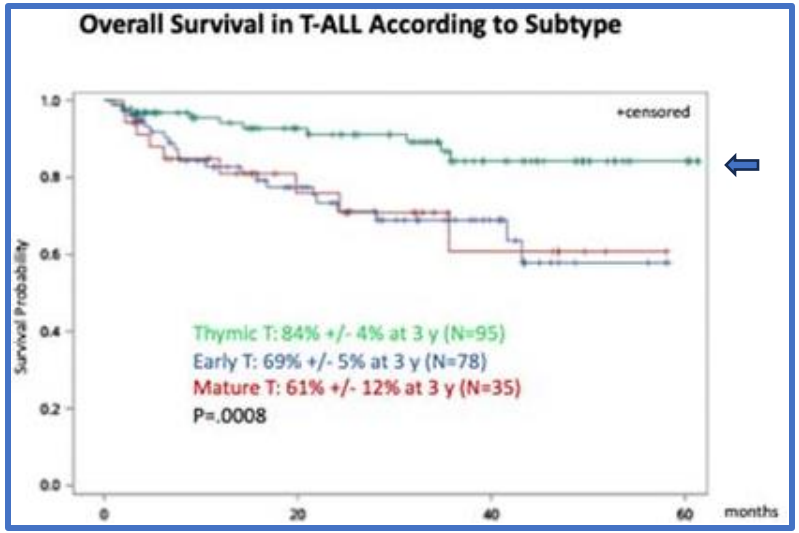
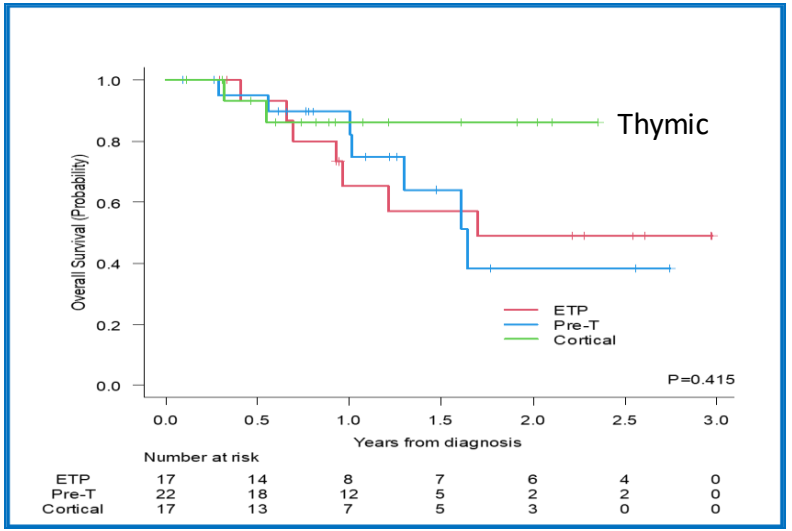
- **Future issue**
  - BCP-ALL with sustained deep MRD negativity achieved with chemoimmunotherapy (including CAR T)

# T-ALL: Standard-risk – room for shortening maintenance?

## GMALL Trial 08/2013




## PETHEMA ALL 19




Gökbuget N, et al. ASH 2021. Abstract 362. PETHEMA data on file.

# Maintenance therapy in ALL

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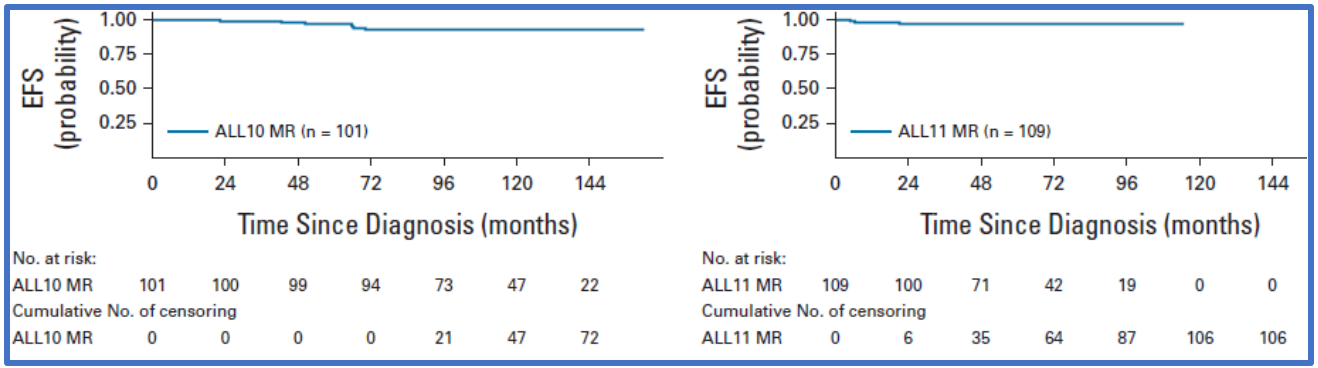
# Maintenance duration according to the ALL risk

**No data in adults. Learning from pediatricians . . .**

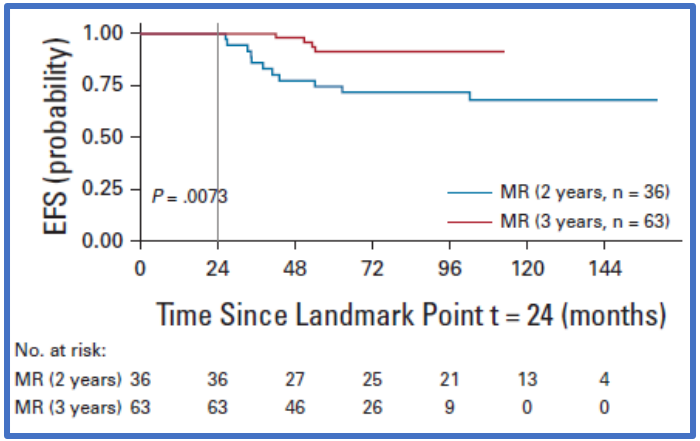
**DCOG**
**ALL10 vs ALL11**
***ETV6::RUNX1***

No maintenance reduction
CHT deintensification




**DCOG**
**ALL10 vs ALL11**
***IKZF1* del**

Increase of maintenance duration




Pieters R, et al. *J Clin Oncol*. 2023;41:4130-4142.

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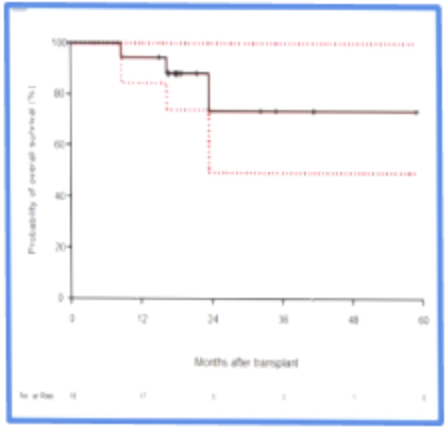
# Immunotherapy for relapse prevention after alloHSCT

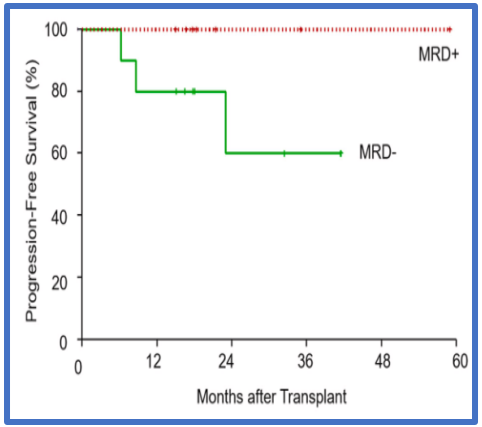
## Post-HSCT maintenance with InO in HR-ALL patients (phase I/II)

CD22+ ALL (n = 18) with HR of relapse after alloHSCT
- MRD+ before or after alloHCT
- HSCT in ≥CR2
- Nonmyeloablative conditioning

MTD: 0.6 mg/m$^2$ cycle (D1)

Thrombocytopenia and neutropenia (G3-4)

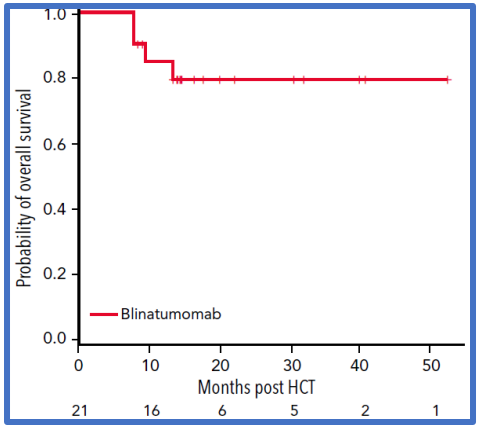


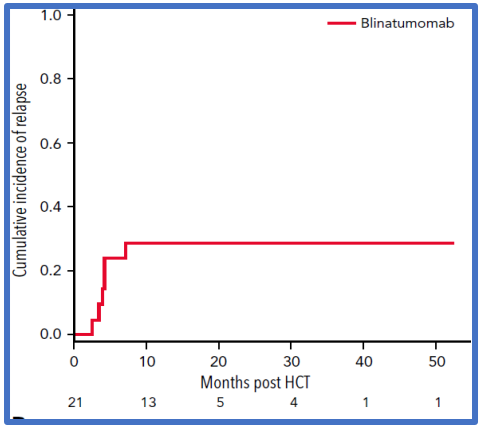



## Post-HSCT maintenance with blinatumomab in HR-ALL patients (phase II)

CD19+ ALL (n = 21) with HR of relapse after alloHSCT
- MRD+
- HSCT in ≥CR2
- HR cytogenetic/molecular profile
- Primary refractory

Blina: 28 µg/d CVI × 28 d, 1–4 cycles




Metheny et al. *Blood*. 2022;140 (suppl):3253-3255; Gaballa MR, et al. *Blood*. 2022;139:1908-1919.

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  - Standard-risk T-ALL in CR1 (reduction of the duration)
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- **Future issue**
  - **BCP-ALL with sustained deep MRD negativity achieved with chemoimmunotherapy (including CAR T)**

# Frontline blinatumomab and inotuzumab combinations in young adults with newly dx ALL

| | Agent | N | Median Age, yr (range) | CR, % | MRD Negativity, % | OS, % (x-yr) |
|---|---|---|---|---|---|---|
| HCVAD-blina | Blinatumomab | 38 | 37 (17–59) | 100 | 97 | 81 (3-yr) |
| HCVAD-blina-inotuzumab | Blinatumomab and inotuzumab | 25 | 24 (18–47) | 100 | 91 | 100 (1-yr) |
| GIMEMA LAL1913 | 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) |

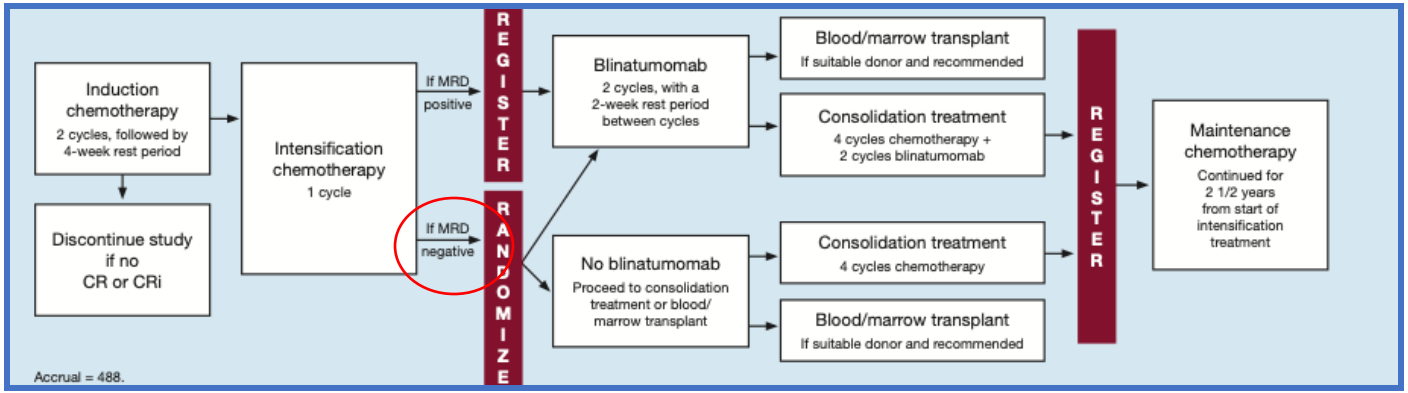
Short. *Blood.* 2021;138:1223; Bassan R, et al. EHA 2022. Abstract S113; Boissel N, et al. *Blood.* 2021;138(suppl 1):1232; Fleming S, et al. *Blood.* 2021;138(suppl 1):1234.

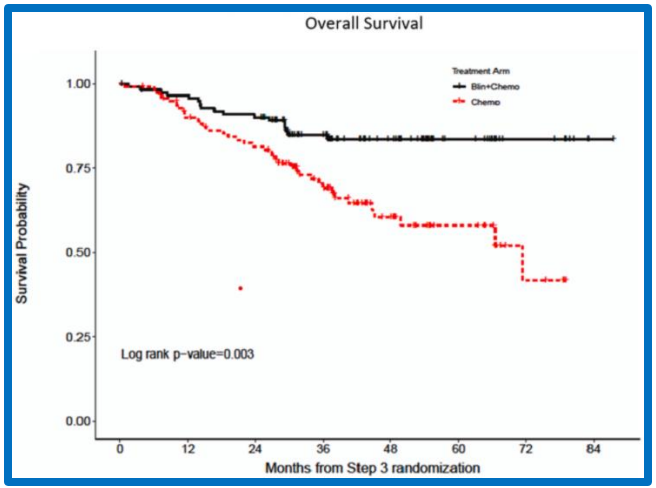
# Frontline blinatumomab and inotuzumab combinations in older adults with newly dx ALL

| | 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;40:1574-1582; Chevallier P, et al. *Blood*. 2021;138(suppl 1):511; Goekbuget N, et al. *Blood*. 2021;138(suppl 1):3399; Stelljes M, et al. *Blood*. 2021;138(suppl 1):2300.

# ECOG 1910: Blinatumomab consolidation for MRD-negative B-ALL




N = 488 enrolled in Step 1
N = 224 randomized 1:1 in Step 2 (negative MRD)

Addition of blinatumomab significantly improved OS (HR 0.42, 95% CI: 0.24-0.75; *P* = .003)
**Effect particularly evident in pts <55 yr and undetectable MRD**

Litzow M, et al. ASH 2022. Abstract LBA1; Litzow M, et al. EHA 2023. Abstract S115.

# Two important unsolved questions

**Will the deep MRD clearance achieved with chemoimmunotherapy in CR1 allow to reduce the duration of maintenance therapy?**

**Will CAR T in early phases be a definitive therapy without further maintenance?**


Thank you
jribera@iconcologia.net

Global Leukemia Academy

# Q&A

APTITUDE HEALTH

Global Leukemia Academy

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

ALL – Nicola Gökbuget

AML – Stephane De Botton

Moderator: Naval Daver

APTITUDE HEALTH

# ALL: Regional Issues

- Need for advanced molecular testing and clinical relevance of molecular entities
- Lack of randomized trial for 1st line immunotherapies
- Redefine role of stem cell transplantation
- Role and position of CAR T-cell therapies
- Need for trials evaluating treatment reductions
- Any role for ‘precision medicine’ in ALL
- Marketing authorization and reimbursement for new compounds
- Complexity of IITs in rare entities
- Buerocratic burden and staff shortages

# AML regional issues

- Can there be a homogeneous group of patients when 2 AML International Consensus Classifications exist in 2023?
- Is incorporation of myelodysplasia-related gene mutations interesting in practice?
- Shall we transplant intermediate-risk group in CR1?
- Shall we transplant *FLT3*-ITD with low AR in CR 1 with the use of FLT3-ITD inhibitors?

Global Leukemia Academy

# 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 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

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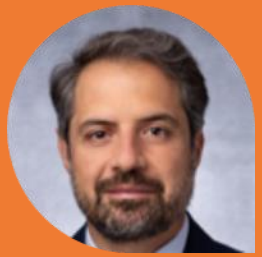
# Session close

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 (CET) | Title | Speaker |
|---|---|---|
| 18.00 – 18.10 | Welcome to Day 2 | Naval Daver |
| 18.10 – 18.25 | Frontline approaches and the role of genetic variants in ALL – Ph+ and Ph-like | Elias Jabbour |
| 18.25 – 18.45 | Current treatment options for relapsed ALL in adult and elderly patients | Josep-Maria Ribera |
| 18.45 – 19.05 | Current treatment options for relapsed AML in adult and elderly patients | Charles Craddock |
| 19.05 – 19.35 | AML case-based panel discussion<br>• Case AML: young, high risk – Vitor Botafogo<br>• Case AML: elderly – Justin Loke<br>• Discussion – panelists: all faculty | Naval Daver and all faculty |
| 19.35 – 19.45 | Break | |
| 19.45 – 20.05 | Long-term safety considerations for AML and ALL | Stephane De Botton |
| 20.05 – 20.35 | Current and future role of transplantation in acute leukemias (including regional insights)<br>• AML – Charles Craddock<br>• ALL – Nicola Gökbuget<br>• Discussion | Charles Craddock and Nicola Gökbuget |
| 20.35 – 21.05 | Panel discussion: How treatment in first line influences further treatment approaches in ALL and AML<br>• Will CAR T and bispecifics change the landscape?<br>• Role of HSCT – is it still confirmed?<br>• What does the future look like? | Elias Jabbour and all faculty |
| 21.05 – 21.15 | Session close | Elias Jabbour and Naval Daver |

Global Leukemia Academy

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16–17 November 2023 – Europe

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