Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

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

October 19–20, 2023 – Latin America

Meeting sponsors AMGEN astellas

APTITUDE HEALTH

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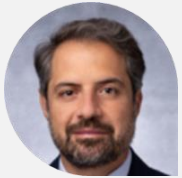
Welcome and meeting overview

Naval Daver

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

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

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

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

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

Objectives of the program

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

Day 2: Virtual Plenary Sessions

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

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

Question 1

What age group is considered elderly for AML patients?

A. ≥50 years

B. ≥55 years

C. ≥60 years

D. ≥65 years

E. ≥70 years

Question 2

How do you assess for minimal residual disease (MRD) for ALL?

A. Multicolor flow

B. Molecular PCR

C. Next-generation sequencing platform

D. We do not check for MRD

Question 3

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. CAR T approaches are active beyond second line in Ph– ALL

Question 4

The prognosis of R/R AML patients depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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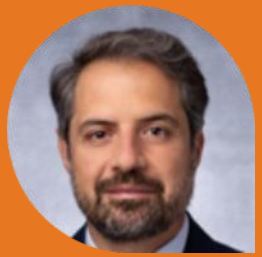
Current treatment options for relapsed ALL in adult and elderly patients

Elias Jabbour



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Adults With Acute Lymphocytic Leukemia in 2023: R/R ALL Management

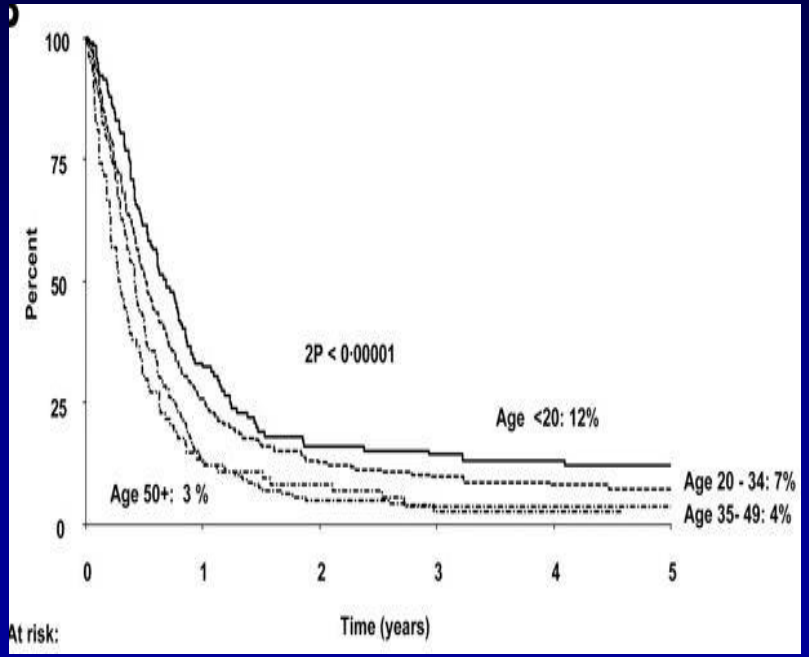
Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center,
Houston, TX

9-2023

ALL – Historical Survival Rates After First Relapse

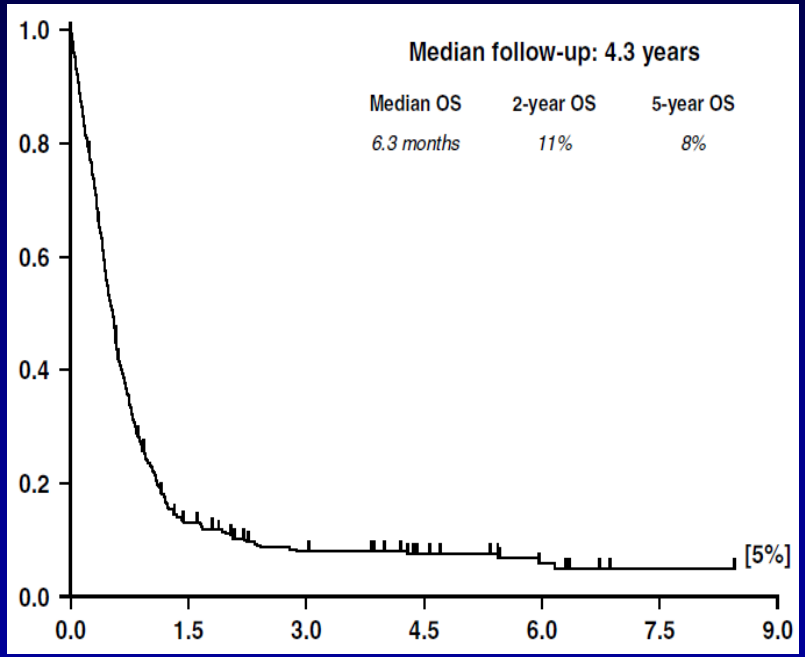
MRC UKALL2/ ECOG2993 Study (n = 609)

Outcome of patients after 1st relapse
5-yr OS: 7%



LALA-94 Study (n = 421)

Outcome of patients after 1st relapse
2-yr OS: 11% and 5-yr OS: 8%

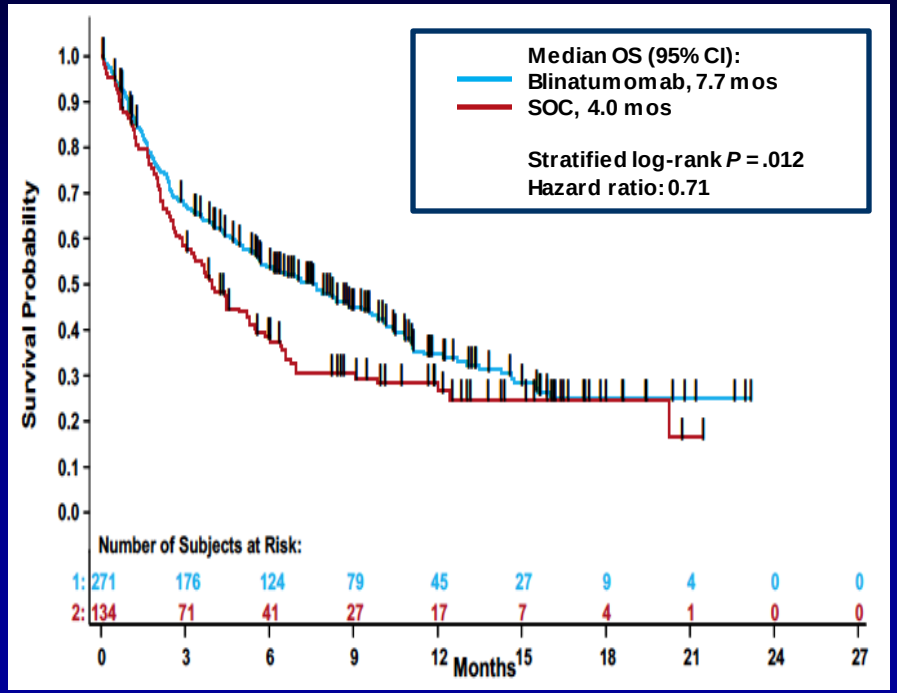


Fielding et al. *Blood*. 2007;109:944-950; Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

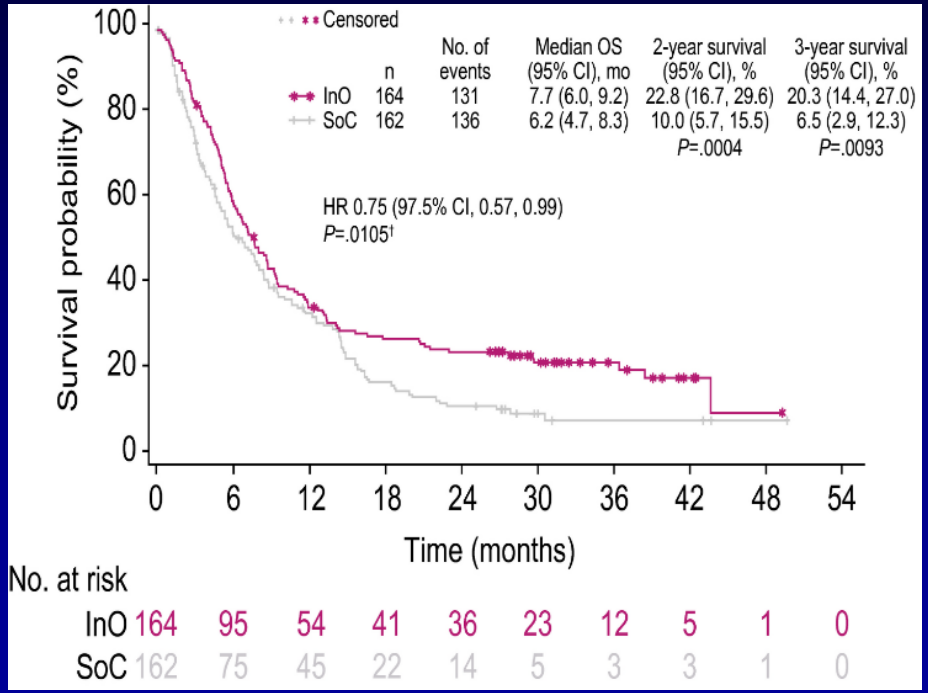
- **Marrow CR**

Blina vs SOC: 44% vs 25%



Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Ino vs SOC: 74% vs 31%

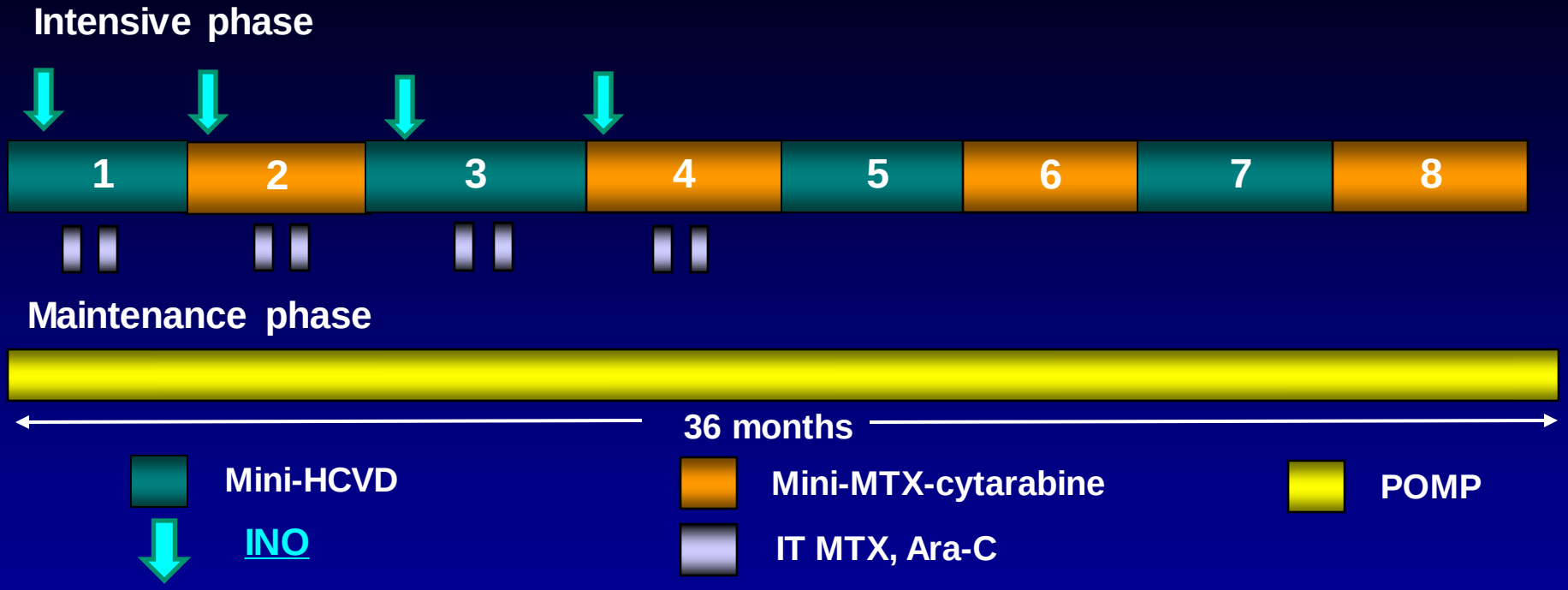


Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

Mini-HCVD + INO ± Blina in R/R B-ALL: Original Design

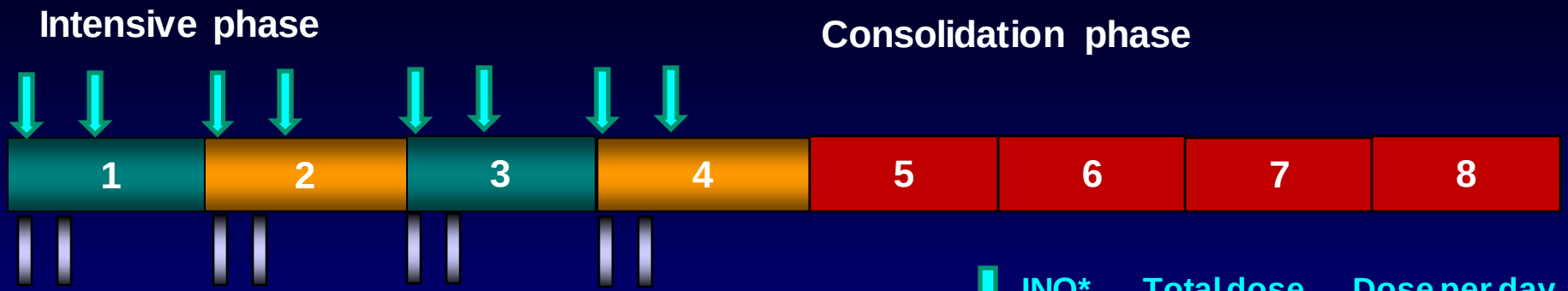
- Dose-reduced, modified hyper-CVAD × 8 courses
  - Cyclophosphamide (150 mg/m^2 × 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 × 4) 83% dose reduction
- INO on day 3 (first 4 courses)
- Rituximab days 2 and 8 (first 4 courses) if CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- POMP maintenance × 3 years

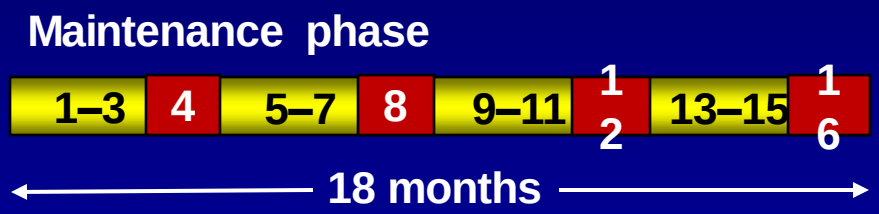
Mini-HCVD + INO ± Blina in R/R B-ALL: Original Design (Pts #1–67)



INO	First 6 pts	7 to 34	35+
C1 (mg/m^2)	1.3	1.8	1.3
C2-4 (mg/m^2)	0.8	1.3	1.0

Mini-HCVD + INO ± Blina in R/R B-ALL: Modified Design (Pts #68–110)





INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

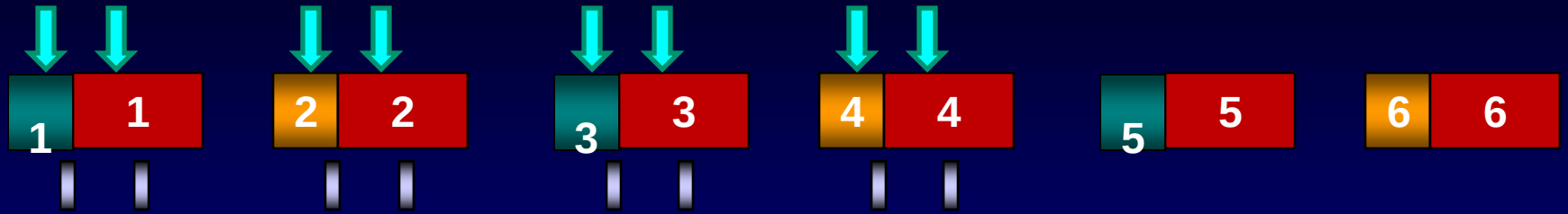
Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for VOD prophylaxis

Mini-HCVD
Mini-MTX-Ara-C
Blinatumomab
IT MTX, Ara-C
POMP

Short N, et al. HemaSphere. 2023;7:abstract S119.

Mini-HCVD + INO ± Blina in R/R B-ALL: "Dose-Dense" Design (Pts #111–125+)



3 days | 18 days | 7 days

Maintenance phase

18 months

INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for VOD prophylaxis

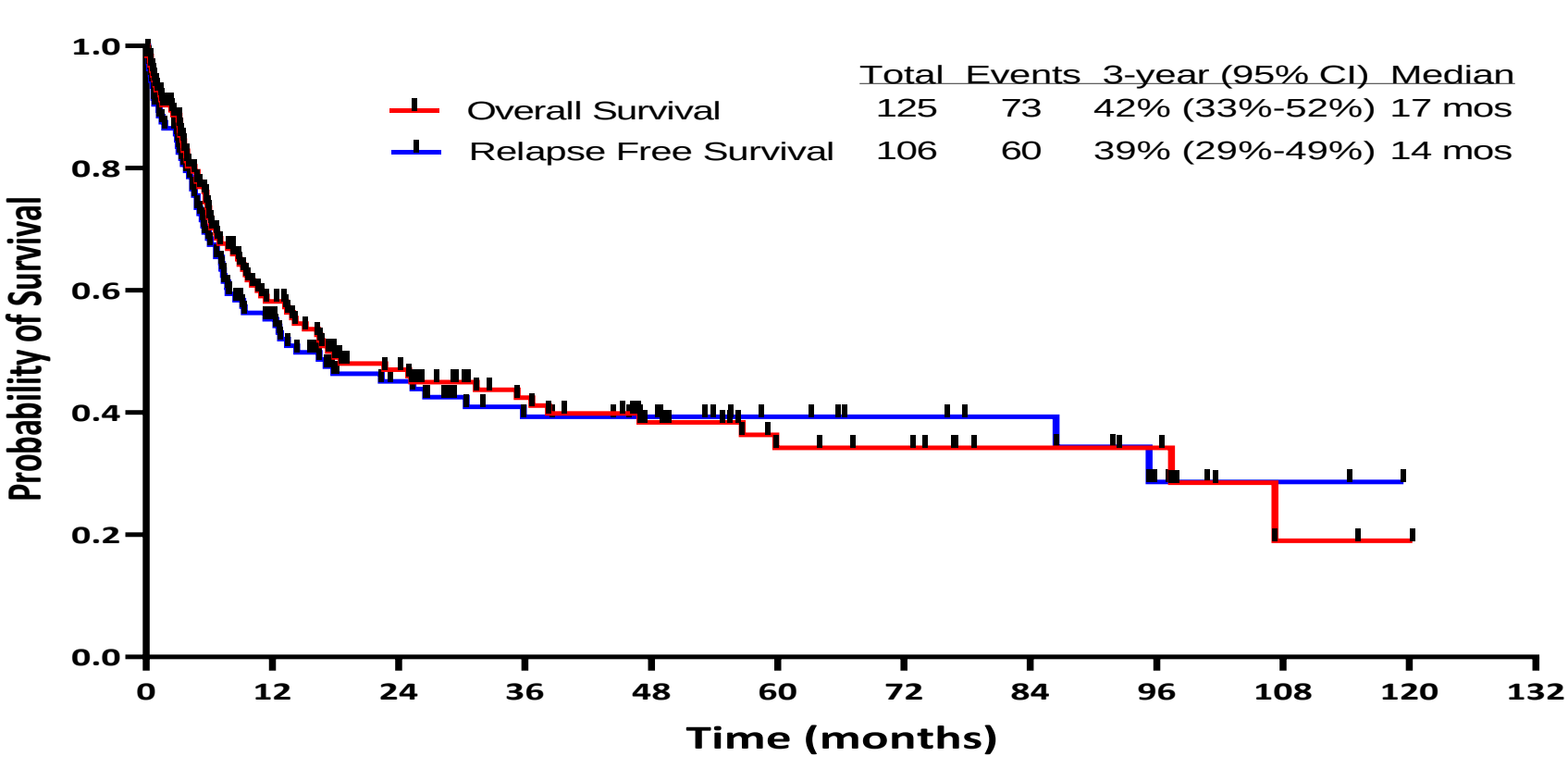
Mini-HCVD
Mini-MTX-Ara-C
Blinatumomab
IT MTX, Ara-C
POMP

Short N, et al. HemaSphere. 2023;7:abstract S119.

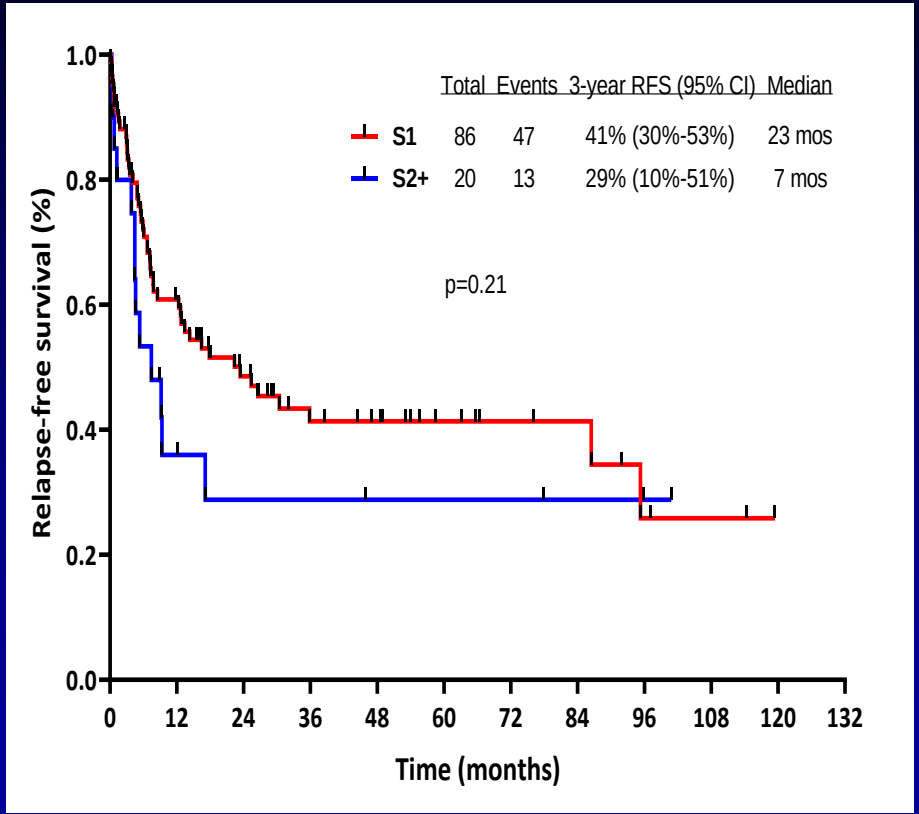
Mini-HCVD + INO ± Blina in R/R B-ALL: MRD Negativity Rates

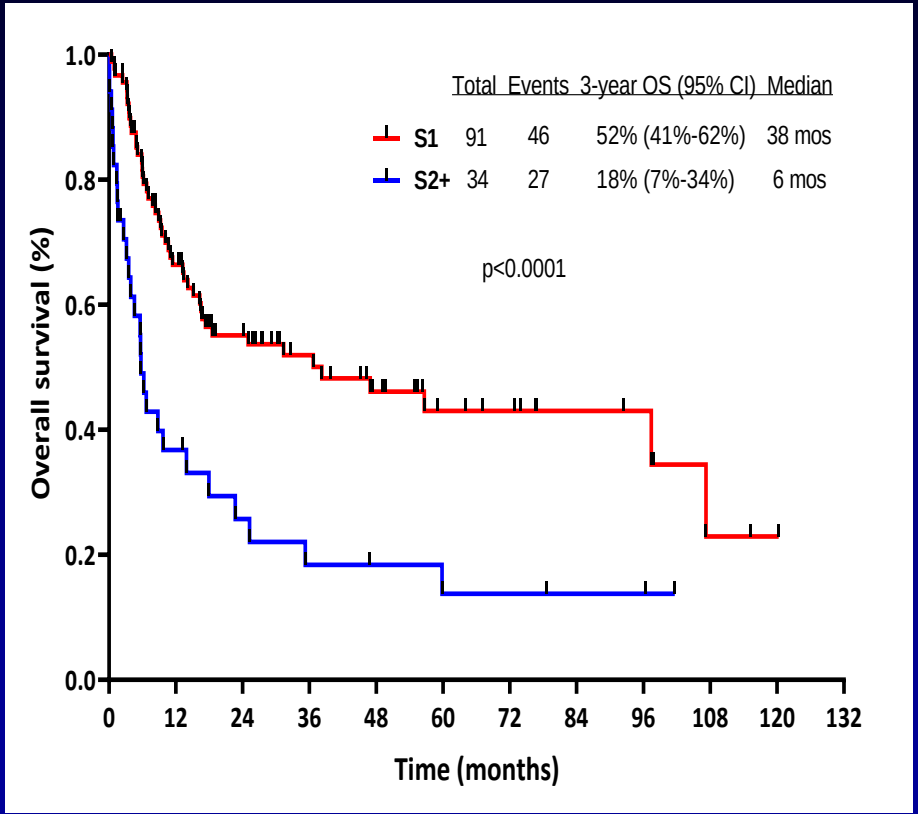
MRD Negativity by Flow Cytometry	N (%)			
	Overall (N = 125)	Before Blinatumomab (n = 67)	After Blinatumomab (n = 43)	Dose Dense (n = 15)
All patients				
End of cycle 1	53/100 (53)	25/49 (51)	18/38 (47)	10/13 (77)
Overall	87/102 (85)	41/50 (82)	34/39 (87)	12/13 (92)
Salvage 1				
End of cycle 1	45/82 (55)	22/34 (65)	17/37 (46)	8/11 (73)
Overall	73/83 (88)	31/35 (89)	32/37 (86)	10/11 (91)
Salvage 2+				
End of cycle 1	6/18 (33)	3/15 (20)	1/1 (100)	2/2 (100)
Overall	14/19 (74)	10/15 (67)	2/2 (100)	2/2 (100)

Mini-HCVD + INO ± Blina in R/R B-ALL: RFS and OS (Entire Cohort)

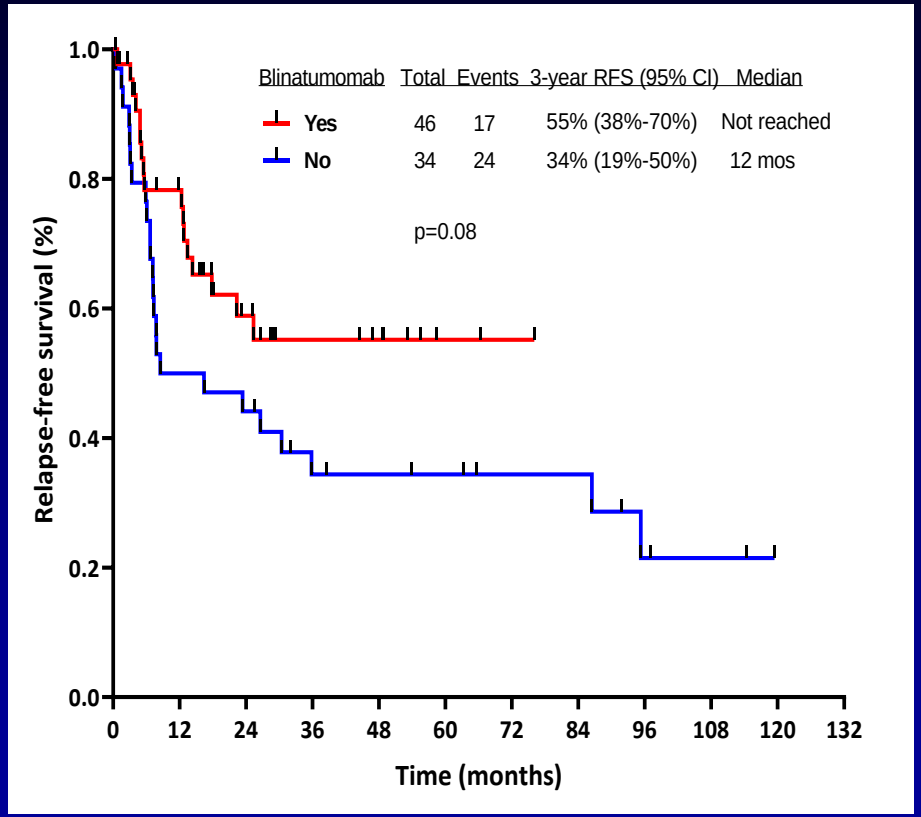


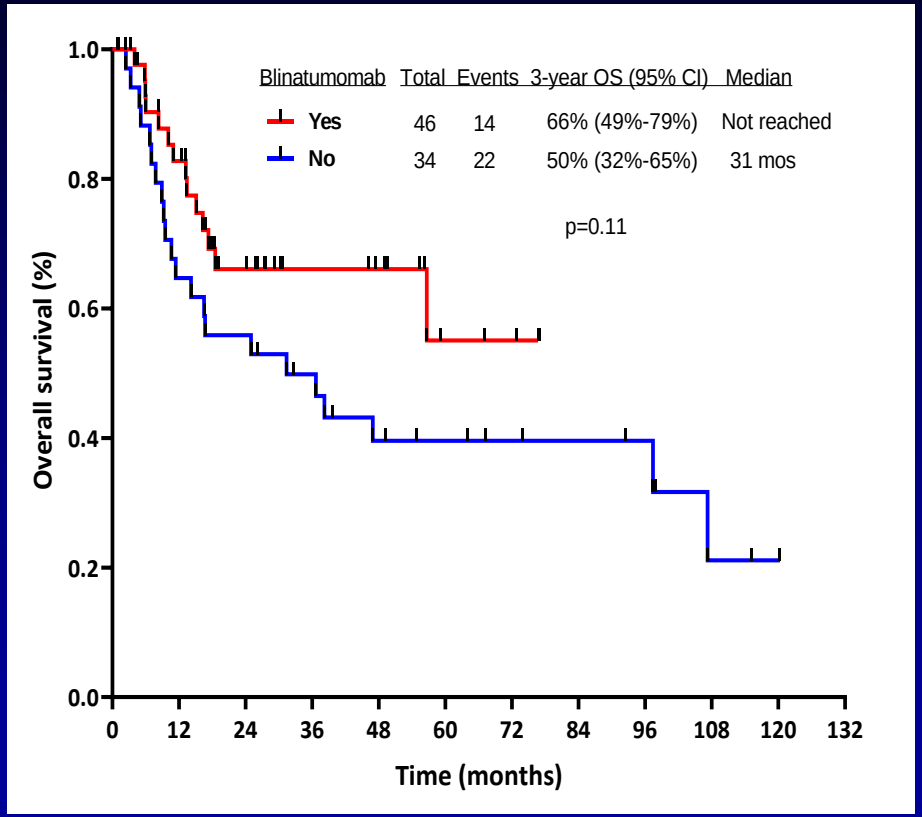
Mini-HCVD + INO ± Blina in R/R B-ALL: RFS and OS by Line of Salvage



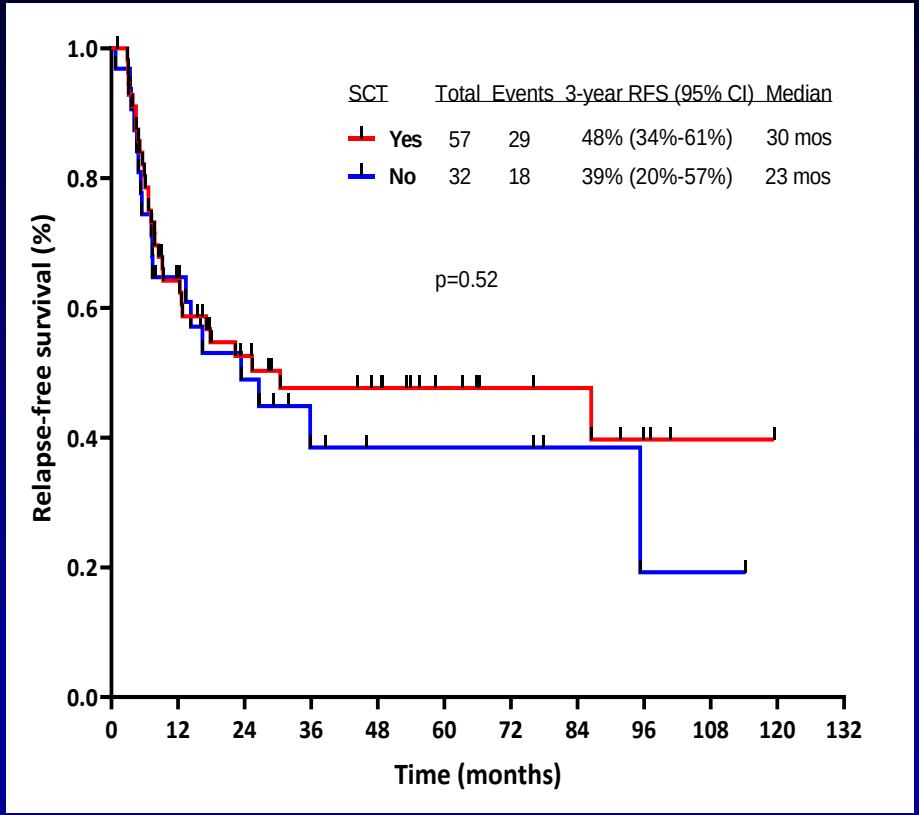


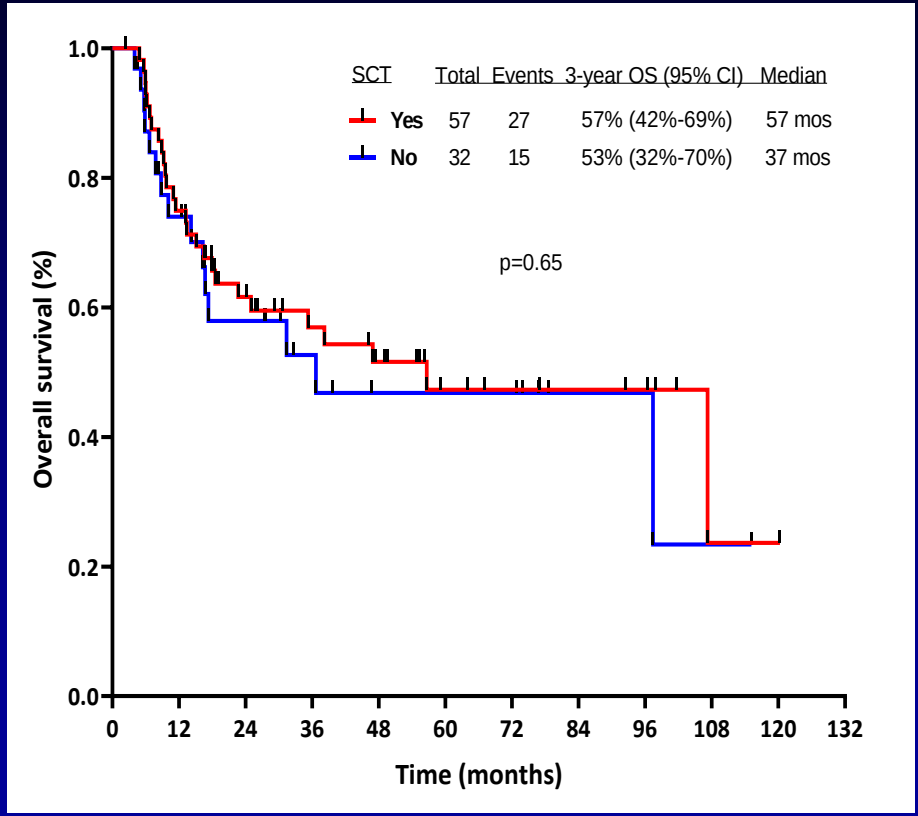
Mini-HCVD + INO ± Blina in R/R B-ALL: OS and RFS by Receipt of Blinatumomab (Salvage 1 Only)





Mini-HCVD + INO ± Blina in R/R B-ALL: OS and RFS by HSCT (Landmark Analysis)



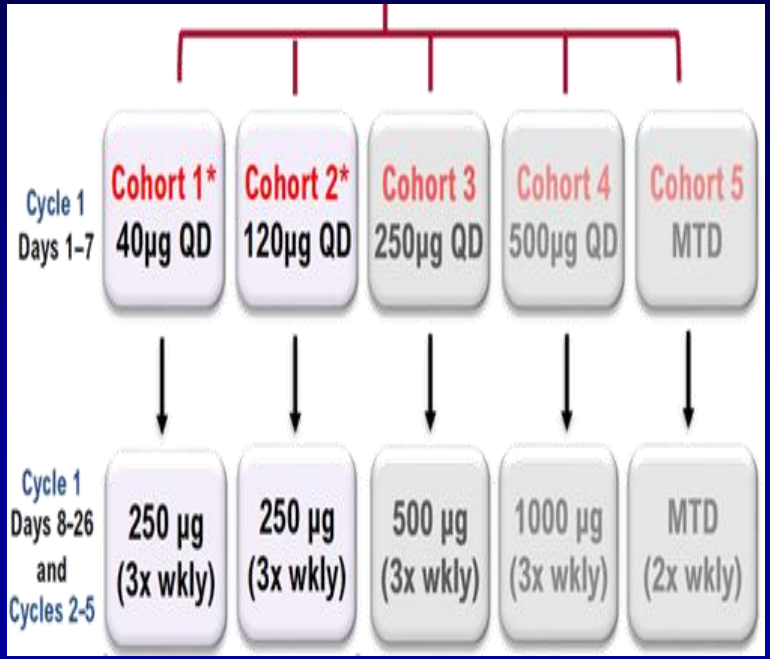


Subcutaneous Blinatumomab in R/R ALL

- 20 R/R pts, median age 58 yr (19–83)
- Median prior Rx = 2 (2–4)
- BLINA 40, 120, 250, 500 µg SQ daily × 7, then 250 µg TIW in cohorts 1 and 2, 500 µg in cohort 3, and 1000 mg in cohort 4
- 9/14 MRD-negative remission

Cohort	Marrow CR
1	3/6
2	2/3
3	4/5
4	5/7

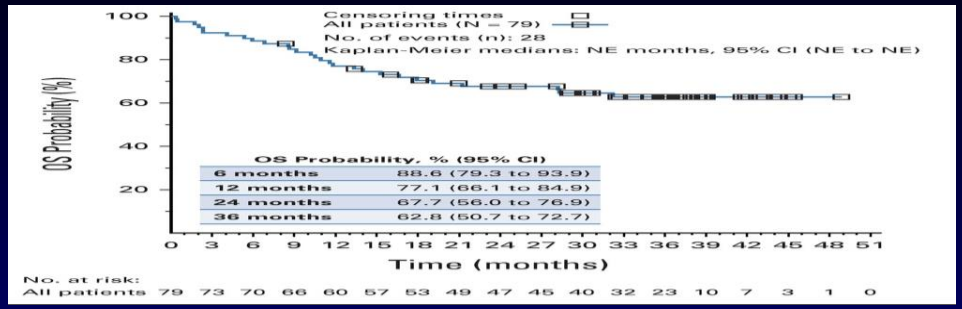
- No DLT; CNS toxicity G3: 4 (20%); CRS G3: 2 (10%)
- PK exposures similar to IV
- Possible phase II dose 250–500 µg

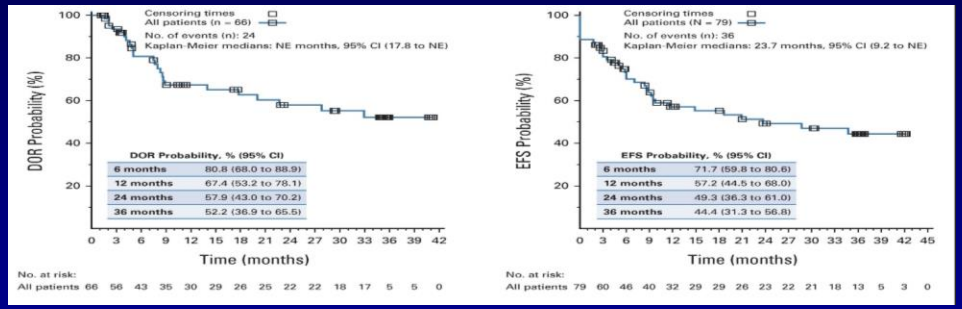


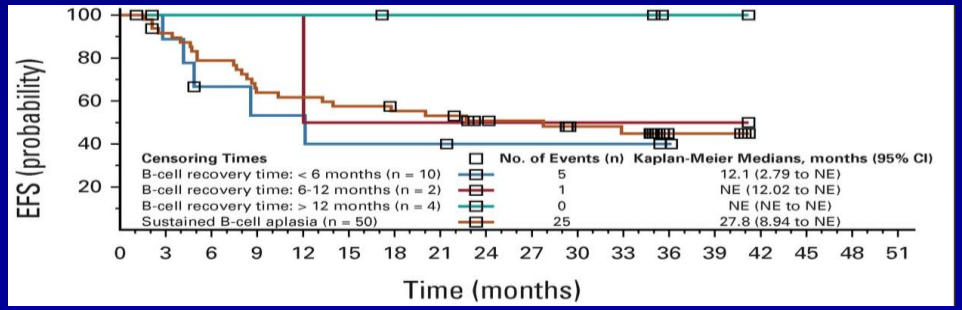
Martinez-Sanchez J, et al. *Blood*. 2022;140(suppl 1)6122-6124. Abstract 2727.

3-Year Update of Tisagenlecleucel in R/R ALL

- 97 pts ≤26 yrs enrolled;
  - 79 (81%) received tisa
- Median age 11 yrs (3–24)
- Median prior Rx 3 (1–8)
- Marrow CR 66 = 82%
  - 66% of denominator
- Median F/U 38.8 mos
- 5-yr RFS 49% in pts in CR/CRi
- 3-yr EFS 44%; 3-yr OS 63%
- G3/4 AE 29%



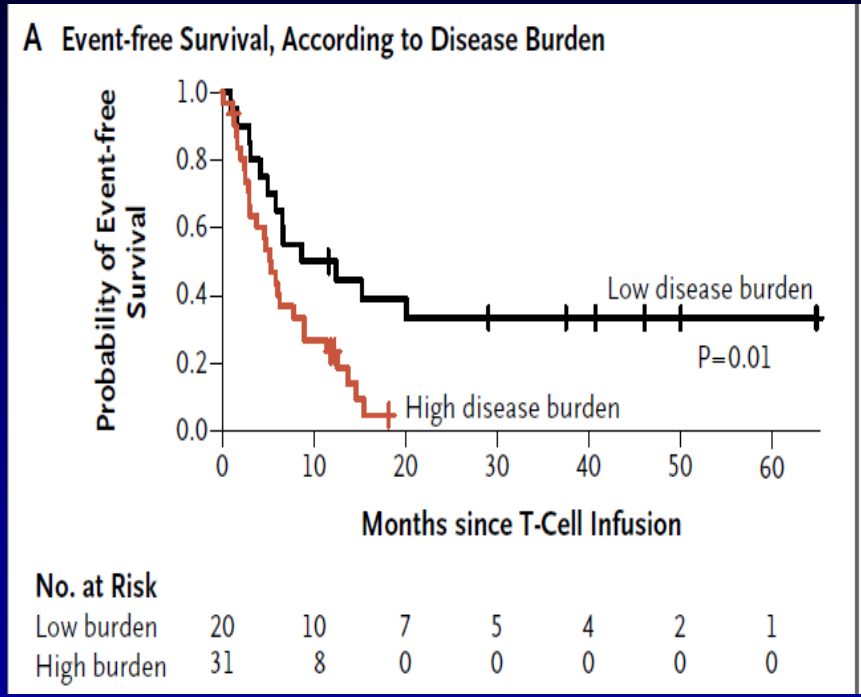


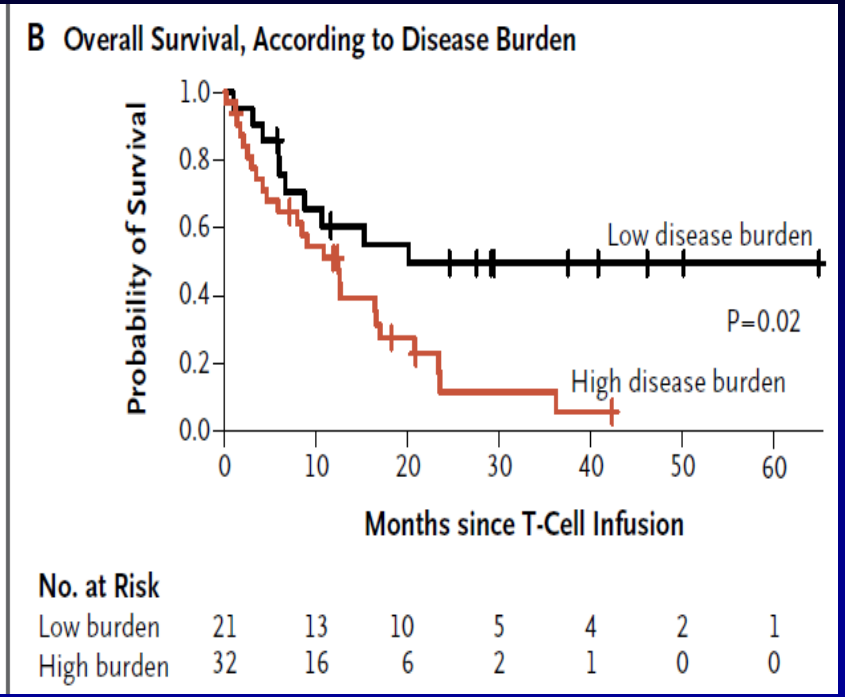


Laetsch et al. *J Clin Oncol.* 2023;41(9):1664-1669.

CD19-CD28z CAR (MSKCC): Responses by Tumor Burden

- High tumor burden: BM blasts ≥5% (n = 27); BM blasts <5% + EM disease (n = 5)
- Low tumor burden (MRD+ disease) (n = 21)





Median EFS
Low tumor burden: 10.6 mos
High tumor burden: 5.3 mos

Median OS
Low tumor burden: 20.1 mos
High tumor burden: 12.4 mos

Park et al. *N Engl J Med.* 2018;378:449.

CAR T (Kite) in ALL

- 55 pts Rx in phase II
- CR 56%; CRi 15%; CR + CRi 71%
- Median RFS 11.6 mo; 18-mo RFS 35%
- Median OS 25.4 mo
- Phase I–II = 78 pts

Parameter	24-mo OS, %
Age 18–39	48
40–59	54
≥60	57
BM blasts, % 25–50	58
51–75	55
>75	37

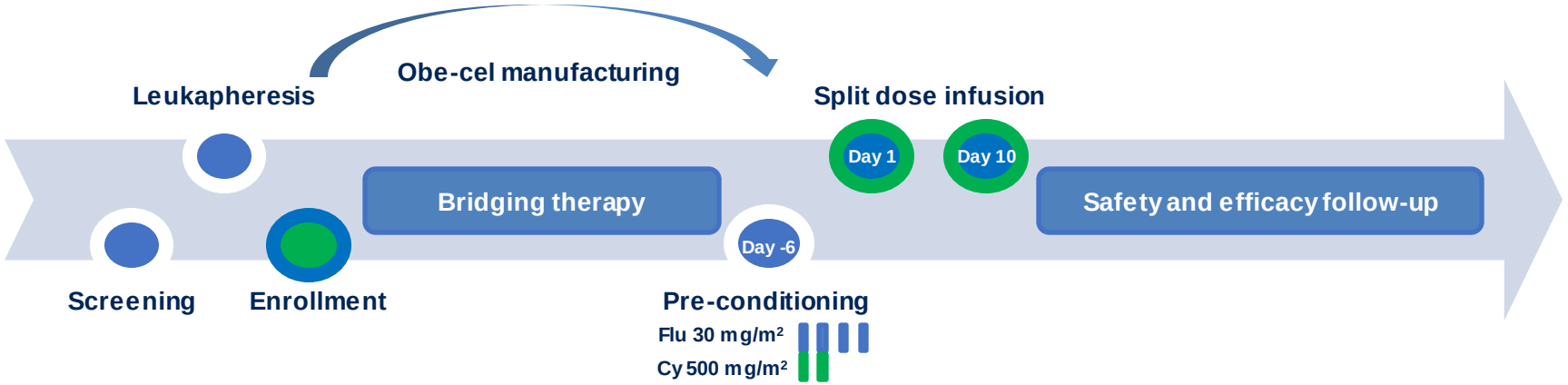
Shah BD, et al. *J Clin Oncol*. 2022;40(suppl 16): abstract 7010.

Obe-Cel – Fast-Off CD19 CAR T in R/R ALL: FELIX

- 112 pts enrolled, 94 infused
  - BM ≤20%: 100 × 10^6 CAR T cells on D1 and 310 × 10^6 CAR T cells on D10
  - BM >20%: 10 × 10^6 CAR T cells on D1 and 400 × 10^6 CAR T cells on D10
    31% S3+
- ORR = 76% (CR = 54%); ITT = 63% (CR = 46%)
- MRD negativity 97%; DOR 14.1 mos
- G3 CRS 3.2% and ICAN 7.4%

Roddie C, et al. *HemaSphere.* 2023;7:abstract S262.

FELIX Study: Obe-Cel for Adults With R/R CD19+ B-ALL



Pre-conditioning

Tumor burden-adjusted split dosing to maximize the therapeutic index

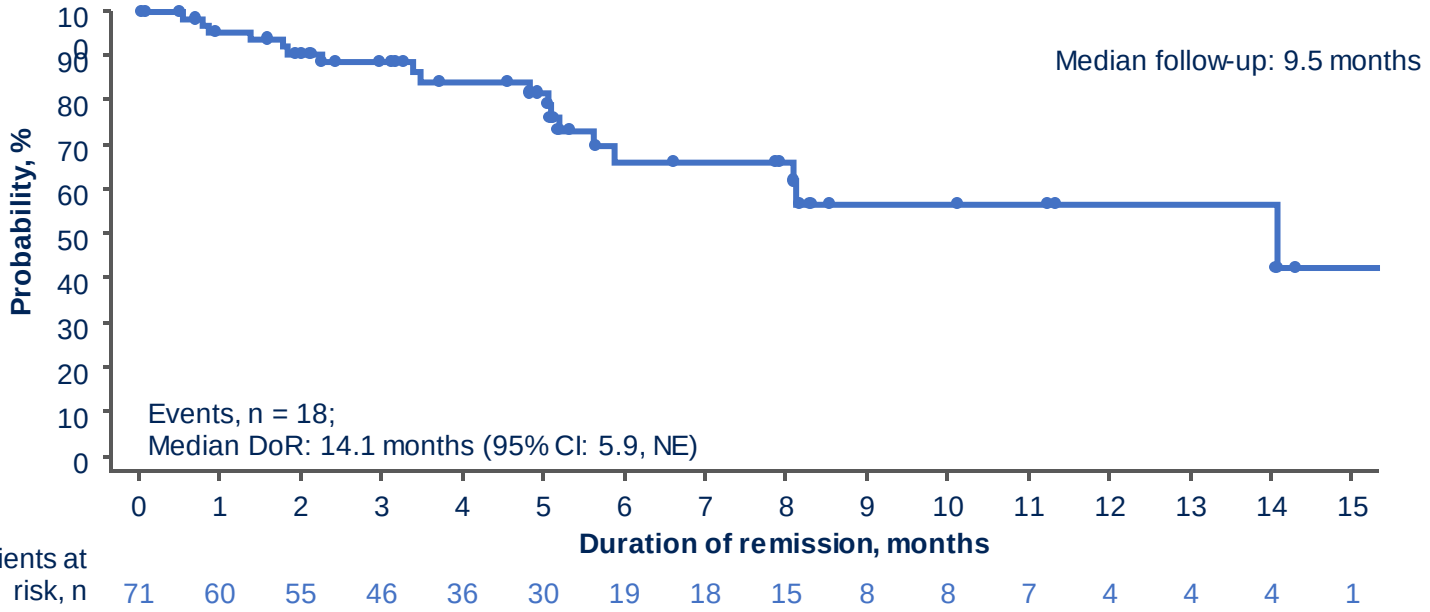
Pre-conditioning	Dose 1		Dose 2
BM blasts ≤20%	100 × 10^6 CAR T cells	CRS Grade <2 No ICANS	310 × 10^6 CAR T cells
BM blasts >20%	10 × 10^6 CAR T cells		400 × 10^6 CAR T cells

94% of infused patients received both obe-cel infusions

CRS, cytokine release syndrome; cy, cyclophosphamide; flu, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome.

FELIX: Duration of Remission

61% responders in ongoing remission without new anticancer therapies

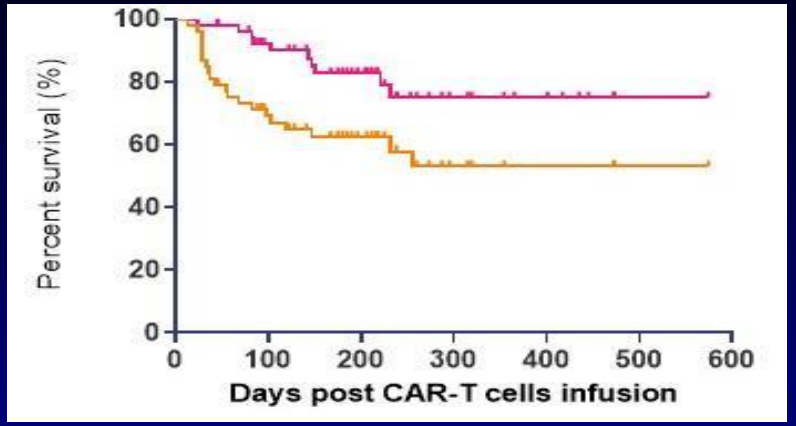


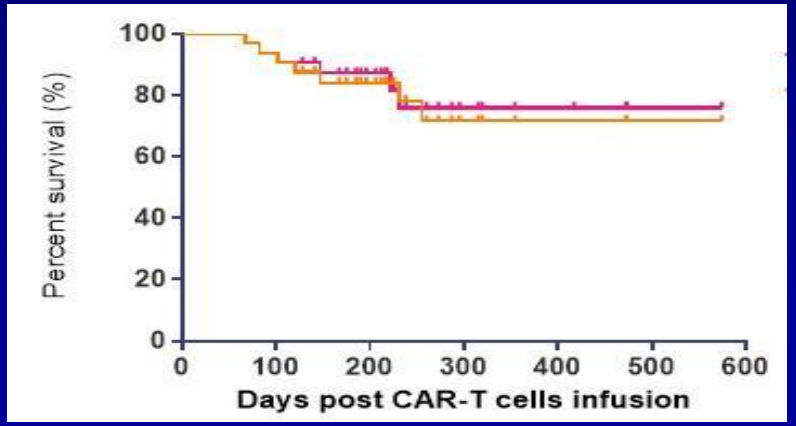
13% responders who proceeded to SCT while in remission were censored at the time of SCT

NE, not estimable.

R/R T-ALL and T-LBL Rx With CD7-Targeted CAR T Cell

- Novel fratricide-resistant approach to derive naturally selected 7 CAR T cells (NS7CAR) from bulk T cells without additional genetic selection
- 52 pts with R/R T-ALL (n = 34) and T-LBL (n = 18); median age 22 yr (2–47)
- Median prior lines of Rx 5 (2–15)
- Median FU 206 days
- MRD-negative CR 96%
- 5 pts G3 CRS, and 1 had G4 CRS
- 18-mo OS 75%; EFS 53%
- 32 pts (61%) had allo SCT; 18-mo OS 76% and EFS 71.5%

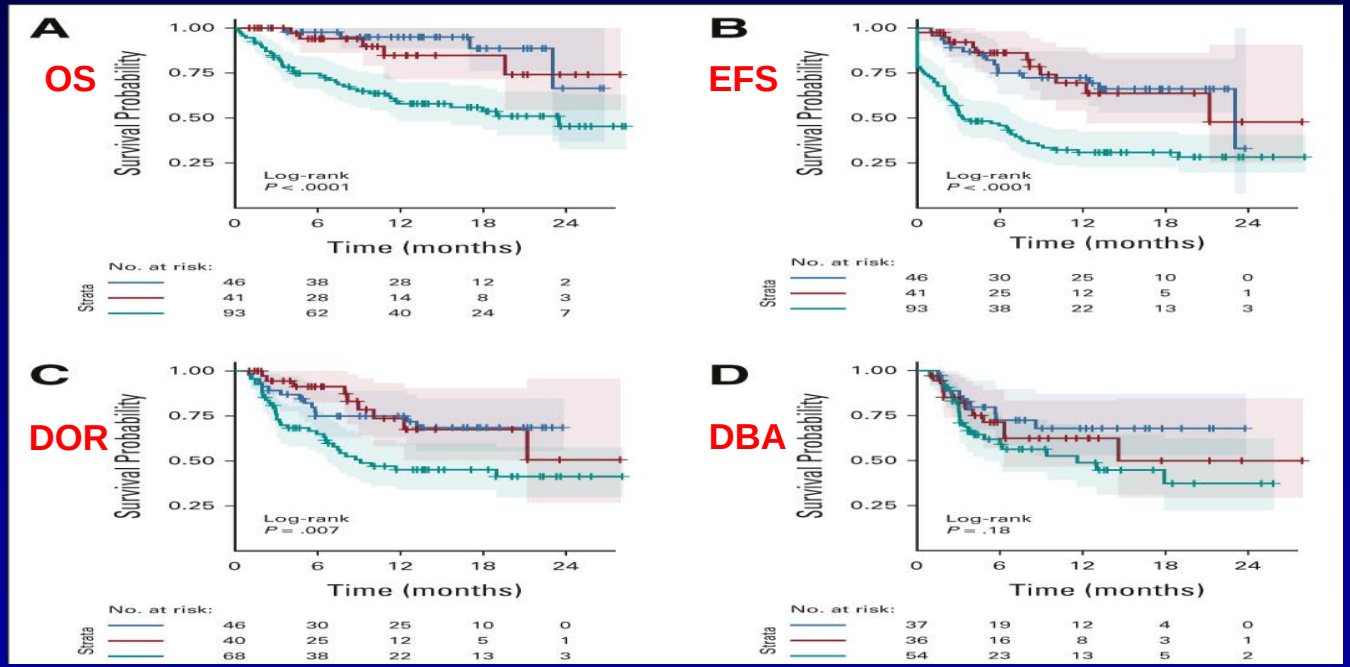




Zhang X, et al. *Blood*. 2022;140(suppl 1):2369-2370. Abstract 980.

Real-World CAR Consortium and Disease Burden

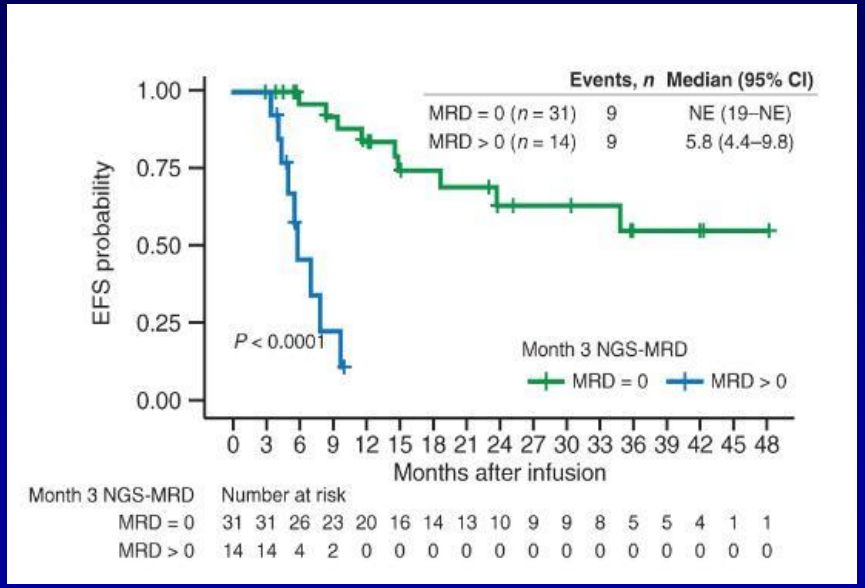
- 200 pts (185 pts infused); median age 12 yr (0–26 yr); CR = 85%
- HBD n = 94 (47%); LBD n = 60 (30%); ND n = 46 (23%)
- 12-mo EFS = 50%, 12-mo OS = 72%
- G3 CRS = 21% (35% in HBD); G3 NE = 7% (9% in HBD)

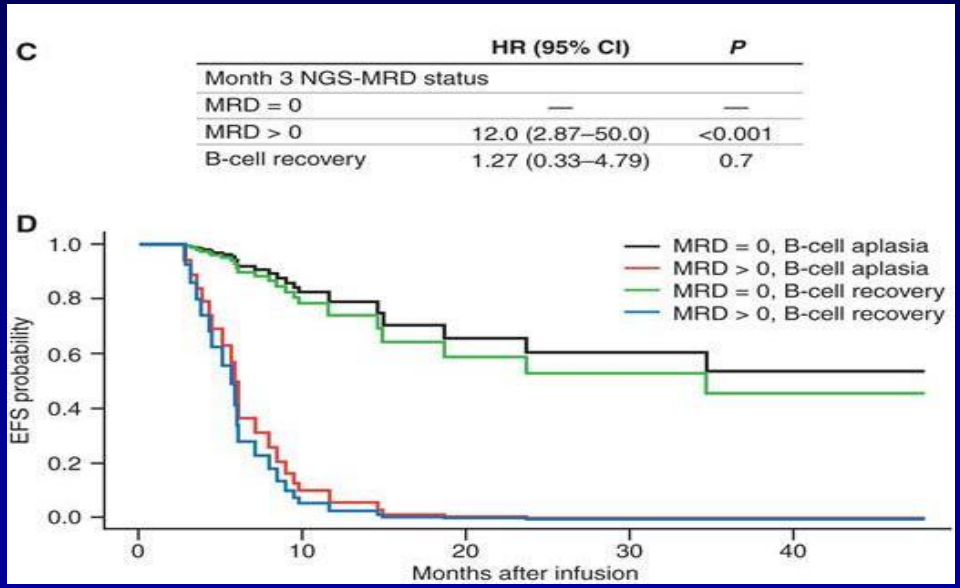


Schultz LM, et al. *J Clin Oncol*. 2022;40(9):945-955.

NGS MRD Negativity After CAR T-Cell Therapy for ALL

- Detectable MRD after tisagenlecleucel by NGS independently predicted for EFS and OS on multivariate analysis
- NGS MRD status at 3 months was superior to B-cell aplasia/recovery at predicting relapse/survival

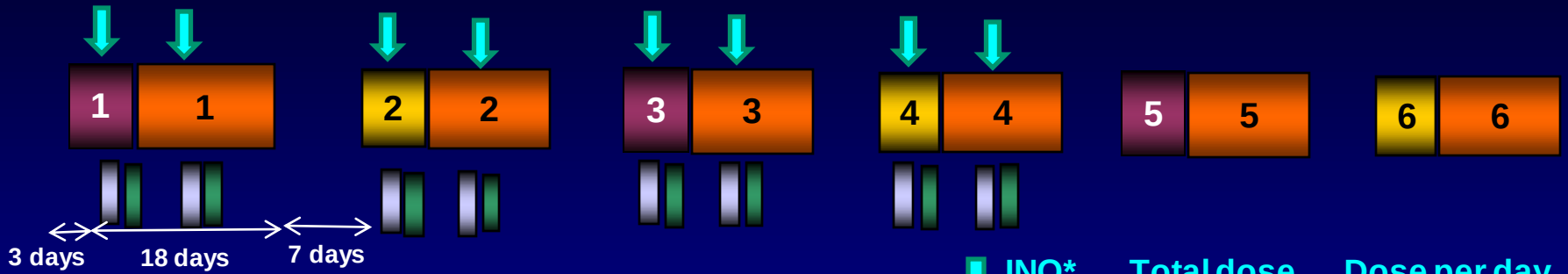




Pulsipher MA, et al. *Blood Cancer Discov.* 2022;3(1):66-81.

Dose-Dense Mini-HCVD + INO + Blina + CAR T Cells in ALL: The CURE

Induction phase: C1–C6



Consolidation phase

CAR T Consolidation

INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Mini-HCVD

Mini-MTX, Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

ALL 2023: Conclusions

- Significant improvements across all Jayakumar categories
- Incorporation of Blina-InO in FL therapy highly effective and improves survival
- Early eradication of MRD predicts best overall survival
- Antibody-based Rxs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather, complementary (together)
- Future of ALL Rx
  1) Less chemotherapy and shorter durations
  2) Combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22
  3) SQ blinatumomab
  4) CAR Ts CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT

Thank You

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Global Leukemia Academy

AML case-based panel discussion

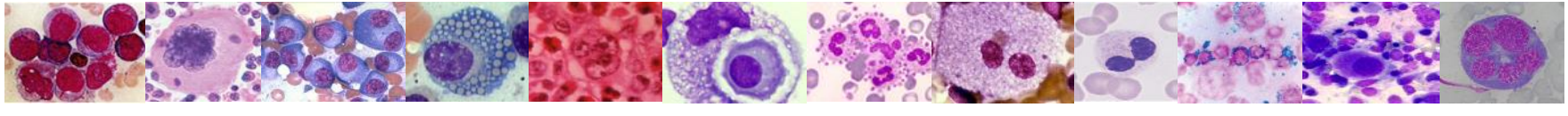
Roberta Demichelis

APTITUDE HEALTH®

AML cases

Roberta Demichelis

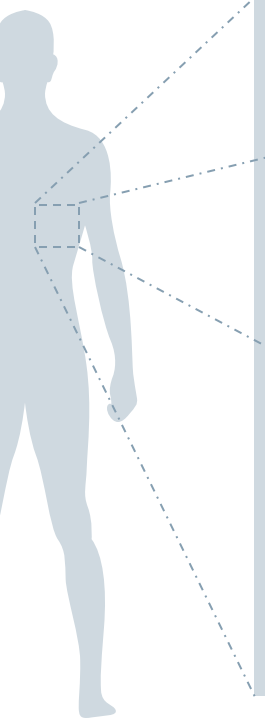
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán



Disclosures

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

Case 1



50-year-old man

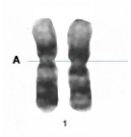
Previous medical history: diabetes

Symptoms: fever and epistaxis

Labs

- Hb 8.8 g/dL, WBC 145 × 10^9/L, platelets 14 × 10^9/L
- 70% blasts with Auer rods

BMA: 76% myeloid blasts CD34+, CD117+, CD13+, CD33+, HLA-DR+ (weak), MPO+ (weak)



46 XY,

Mutation	VAF
FLT3-ITD	12.0%
NPM1	26.6%
DNMT3A	28.0%

AML challenges in Mexico

Retrospective registry
2013–2017
13 centers
N = 525

- Median age **47 years**
- **80.2% candidates for intensive treatment**

Induction-related mortality: 17.8%

- Risk factors: age >60, ECOG >2, secondary LMA, active infection at diagnosis

Allo-HCT in first CR in 8.2%

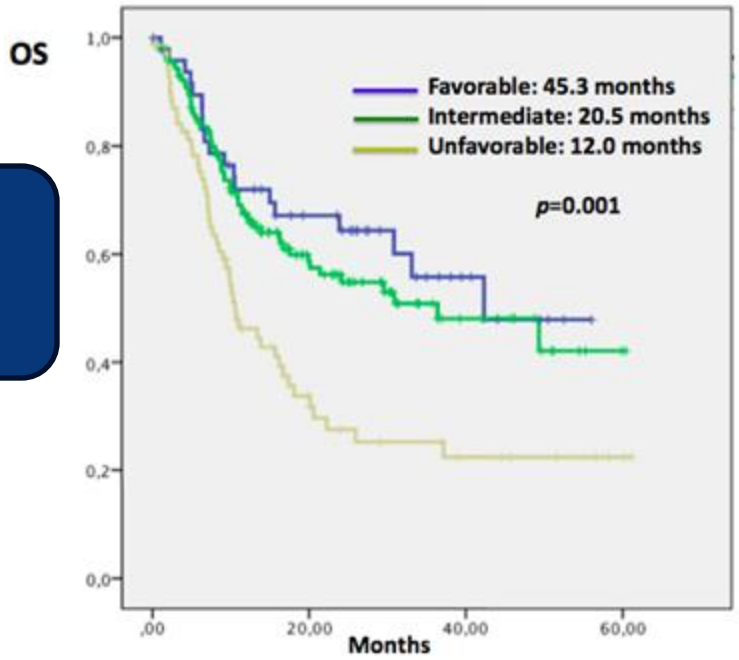
Assessable karyotype: 69.1%

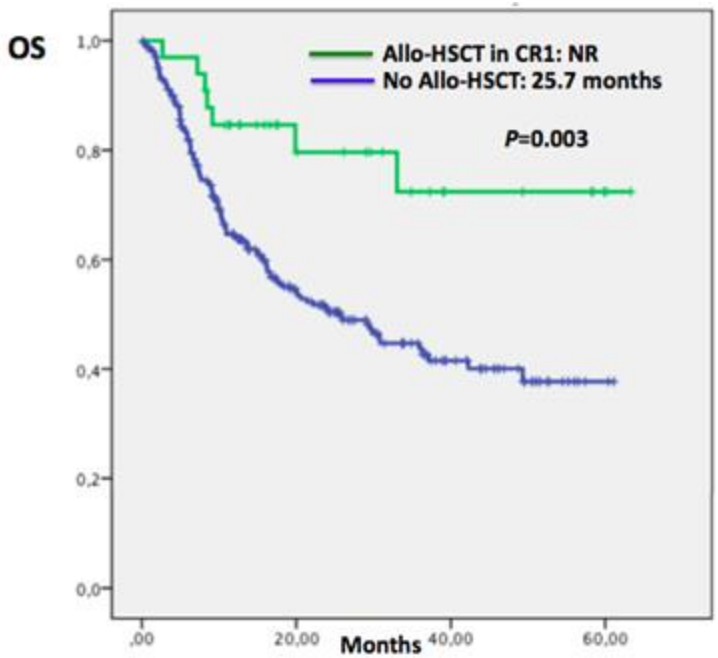
Molecular: *FLT3* 12.2%, *NPM1* 8.2%

Demichelis-Gómez R, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20(6):e295-e303.

AML challenges in Mexico

3-year OS: 34.8%





Demichelis-Gómez R, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20(6):e295-e303.

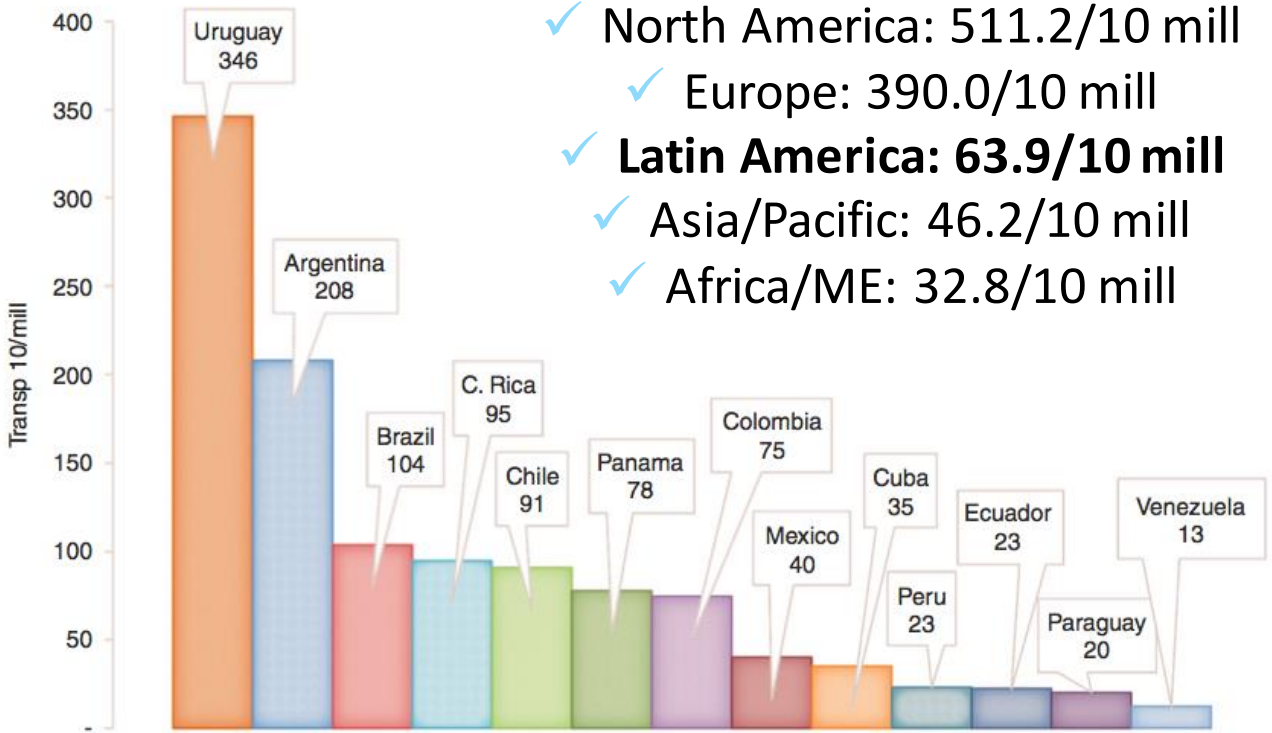
Identified challenges

- Excessive treatment-related mortality
- Low transplant rates
- Little access to molecular tests
- Access to new drugs

Access to transplantation

Centers treating AML

Center with access to transplantation



- ✓ North America: 511.2/10 mill
- ✓ Europe: 390.0/10 mill
- ✓ **Latin America: 63.9/10 mill**
- ✓ Asia/Pacific: 46.2/10 mill
- ✓ Africa/ME: 32.8/10 mill

Jaimovich G, et al. *Bone Marrow Transplant*. 2021;56(10):2382-2388; Niederwieser D, et al. *Blood*. 2019;134(suppl 1):abstract 2035; Passweg JR, et al. *Bone Marrow Transplant*. 2021;56(7):1651-1664.

In Mexico?

Hematopoietic Cell Transplantation in First Remission in AML in Mexico: Very Low Rates Derived from Early Relapses and Lack of Access

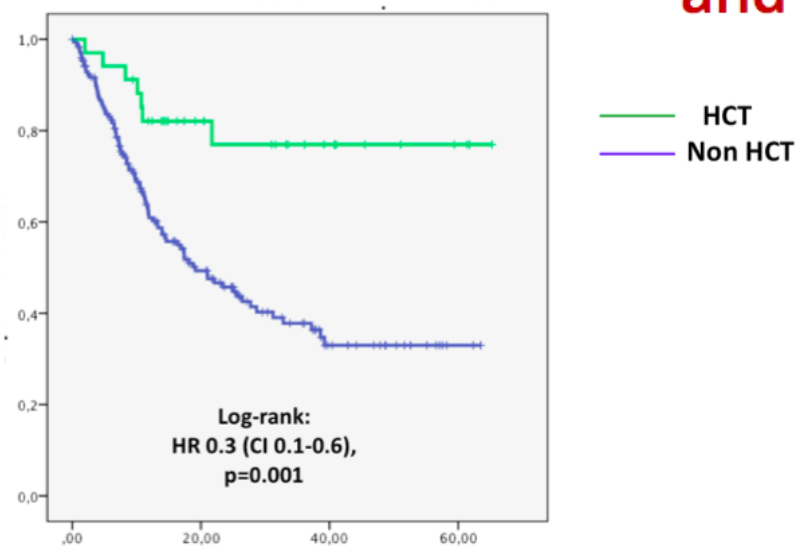
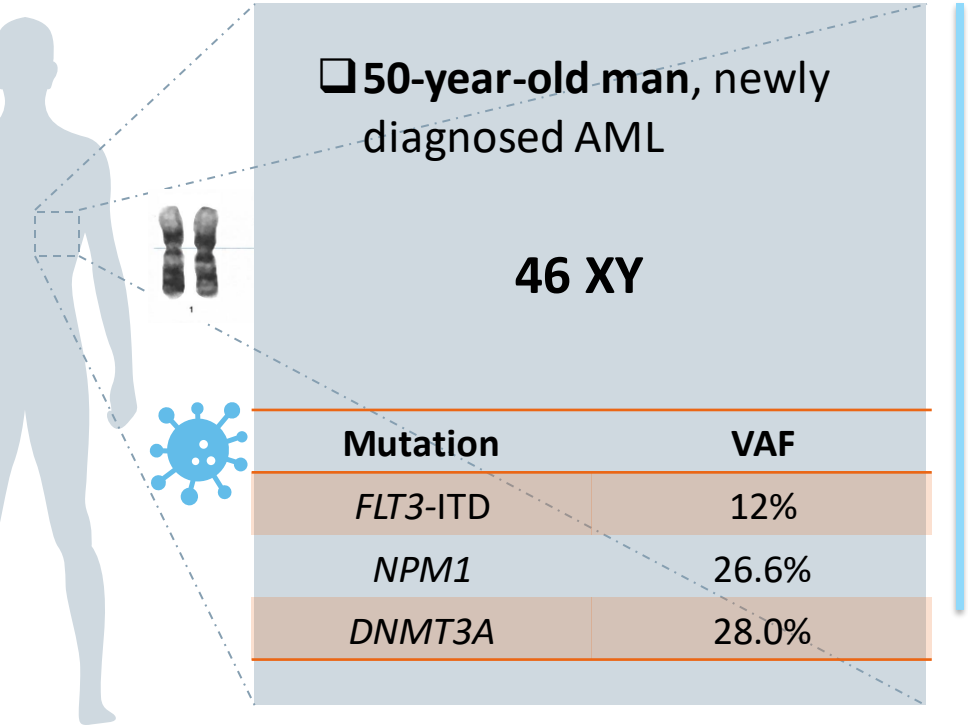


Figure 1. Overall survival landmark analysis since complete remission
HCT: hematopoietic cell transplantation

- ✓HLA typing 34%
- ✓Only 24% received a consultation with transplant team
- ✓Only 48% of those who came to that consultation had a transplant

Solís-Armenta R, et al. *Blood*. 2022;140(suppl 1):10830-10832.

Case 1



- **50-year-old man**, newly diagnosed AML

46 XY

Mutation	VAF
FLT3-ITD	12%
NPM1	26.6%
DNMT3A	28.0%

AML with defining recurrent genetic abnormalities

Intermediate risk

7+3 + midostaurin

MRD: how and when?

MRD, measurable residual disease.

Questions for the audience 1

What do you consider the best method to determine MRD in this case?

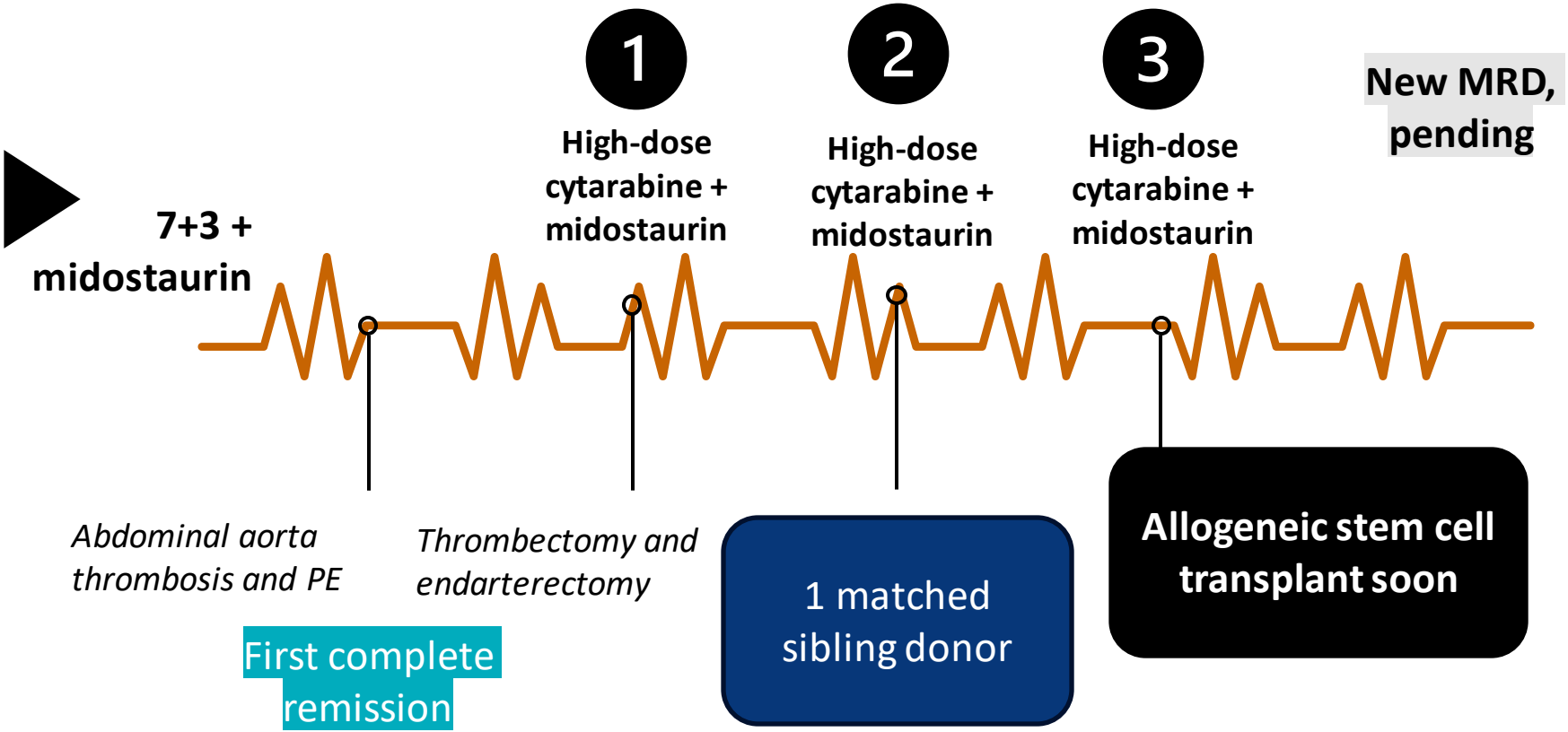
A. Flow cytometry
B. Next-generation sequencing
C. qPCR for *FLT3*
D. qPCR for *NPM1*
E. I don't know

Questions for the audience 2

When is the best time to measure MRD?

A. After induction
B. After 2 cycles
C. After 3 cycles

PCR by NPM1 could not be performed. MRD by flow: 0.2%



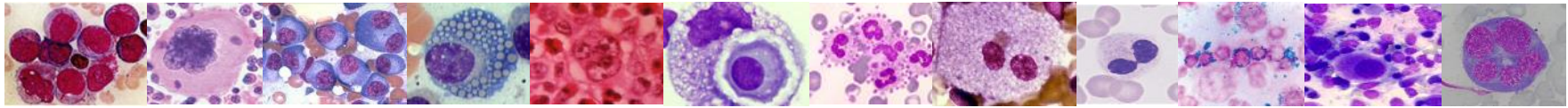
Question for the audience

Which option would you choose for post-transplant maintenance?

A. None; there is not enough evidence
B. Sorafenib
C. Midostaurin
D. Gilteritinib
E. It will depend on the MRD result

Adult AML case

Sergio Rodriguez Rodriguez, MD, MSc
Hematology and Oncology Department – INCMNSZ
Mexico City



Disclosures

- Nothing to declare

Case

66-year-old woman

Unemployed lawyer

- Hemorrhoidal Disease
- Lower GI Bleeding
- Osteoporosis

History

Anemic syndrome, lower GI bleeding, lower extremities palpable purpura

November 2022

Labs: anemia, monocytosis; hemorrhoidectomy and transfusion of 2 packed red blood cells (PRBC)

December 2022

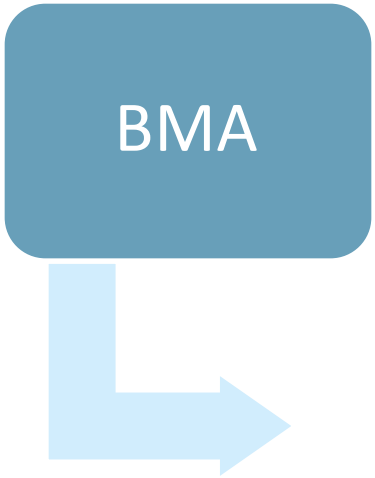
ER @ INCMNSZ: anemic syndrome, perianal pain, lower-extremity dermatosis

ECOG PS 2

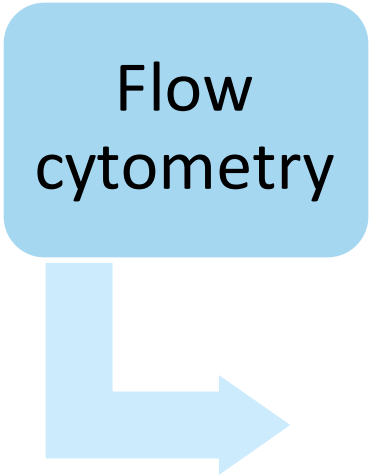
January 2023

Hb 4.2 g/dL
WBC 28 × 10^9/L
ANC 19.6 10^9/L
Plat 80 × 10^9/L
Blood smear: 3% blasts with Auer rods

Case: Bone marrow



Hypercellular, 4% myeloid blasts, trilineage dysplasia



Flow cytometry: 8% monocytes, 1% blasts

- Karyotype: 46,XX
- NGS: ***DNMT3A, NPM1, NRAS***

Skin biopsy by dermatology

Skin biopsy: myeloid neoplasm infiltration with myelomonocytic differentiation; **IHQ:** CD4+, CD68+, MPO+, CD117–, CD34–

Variantes identificadas en el DNA obtenido de la muestra de piel (CA1978-2)

Symbol	*HGVSc*	*HGVSp*	*Clinical Significance*
DNMT3A	NM_022552.4:c.2644C>T	NP_072046.2:p.Arg882Cys	Tier I, Patogénica
NPM1	NM_002520.6:c.860_863dup	NP_002511.1:p.Trp288CysfsTer12	Tier I, Patogénica
BRAF	NM_004333.4:c.1781A>G	NP_004324.2:p.Asp594Gly	Tier III, para LMA Pathogenica en otros tumores
IDH2	NM_002168.3:c.419G>A	NP_002159.2:p.Arg140Gln	Tier I, Patogénica

Symbol	*Genomic Location*	*COSMIC_ID*	*Depth X*	*AF(%)*
DNMT3A	chr2:25457243	COSM53042	1061	20
NPM1	chr5:170837543	COSM158604	1173	13
BRAF	chr7:140453154	COSM467	571	20
IDH2	chr15:90631934	COSM41590	4606	21

Significant clinically relevant differences between ELN 2022, 5th edition WHO, and ICC 2022

	ELN/ICC 2022	5th Edition WHO
MDS/AML (without AML-defining genetic alterations)	10%–19% blasts	MDS-IB2 (10%–19% BM or 5%–19% PB or Auer rods)
AML with antecedent MDS, MDS/MPN, or prior exposure to therapy	Myelodysplasia added as a diagnostic qualifier	Separate entity: AML-MR
AML with *NPM1* mutations, *KMT2A*, *MECOM*, or *NUP98* rearrengements	**≥10 blasts in BM or PB**	**Diagnosed irrespective of blast count**
AML with *CEBPA* mutations	≥10% blasts in BM or PB (only bZIP mutations)	≥20% blasts in BM or PB (biallelic and bZIP mutations)
***TP53* mutation**	Different hierarchic classification	Not included as a separate entity
Therapy related	Added as a diagnostic qualifier	Separate entity: AML-pCT

Question for the audience

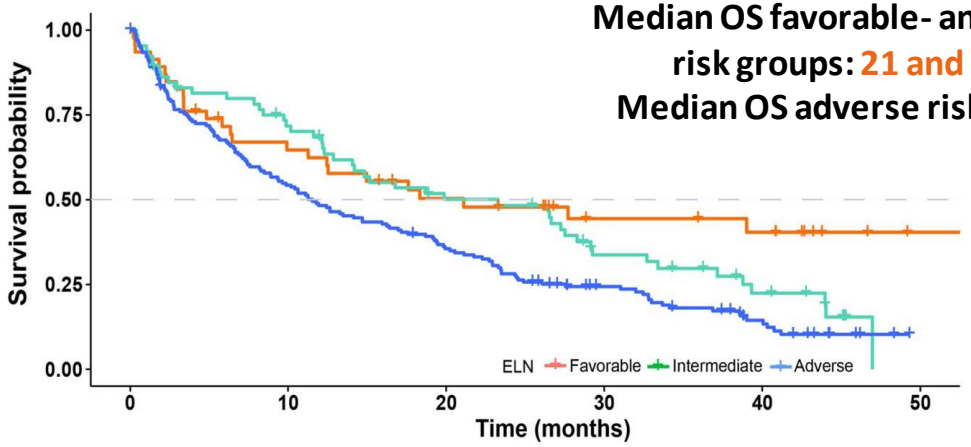
In your practice, how would you treat this patient?

A. Standard intensive chemotherapy (7+3)
B. Low-dose cytarabine (LDAC) or hypomethylating agents (HMA)
C. Venetoclax + LDAC or HMA
D. HMA + ivosidenib

ELN Risk Stratification Is Not Predictive of Outcomes for Treatment-Naïve Patients with Acute Myeloid Leukemia Treated with Venetoclax and Azacitidine

Hartmut Döhner, Keith W. Pratz, Courtney D. DiNardo, Brian A. Jonas, Vinod A. Pullarkat, Michael J. Thirman, Christian Recher, Andre C. Schuh, Sunil Babu, Monique Dail, Grace Ku, Yan Sun, Jalaja Potluri, Brenda Chyla, Daniel A. Pollyea

Figure 2: Overall survival among patients treated with VEN+AZA



Median OS favorable- and intermediate-risk groups: 21 and 23 months

Median OS adverse risk: 11.5 months

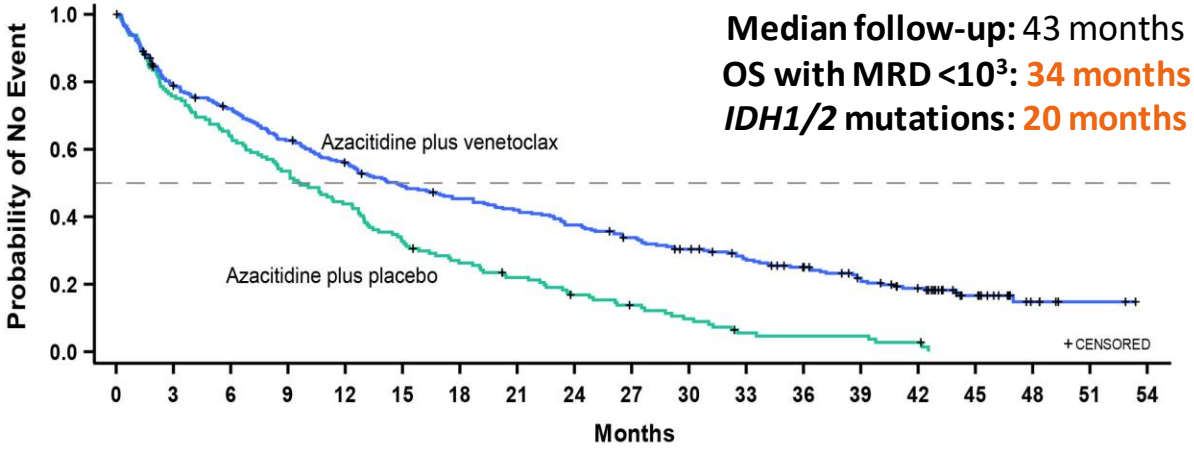
No. at risk:						
ELN Favorable	46	28	20	12	10	2
ELN Intermediate	65	44	29	17	9	0
ELN Adverse	168	90	58	31	14	0

ELN, European LeukemiaNet; Ven, Venetoclax; Aza, Azacitidine

Döhner H, et al. *Blood.* 2022;140(suppl 1):1441-1444.

Long-Term Follow-up of the Phase 3 Viale-a Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

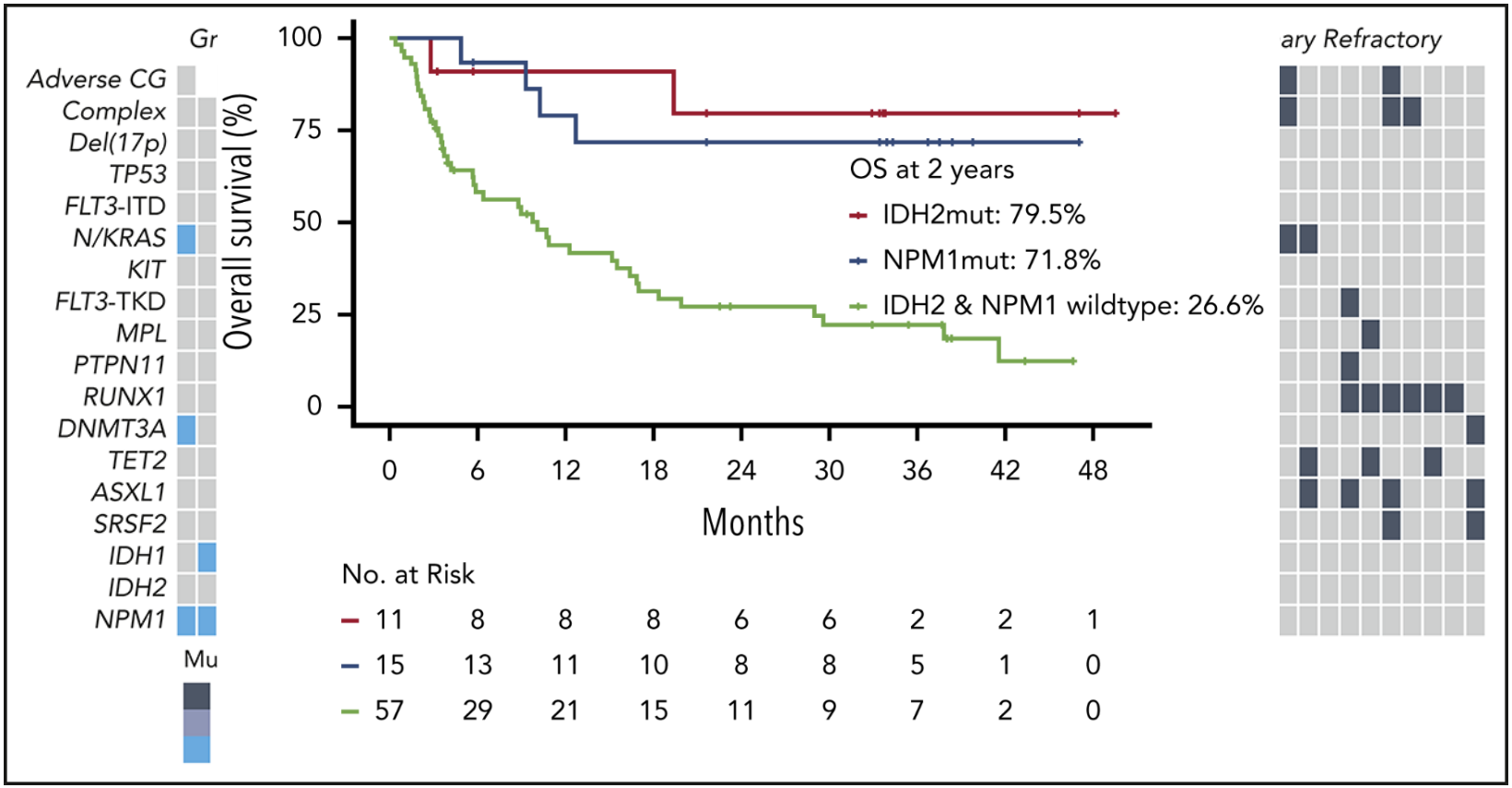
Figure 1. Overall Survival



Median follow-up: 43 months
OS with MRD <10^3: 34 months
***IDH1/2* mutations:** 20 months

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



Prolonged responses with
NPM1* and *IDH2

Evolution

#1 AZA 75 mg/m² D1-7
VEN 100 mg D1-14 +
itraconazole 200 mg BID

+29: complete hematologic recovery, no skin lesions

#2 VEN 21 days
Cytopenias → BMA <5% blasts; BMB 30% cellularity

- ✓ **MRD: not performed**
- ✓ **Transfusion independent**
- ✓ **Continuous G-CSF**
- ✓ **ECOG PS 1**
- ✓ **Recurrent infections**

G-CSF

Febrile neutropenia: proctitis/bacteremia due to *P. aeruginosa;* **neutrophil recovery +72**

#3 VEN: 7 days;
+57: BMA no blasts, **BMB 10% cellularity; neutrophil recovery +65**

4th cycle

Without VEN due to cytopenia;
MRD PCR *NPM1* pending

Open questions for the panelists

- ✓ **How to stratify risk in patients who are not candidates for intensive chemotherapy?**
- ✓ **What would be the best regimen for *NPM1*^{mut} AML without blasts?**
- ✓ **What is the role of MRD measurement with non-intensive regimens?**
- ✓ **Is there a role for *IDH1* mutation inhibitors in the treatment of this patient?**

Thank you

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Global Leukemia Academy

Current treatment options for relapsed/refractory AML

Naval Daver

APTITUDE HEALTH®

Optimizing the Management of Relapsed/Refractory AML: 2023

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

Options for R/R AML With *IDH* Mutations

NCCN Recommendations, 2021

Targeted therapy

- Therapy for AML with *FLT3*-ITD mutation
  - Gilteritinib (category 1)
  - Hypomethylating agents (azacitidine or decitabine) + sorafenib
- Therapy for AML with *FLT3*-TKD mutation
  - Gilteritinib (category 1)
- Therapy for AML with *IDH2* mutation
  - Enasidenib
- Therapy for AML with *IDH1* mutation
  - Ivosidenib
- Therapy for *CD33*-positive AML
  - Gemtuzumab ozogamicin

Aggressive therapy for appropriate patients

- Cladribine + cytarabine + G-CSF ± mitoxantrone or idarubicin
- HiDAC (if not received previously in treatment ± idarubicin or daunorubicin or mitoxantrone)
- Fludarabine + cytarabine + G-CSF ± idarubicin
- Etoposide + cytarabine ± mitoxantrone
- Clofarabine ± cytarabine ± idarubicin

Less-aggressive therapy

- Hypomethylating agents (azacitidine or decitabine)
- LDAC (category 2B)
- Venetoclax + HMA/LDAC

Clinical trials are always recommended as an option

NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.

Clinical Applications of Molecular Studies in AML

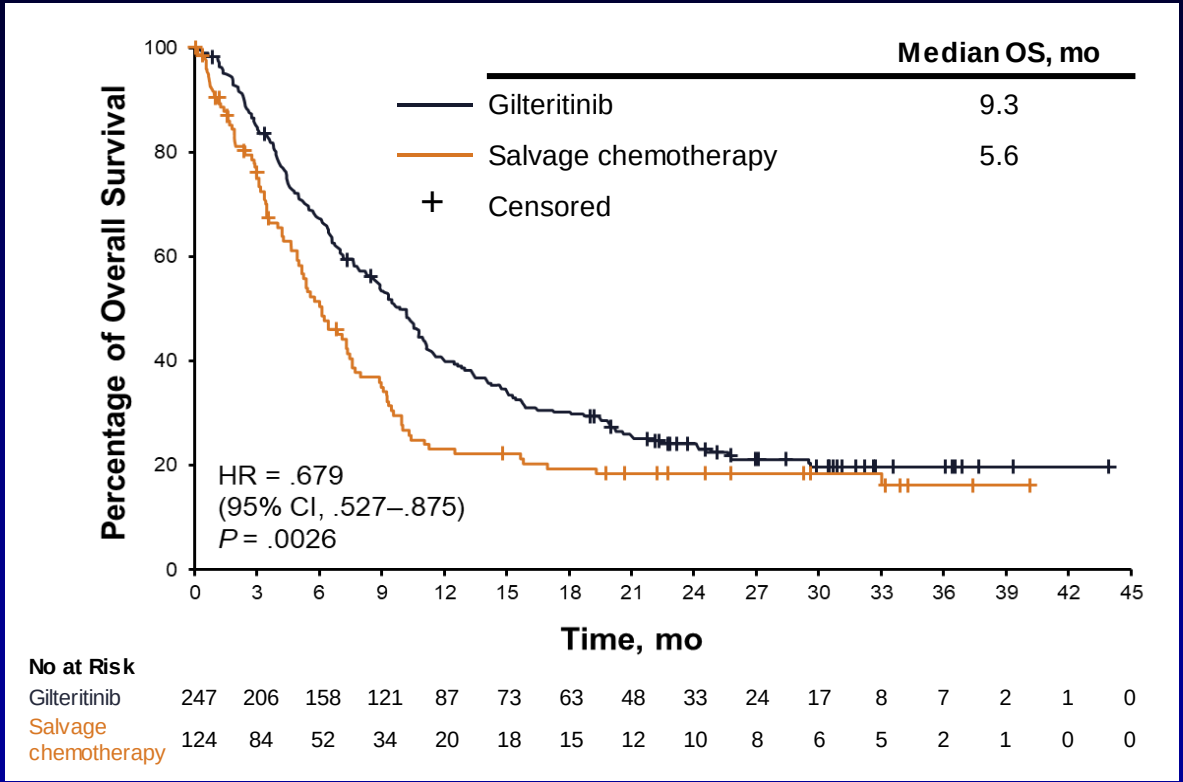
- ***FLT3-ITD* mutations – Add FLT3 inhibitor (gilteritinib, midostaurin, sorafenib), consider allo-SCT and post-SCT FLT3i**
- ***IDH1-2* mutations – Add IDH inhibitor: enasidenib (AG-221/IDH2 inhibitor), ivosidenib (AG-120/IDH1 inhibitor)**
- ***NPM1* mutation in diploid CG – ara-C sensitivity**
- ***TP53* mutation – Consider decitabine 10 days ± others (GO, venetoclax); refer to allo-SCT; role of CD47 Ab (magrolimab)**
- **MLL-AML; t (11q23;---) – Menin inhibitors**

NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2018.

1. *FLT3*-mutated AML – ADMIRAL: Longer Follow-Up Continues to Show OS Benefit With Gilteritinib in R/R *FLT3*-Mutated AML

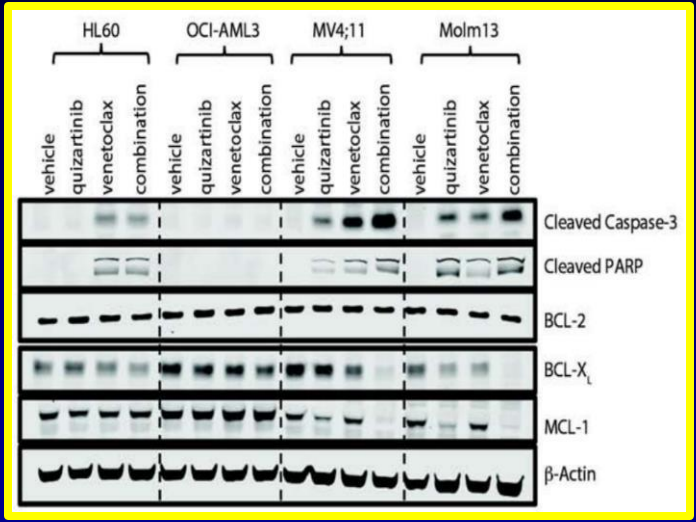
Median duration of follow-up: 29.2 mo

- **Continued prolonged median OS with gilteritinib vs salvage chemotherapy**
- **Long-term survivors typically remained in remission, frequently proceeded to HCT, and received post-HCT gilteritinib**

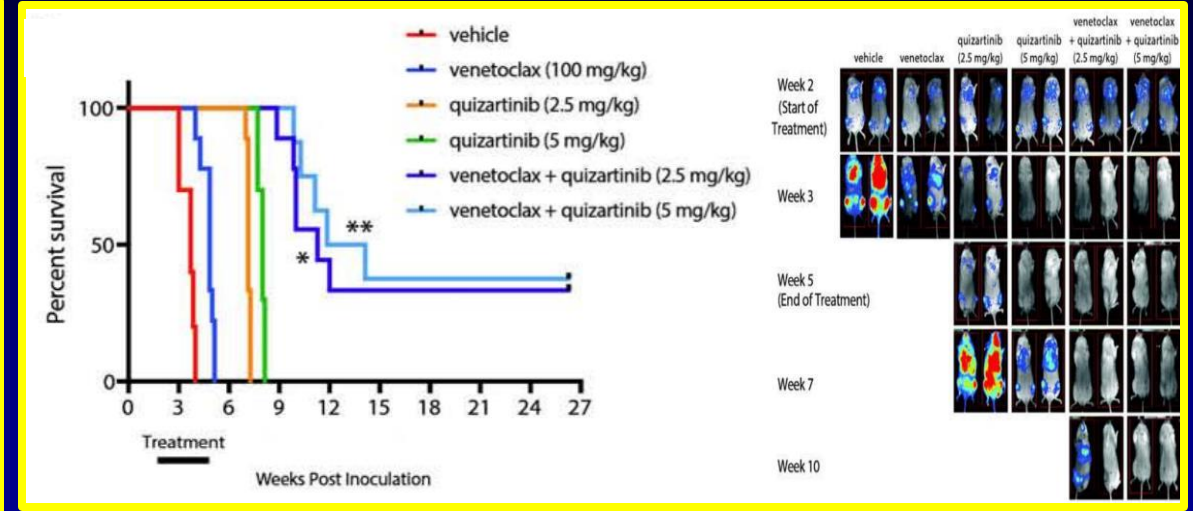


Perl A, et al. EHA 2021. Abstract EP543.

Venetoclax Combines Synergistically With Quizartinib



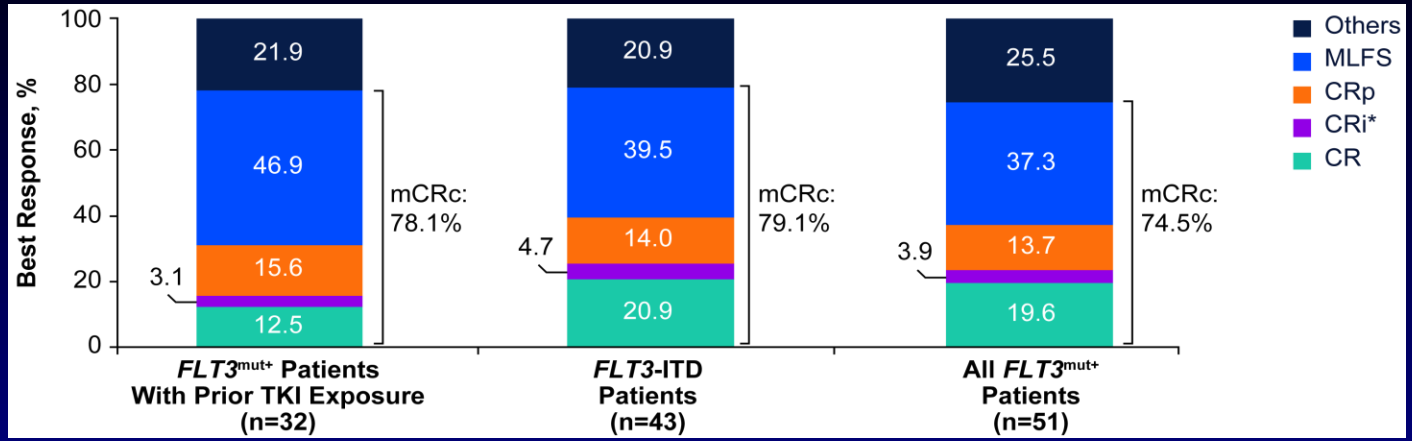
Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X_L



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

Mali RS, et al. *Haematologica*. 2021;106. doi:10.3324/haematol.2019.244020

Summary of Best Responses



	FLT3^{mut+} Patients With Prior TKI Exposure (n = 32)	*FLT3*-ITD Patients (n = 43)	All *FLT3*$^{mut+}$ Patients (n = 51)
mCRc[a], n (%)	25 (78.1)	34 (79.1)	38 (74.5)
CR+CRp+CRi*[b]	10 (31.3)	17 (39.5)	19 (37.3)
MLFS	15 (46.9)	17 (39.5)	19 (37.3)

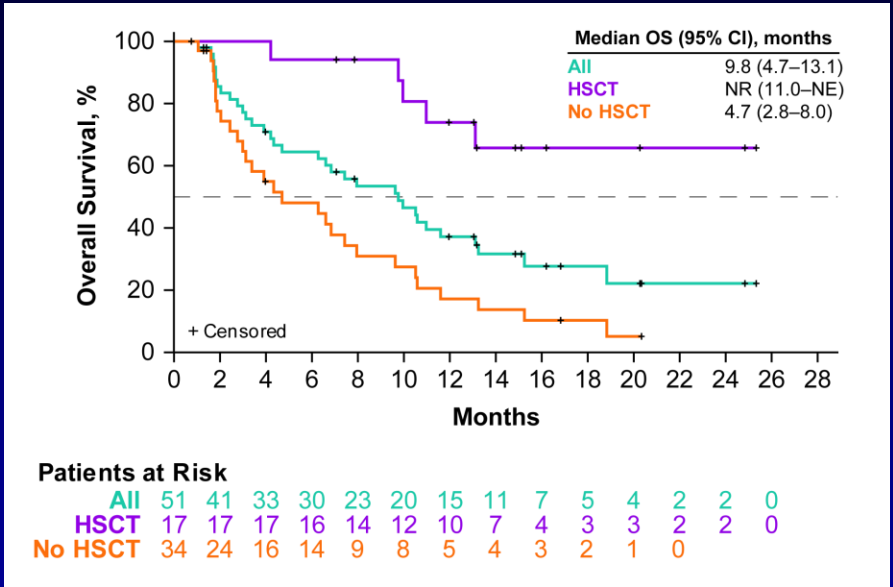
The mCRc rate in this study was **74.5**%. The CRc rate in the ADMIRAL phase III study for single-agent Gilt was 54.3% (using the same response parameters).

[a]mCRc defined as CR+CRp+CRi*+MLFS, per modified IWG response criteria. [b]Hematology criteria for CRi* is ANC ≤1×10^9/L and platelet >100×10^9/L, which is mutually exclusive with IWG response CRp. CR, complete remission; CRi*, complete remission with incomplete neutrophil count recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; IWG, International Working Group; mCRc, modified composite complete remission; MLFS, morphologic leukemia-free state; TKI, tyrosine kinase inhibitor.

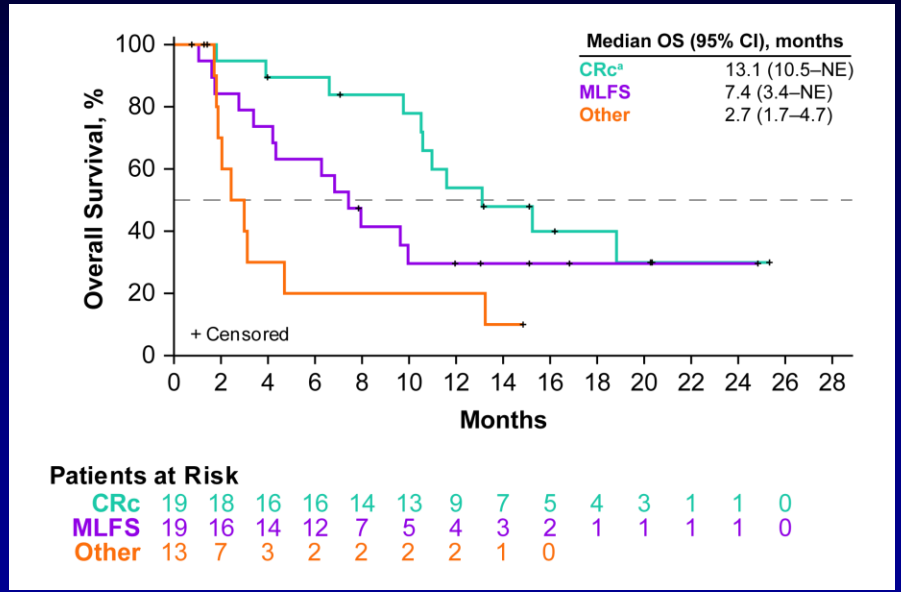
Perl A, et al. *N Engl J Med*. 2019;381:1728-1740.

OS by Transplant or Response Status

OS by Transplant Status (*FLT3*$^{mut+}$ Patients)



OS by Best Response Status (*FLT3*$^{mut+}$ Patients)



- Median duration of follow-up was 15.1 months (range, .8–25.3)
- Median OS for *FLT3*-ITD patients was 10.0 months (95% CI, 6.6–13.2)

[a]CRc defined as CR+CRp+CRi*.

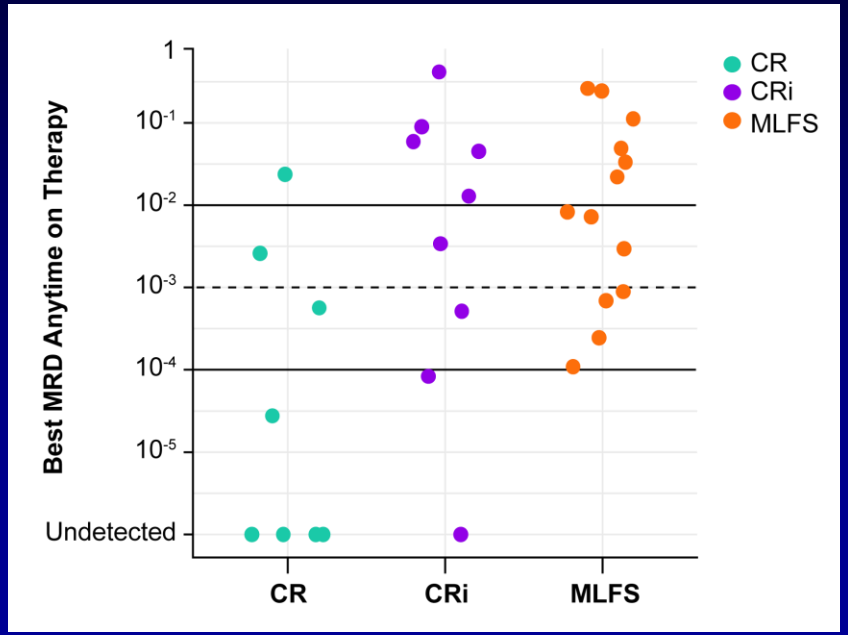
CR, complete remission; CRc, composite complete remission; CRi*, complete remission with incomplete neutrophil count recovery; CRp, complete remission with incomplete platelet recovery; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; MLFS, morphologic leukemia-free state; NE, not estimable; NR, not reached; OS, overall survival.

Ven + Gilt Demonstrated Deep Reductions in *FLT3* Allelic Burden in Patients Achieving mCRc

FLT3-ITD burden, n (%)	<10^{-2} (1%)	<10^{-3}	<10^{-4}
Cycle 1, Day 28	9 (30.0)	3 (10)	0
Any time on therapy	18 (60.0)*	13 (43.3)	7 (23.3)

**The molecular best response (<10^{-2}) of Ven + Gilt was 60.0% in FLT3-ITD patients achieving mCRc*
The molecular best response (<10^{-2}) for Gilt alone in a subset analysis from CHRYSALIS was 25%

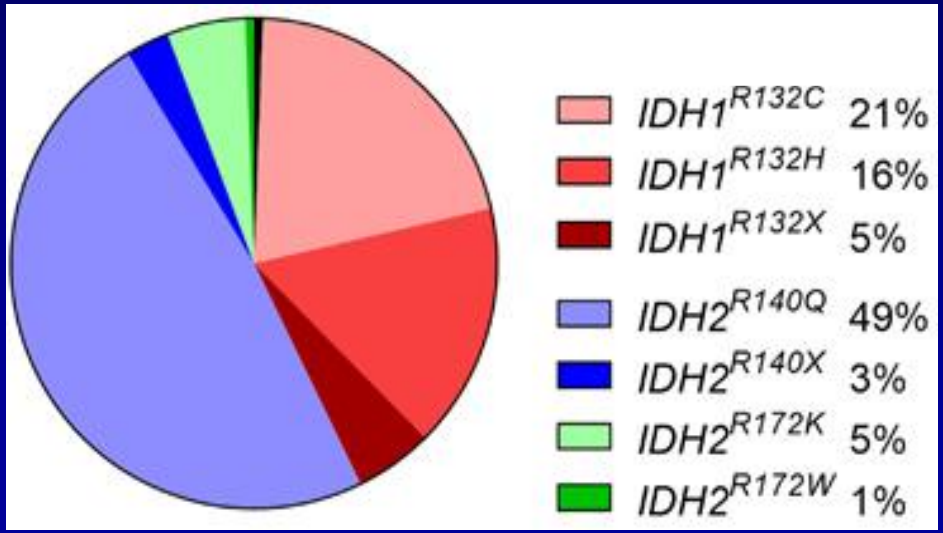
- **30/34 *FLT3*-ITD mCRc patients were evaluable for longitudinal reduction in *FLT3*-ITD using an assay with sensitivity of 10^{-6}**



Gilt, gilteritinib; ITD, internal tandem duplication; mCRc, modified composite complete remission; RP2D, recommended Phase 2 dose; Ven, venetoclax.
Levis MJ, et al. *Blood Adv.* 2018;2(8):825–31.

2. IDH Inhibitors in R/R and Newly Diagnosed AML
Characteristics of mIDH AML

- *IDH* mutations occur in ~20% of AML
  - *IDH1* in ~8% AML, *IDH2* in ~12% AML
  - ↑ prevalence with ↑ patient age
- Hot-spot mutations in enzymatic active site
  - *IDH1*-R132, *IDH2*-R140, or *IDH2*-R172
- Can be acquired at progression
  - ~10%–15% of AML from MDS
  - ~20%–25% of AML from MPN

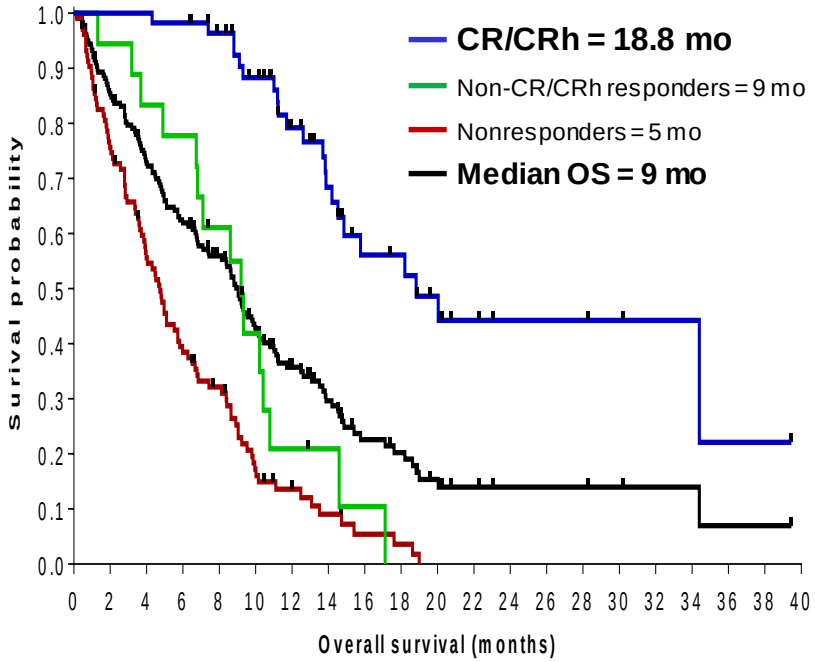


Dang L, et al. *Trends Mol Med*. 2010;16(9):387-397; Chou WC, et al. *Leukemia*. 2011;25(2):246-253; Molenaar RJ, et al. *Leukemia*. 2015;29(11):2134-2142.

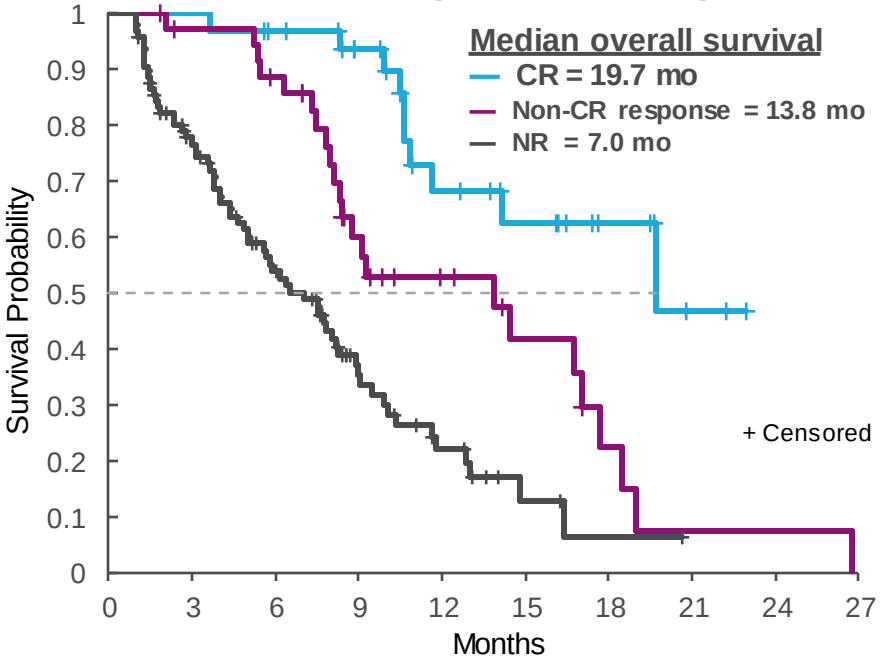
IDH1 or IDH2 Inhibitor Monotherapy

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

Ivosidenib (IDH1 inhibitor)[1]



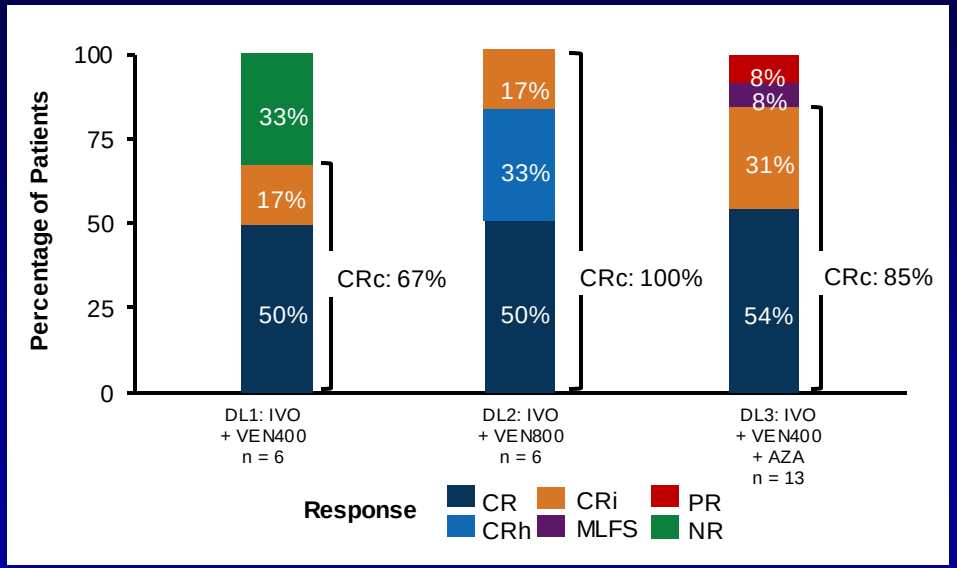
Enasidenib (IDH2 inhibitor)[2]

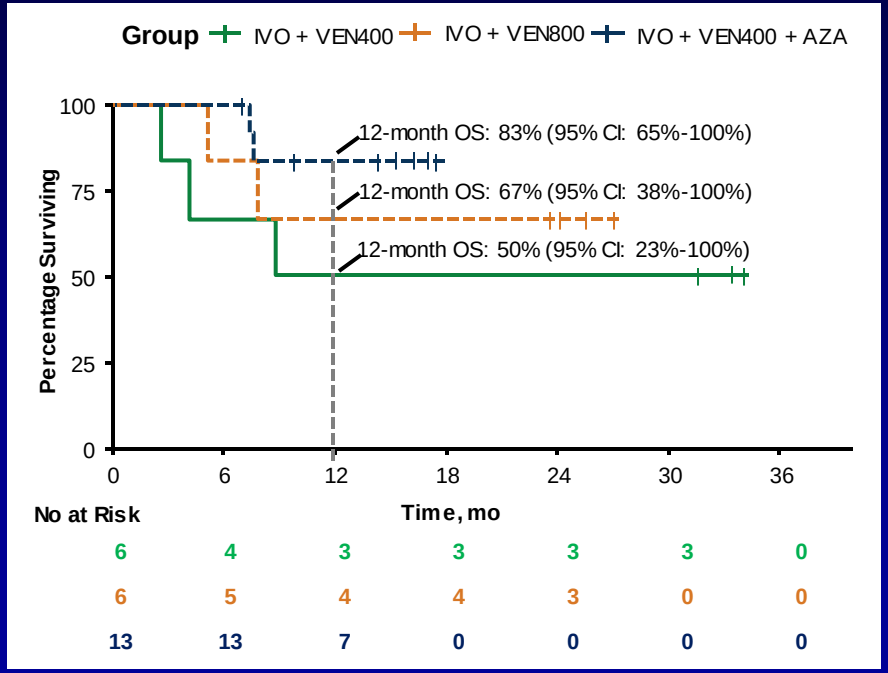


1. DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398; 2. Stein EM, et al. *Blood*. 2017;130(6):722-731.

A Role for Doublet and Triplet Therapy in *IDH1*-Mutant AML? Ivosidenib and Venetoclax ± AZA

- N = 25 patients with newly diagnosed AML, R/R AML, or MDS/MPN
- IVO + VEN ± AZA is active against *IDH1*-mutated myeloid malignancies, with an acceptable and expected toxicity profile and high rates of MRD-negative CRc in AML





Lachowiez C et al. ASCO 2021. Abstract 7012.

3. MLL and *NPM1*-Mutated AML: SNDX-5613 Is a Potent, Selective Protein–Protein Interaction Inhibitor of Menin

Currently being evaluated in the phase I/II AUGMENT-101 study (N = 54)

Median age was 49 years

- 82% (n = 44) of patients had AML
- 65% (n = 35) had MLLr leukemia
- 19% (n = 10) had mutated *NPM1* leukemia

Two parallel dose-escalation cohorts

- Arm A: patients not taking strong CYP3A4 inhibitors
- Arm B: patients taking strong CYP3A4 inhibitors
- SYNDX-5613 dosing: orally Q12h in continuous 28-day cycles

MTD was 276 mg Q12h in arm A and 163 mg Q12h in arm B

Best Overall Response	Overall (N = 54), n (%)
CRc (CR + CRh + CRp + CRi/MLFS)	20 (44.4)
CR + CRh	10 (22.2)
CR	7 (15.6)
CRh	3 (6.7)
CRp	3 (6.7)
CRi/MLFS	7 (15.6)

ASH 2021: Monday, December 13: 2:45 PM

Stein E, et al. ASH 2021. Abstract 699.

In AUGMENT, SNDX-5613 Was Safe and Tolerable Across Treatment Cohorts

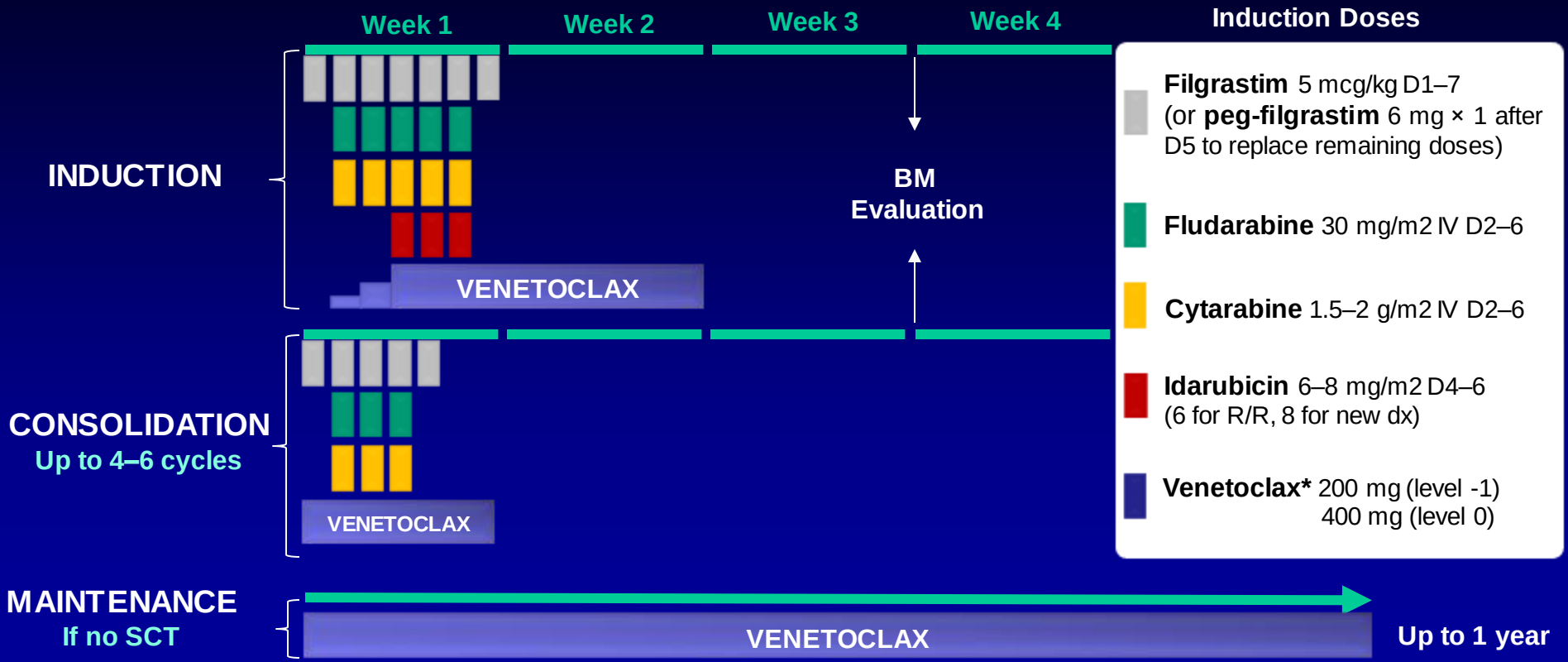
- The frequency of grade 3 prolonged QTc at these doses was 8% (3/38)
- No ventricular arrhythmias were reported, and no patients discontinued 5613 due to a treatment-related event

	Arm A Overall (n = 25), n (%)	Arm B Overall (n = 29), n (%)	Overall (N = 54), n (%)
Subjects with ≥1 grade 3 or greater related TEAE	5 (20)	5 (17.2)	10 (18.5)
ECG QT prolonged	4 (16)	3 (10.3)	7 (13)
Anemia	0	1 (3.4)	1 (1.9)
Asthenia	0	1 (3.4)	1 (1.9)
Diarrhea	0	1 (3.4)	1 (1.9)
Fatigue	0	1 (3.4)	1 (1.9)
Hypokalemia	0	1 (3.4)	1 (1.9)
Neutropenia	0	1 (3.4)	1 (1.9)
Thrombocytopenia	0	1 (3.4)	1 (1.9)
Tumor lysis syndrome	1 (4.0)	0	1 (1.9)

ASH 2021: Monday, December 13: 2:45 PM

Stein E, et al. ASH 2021. Abstract 699.

4. Venetoclax-Based Options in R/R AML: FLAG-IDA-VEN Treatment Plan

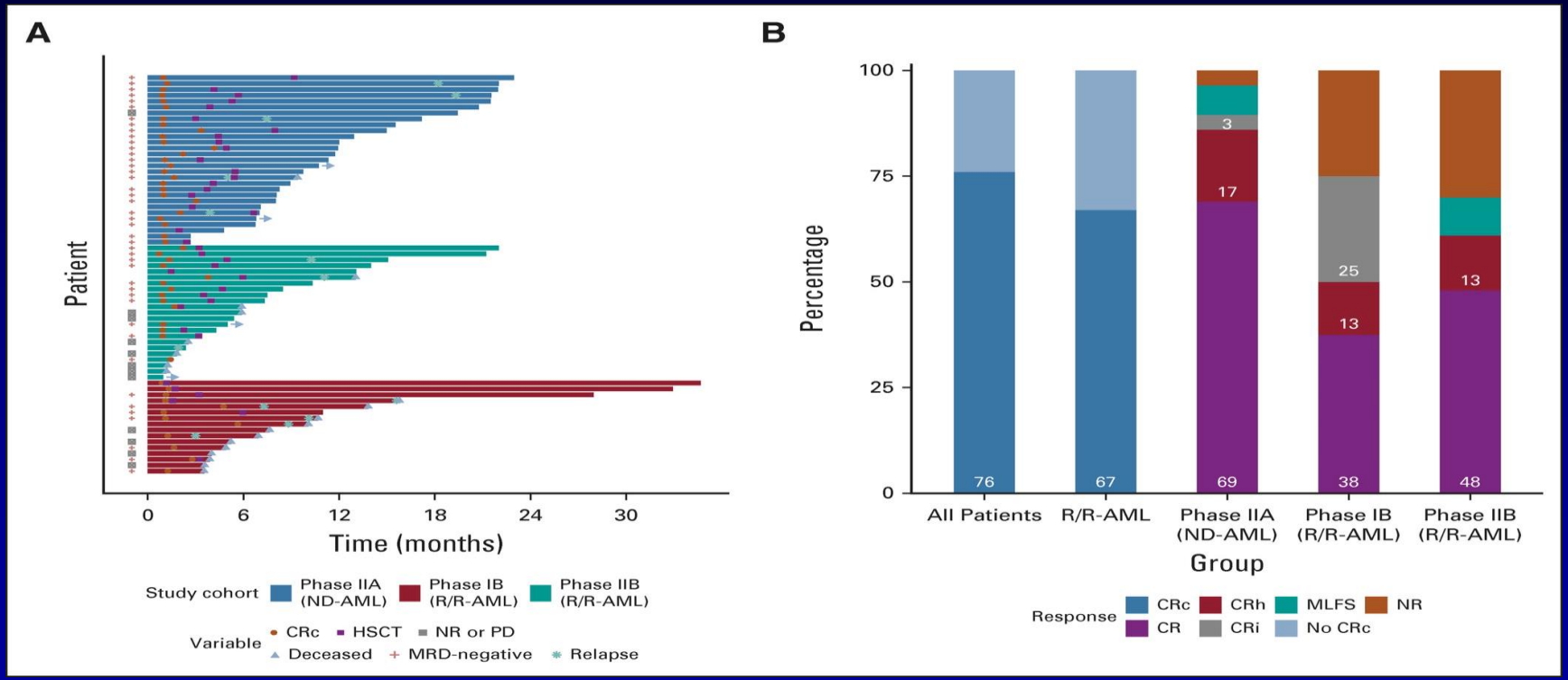


DiNardo CD, et al. *J Clin Oncol.* 2021;39(25):2768-2778.

*Concomitant azole permitted with adequate dose reduction

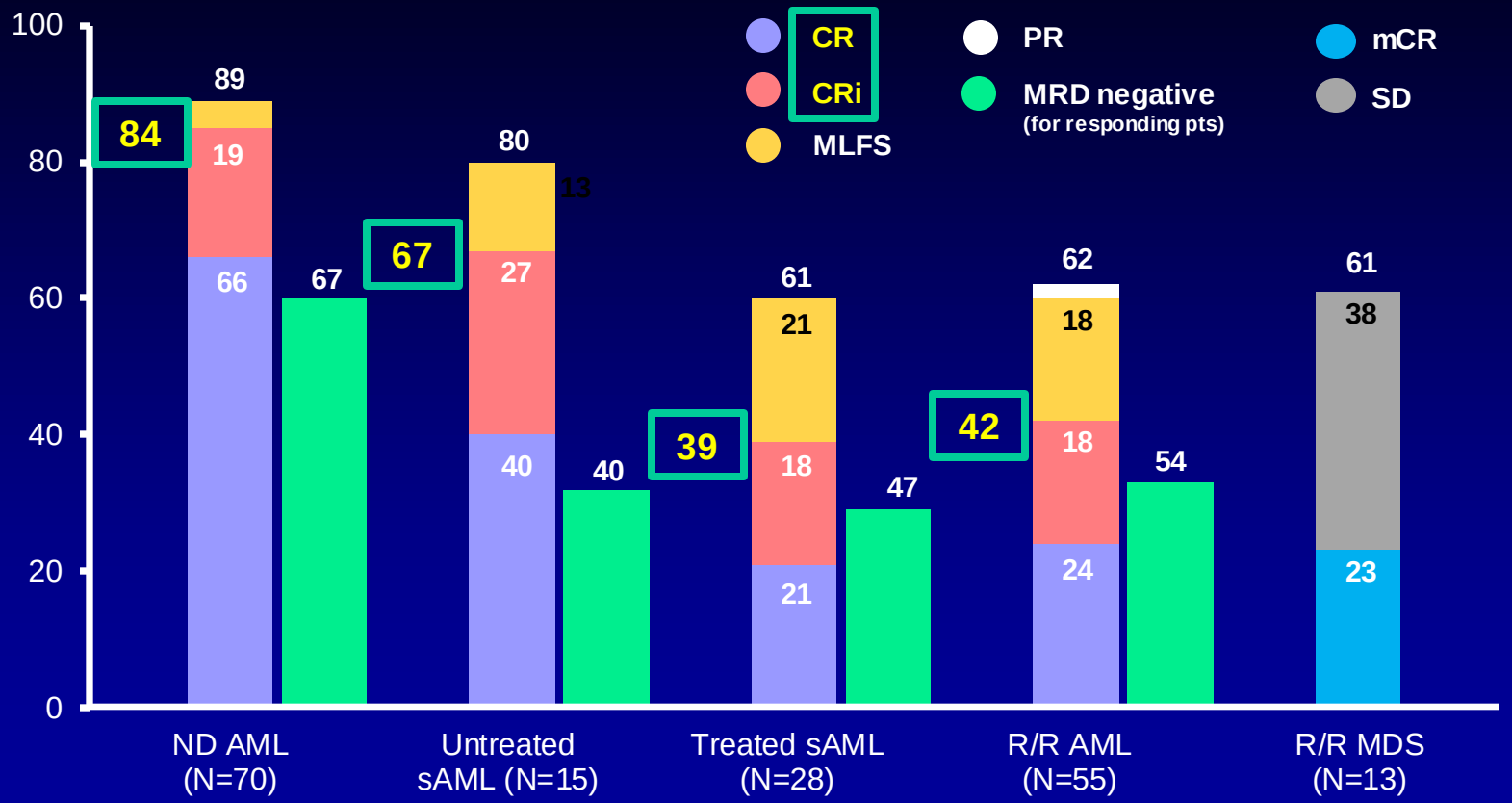
FLAG-IDA + Venetoclax in Frontline and R/R AML

- FLAG-IDA + VEN evaluated in R-R AML, then newly Dx AML
- 68 pts Rx: ND AML 29; R-R AML 39



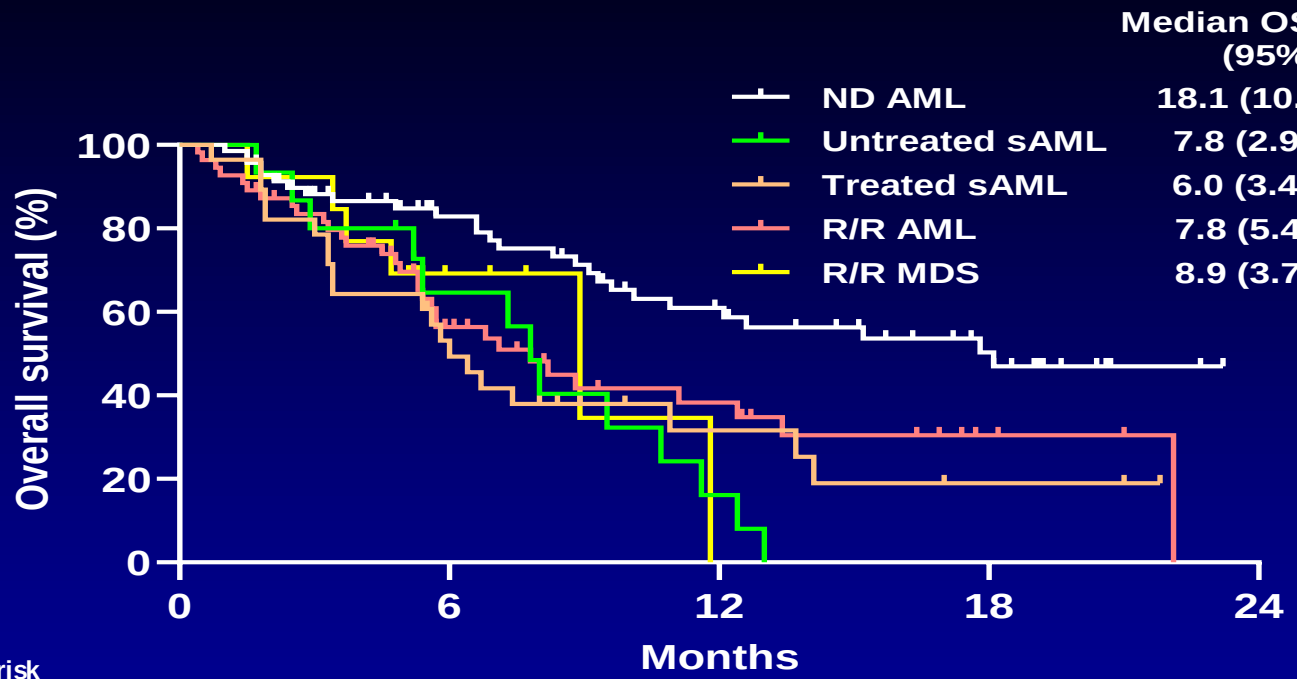
DiNardo CD, et al. *J Clin Oncol.* 2021;39(25):2768-2778.

DEC10-VEN in AML and HR MDS: Results



DiNardo CD, et al. *Lancet Haematol.* 2020;7(10):e724-e736.

DEC10-VEN in AML and HR MDS: Results

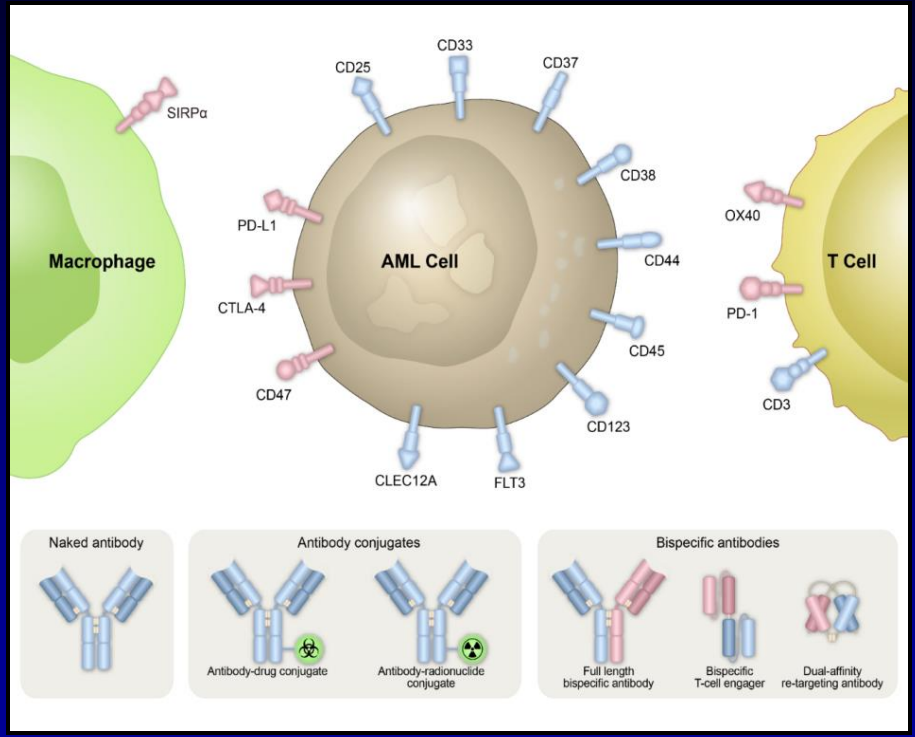


No at risk					
ND AML	70	45	28	15	0
Untreated sAML	15	9	3	0	0
Treated sAML	28	14	6	2	0
R/R AML	55	24	12	3	0
R/R MDS	13	4	0	0	0

DiNardo CD, et al. *Lancet Haematol.* 2020;7(10):e724-e736.

5. Immune-Based Approaches in AML May Soon Provide Another Treatment Modality[1]

- **Two major approaches**
  - Antibody-drug conjugates (CD33, CD123, CLL1)
  - Adaptive or innate immune system-harnessing therapies
- **Bispecific antibodies (CD3 × AML antigen, CD47 × CD3, others)**
- **Immune checkpoint-based approaches: T-cell and macrophage checkpoints**
- **CAR-T, CAR NK, high-volume hn-NK cells**
- **Vaccines**



Short N, et al. *Cancer Discov*. 2020;10:506-525.

A Number of Immunotherapy Options Are in Development for AML, With Applications in R/R Disease

IMGN632 (CD123): ADC with novel single-strand alkylating payload

Flotetuzumab (MGD006): CD123xCD3 dual-affinity retargeting (DART) molecule

XmAb 14045: CD3xCD123 bispecific

AMG330 and AMG673: CD3xCD33

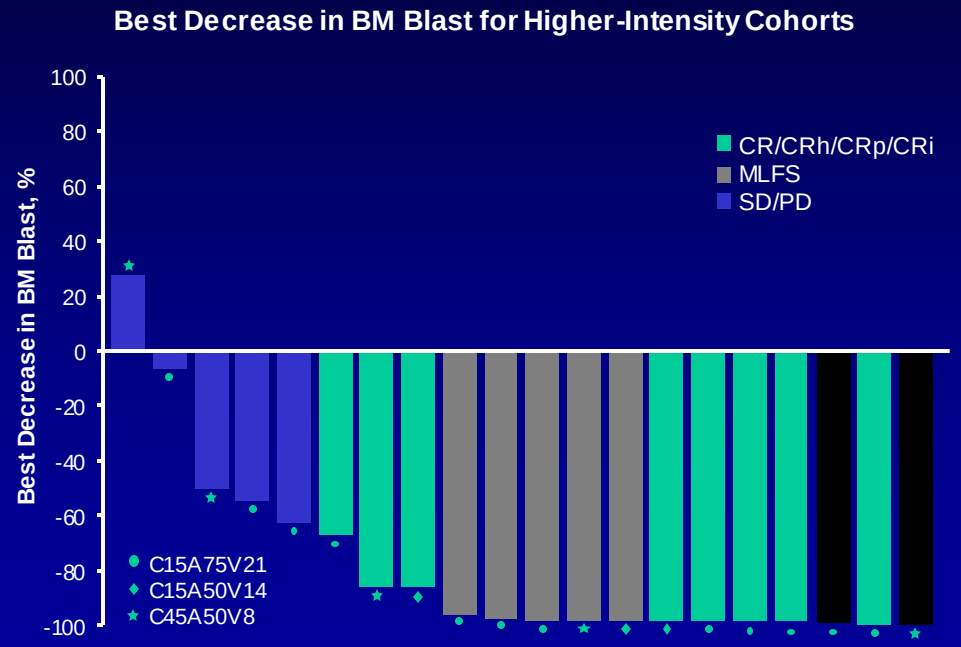
AMV564: CD3xCD33 bispecific

Novel IMGN632 Triplet Is Safe and Highly Active in CD123-Positive R/R AML

Phase Ib/II study designed to determine the safety, tolerability, and activity of IMGN632 combined with AZA and VEN in CD123-positive AML

Results

- Efficacy was seen across all cohorts/doses and schedules (N = 29)
  - ORR: 55%; cCR rate: 31%
- Higher-intensity cohorts (n = 20)
  - ORR: 75%; cCR rate: 40%
- No TLS, VOD, capillary leak, or cytokine release were observed
- 30-day mortality: 0%



Daver N, et al. ASH 2021. Abstract 372.

Immune Strategies to Kill AML

- Recruiting CD3 T cell – BiTEs linking to CD3 and targeting CD33/123; CAR Ts with modified CD3 killer cells
- Recruiting macrophages – targeting CD47 on AML (magrolimab, ALX) or SIRP alpha on macrophages (Trillium, CC95251)
- Recruiting NK cells – allo–NK-CAR Ts; NK-engineered cells/repeated infusions
- Targets other than CD33/123; eg, CLL1

Leukemia Questions?

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

Global Leukemia Academy

BREAK

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Long-term safety considerations for leukemias (focus on ALL)

Josep-Maria Ribera

APTITUDE HEALTH®

GLOBAL LEUKEMIA ACADEMY LATIN AMERICA
October 19–20, 2023

Long-Term Safety Considerations for Leukemias: Focusing on ALL

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

Disclosures

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

ALL in Adults Is Becoming Highly Curable

Subtype	Treatment	Curability
Mature B (Burkitt)	Specific chemotherapy + **rituximab** DA-R-EPOCH	70%–80%
Ph-pos	**TKI** ± CHT ± **immunotherapy** ± HSCT ± maintenance TKI	>50%, >70%
T-ALL, non-ETP **T-ALL ETP**	Chemotherapy (HDMTX, HDARAC, Asp) ± **nelarabine?** Chemotherapy (HDMTX, HDARAC, Asp) + Allo-HSCT	60% 30%
ALL in AYA	Pediatric-based or -inspired chemotherapy	70%
CD20-pos ALL	Chemotherapy + **rituximab**	50%
Ph-like ALL	Chemotherapy + **TKI? or JAK inhibitors?** + Allo-HSCT	??
Any ALL MRD positivity	Chemotherapy + **immunotherapy** + Allo-HSCT in CR1	~40%

Lack of systematic approach to analyze the health condition of long-term survivors of adult ALL

Consensus Identification of Long-Term Severe Toxicities (n = 21) (Ponte di Legno Working Group)

- Hearing loss
- Blindness
- Heart failure
- Coronary artery disease
- Arrythmia
- Heart valve disease
- Gastrointestinal failure
- Hepatic failure
- Insulin-dependent diabetes
- Renal failure
- Pulmonary failure

- Osteonecrosis
- Amputation and physical deformations
- Cognitive dysfunction
- Seizures
- Psychiatric disease
- Neuropathy, myopathy, and movement disorders
- Vocal cord paralysis
- Cytopenia
- Immunodeficiency
- Solid malignant neoplasms

Andrés-Jensen L, et al. *Lancet Haematol*. 2021;8:e513-e523.

Severe toxicity free survival: physician-derived definitions of unacceptable long-term toxicities following acute lymphocytic leukaemia

*Liv Andrés-Jensen, Andishe Attarbaschi, Edit Bardi, Shlomit Barzilai-Birenboim, Deepa Bhojwani, Melanie M Hagleitner, Christina Halsey, Arja Harila-Saari, Raphaele R L van Litsenburg, Melissa M Hudson, Sima Jeha, Motohiro Kato, Leontien Kremer, Wojciech Młynarski, Anja Möricke, Rob Pieters, Caroline Piette, Elizabeth Raetz, Leila Ronceray, Claudia Toro, Maria Grazia Valsecchi, Lynda M Vrooman, Sigal Weinreb, Naomi Winick, Kjeld Schmiegelow, on behalf of the Ponte di Legno Severe Toxicity Working Group**

Andrés-Jensen L, et al. *Lancet Haematol*. 2021;8:e513-e523; Nielsen CG, et al. *Front Pediatr.* 2023;11:1155449.

Limitations for Safety Considerations in Adult ALL

- **Toxicities defined according to pediatric trials**
- **Other toxicities not considered**
  - Infertility
  - Sexual dysfunction
  - Chronic pain
  - Fatigue
  - Work impairment
  - Social function impairment
  - … / …

General Condition and Comorbidity of Long-Term Survivors of Adult ALL

- 1,413 long-term survivors from databases of GMALL trials (1984–2003)
- 584 questionnaires from 538 patients eligible
- Median f/u: 7.5 years (range, 3–24)
- Age at Dx: <25 years (n = 191, 36%), >55 years (n = 26, 5%)
- Median age at f/u: 39 years (range, 19–74)
- Alive >5 years from Dx (416, 78%), >10 years 35%
- HSCT: 168 (31%) (allo/auto 147/21)
- ≥4-year f/u after HSCT: 73%

Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

Questionnaire

- **Part 1**
  - Comorbidity in 1 of 8 organ systems (skin, lung, neurologic, endocrine, kidney/liver, cardiac, gastrointestinal, eyes)
- **Part 2**
  - Specific syndromes (eg, fatigue, GvHD, secondary malignancies, infections, osteonecrosis, hyperthyroidism/hypothyroidism)
- **Part 3**
  - General health condition (ECOG performance status at last visit)
- Classification of severity according to CTCAE

Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

Overall Incidences of Comorbidities and Specific Syndromes

Incidences	Comorbidity		Evaluable per item
	N	%	N
No comorbidity	355	66	538
Comorbidities according to organ classes			
Skin	97	18	538
Lung	41	8	538
Cardiac system	70	13	538
Gastrointestinal system	30	6	537
Neurologic system	147	27	538
Kidney/liver	56	10	538
Eyes	65	12	537
Endocrine system			
Women	50	24	211
Men	55	17	327
Specific syndromes			
Infection (in past 12 months)	64	12	533
Fatigue	71	13	533
GvHD	79	15	538
Osteonecrosis	41	8	538
Secondary malignancy	21	4	538
Hypothyreodism	26	5	537
Hyperthyreodism	7	1	538

GvHD: graft-*versus*-host disease.

Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

Predictive Factors for Comorbidities

	HSCT vs CHT	Male vs Female	Aged ≤55 Yr vs >55 Yr
ECOG 0–1	<.0001		.02
Skin	<.0001	.02	
Lung	<.0001		
Cardiac	.03		.02
GI system	.02		
Neurologic	.002	.02	
Kidney/liver	<.0001		
Endocrine	.001		
Eye	<.0001		.04
Infection	.0001	.01	
Fatigue	.007		
Sec. malignancies			.03

Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

Remarks

- Incorporation of recommendations for long-term follow-up in the design of specific trials in ALL
- Multidisciplinary approach of f/u of long-term survivors
- Need for studies of long-term safety with the incorporation of immunotherapies (MoAb, CAR T) and new targeted therapies (TKI and others)
- Prophylaxis of long-term toxicity during the development of trials

Global Leukemia Academy

Current and future role of transplantation in acute leukemias in Latin America

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APTITUDE HEALTH

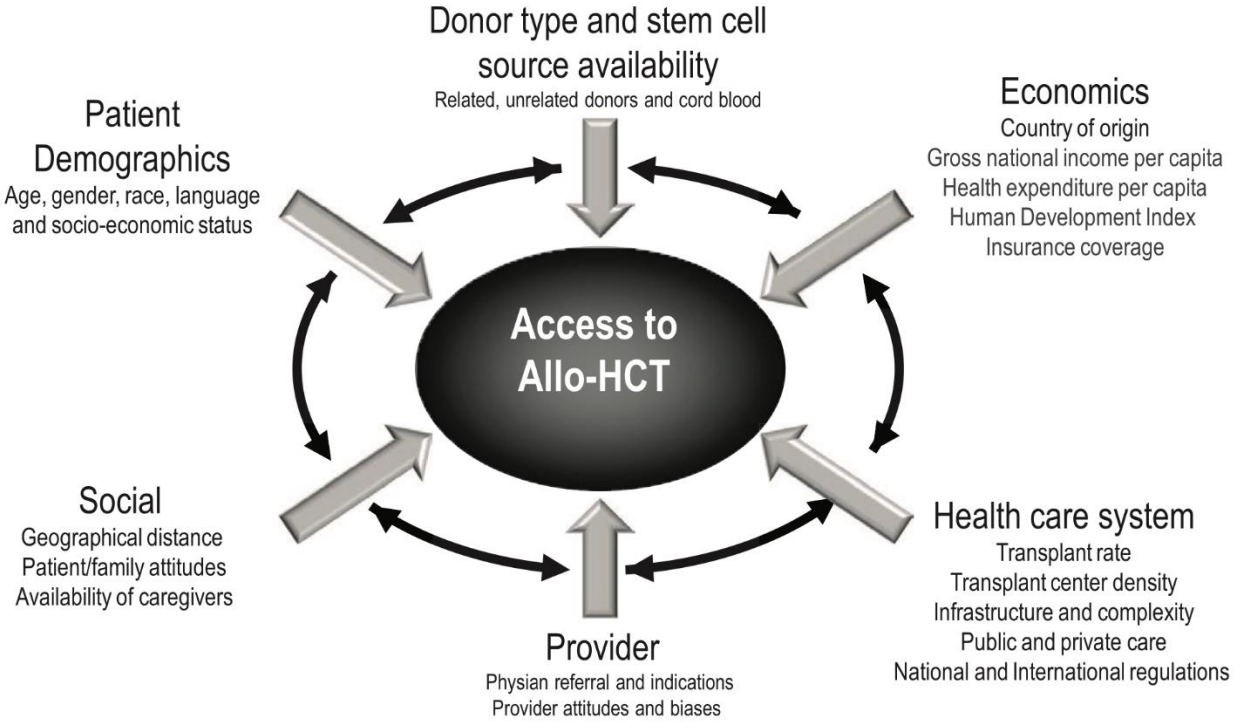
Disclosures

> Advisory: Pfizer, Amgen, Daiichi, Takeda

> Speaker: Pfizer, Amgen, Servier, Pint-Pharma

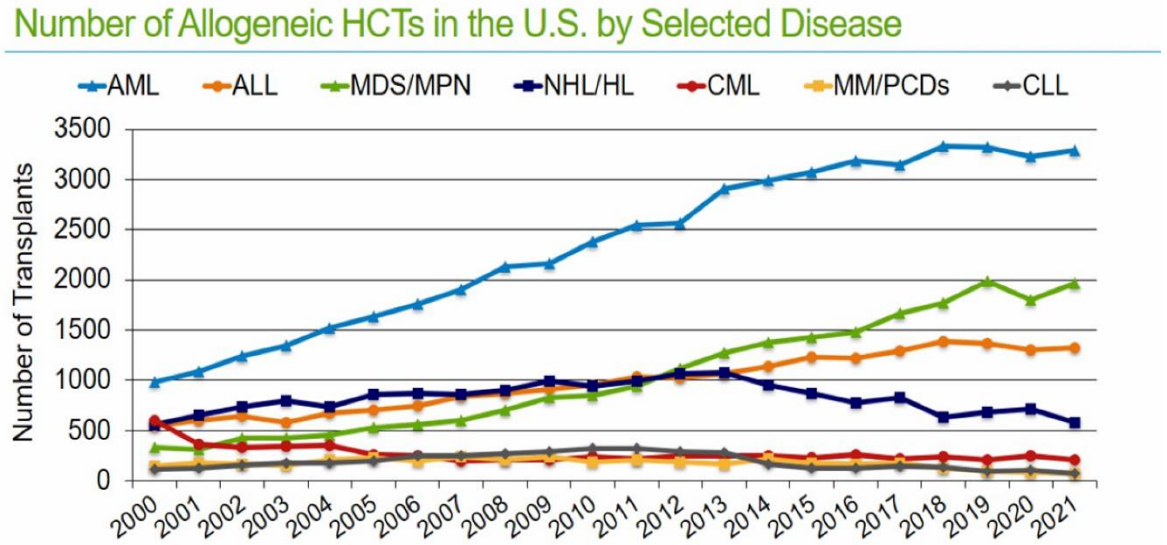
> Research funding: Servier, Libbs

Allogeneic Transplantation Worldwide



Allogeneic Transplantation Worldwide

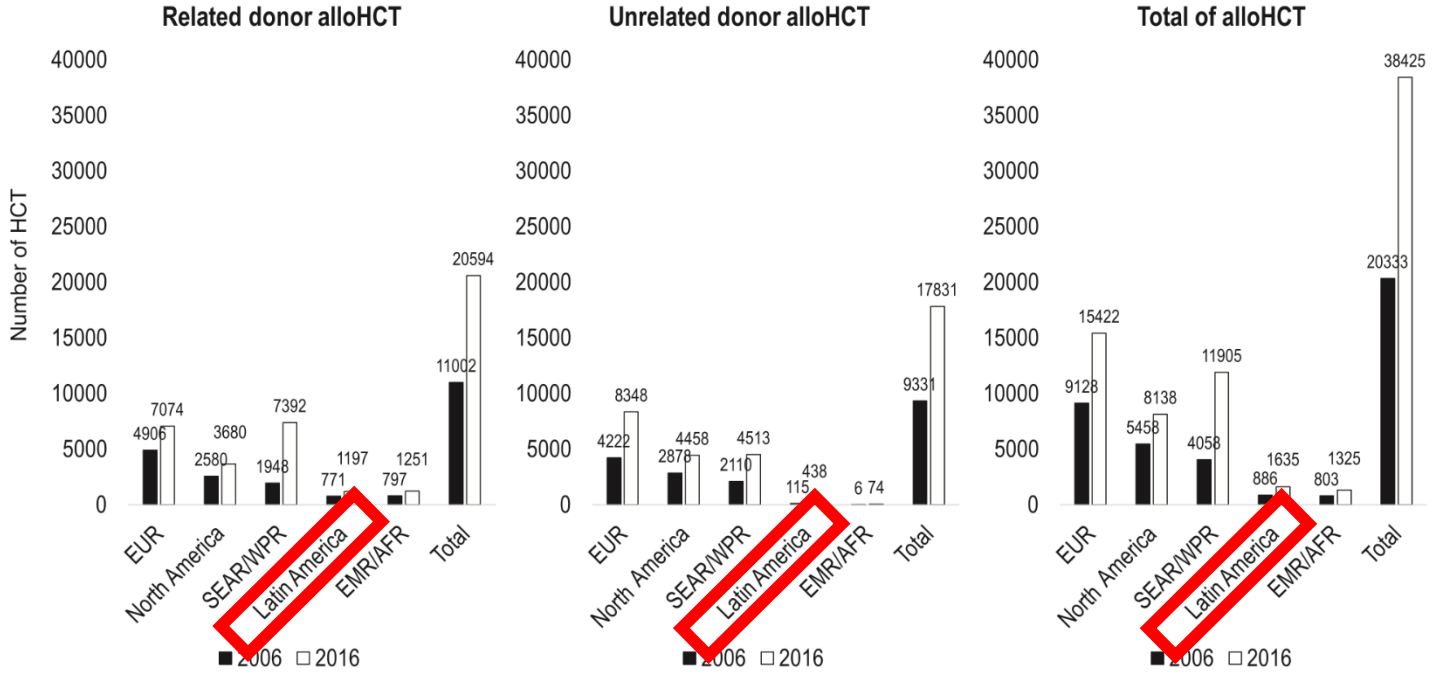
> Adult acute leukemias – increasingly used in AML with modest increase in ALL



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

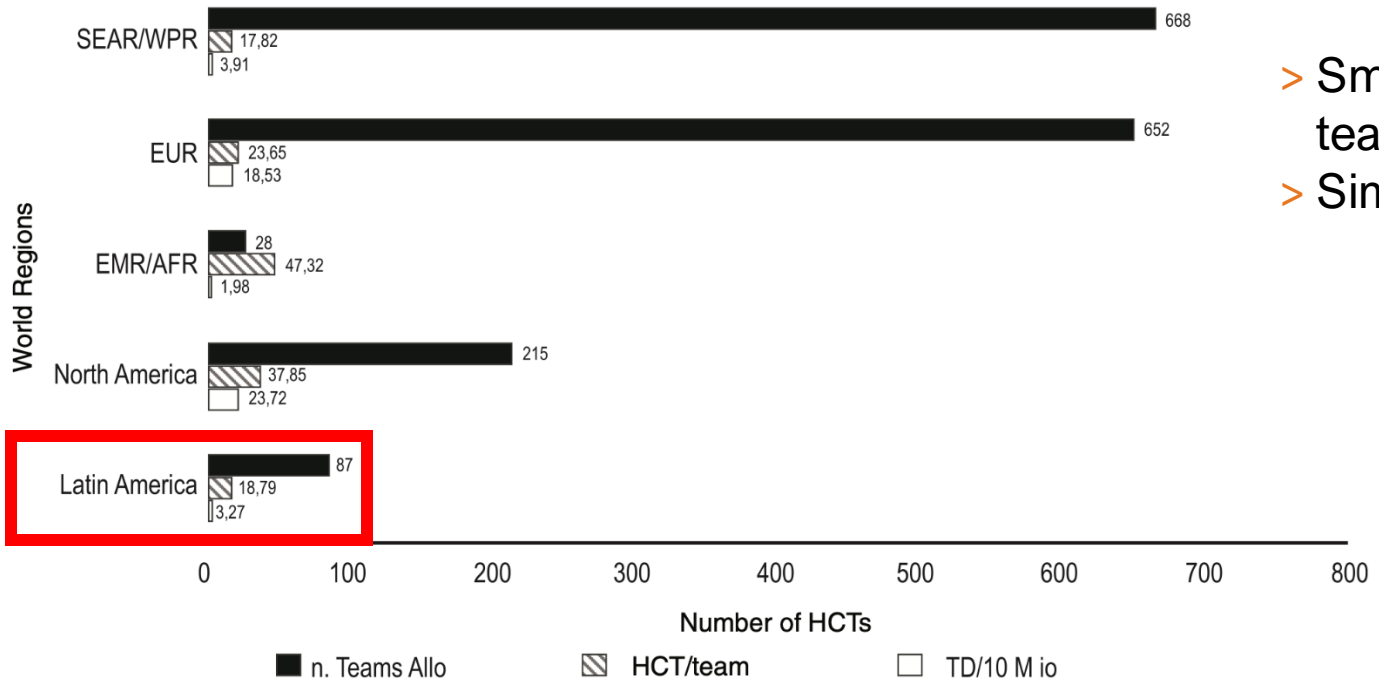
Abbreviations –
AML: Acute Myeloid Leukemia;
ALL: Acute Lymphoblastic Leukemia;
MDS: Myelodysplastic Syndromes;
MPN: Myeloproliferative Neoplasms;
NHL: Non-Hodgkin Lymphoma;
HL: Hodgkin Lymphoma;
CML: Chronic Myeloid Leukemia;
MM: Multiple Myeloma;
PCDs: Plasma Cell Disorders;
CLL: Chronic Lymphocytic Leukemia.

Allogeneic Transplantation in LATAM



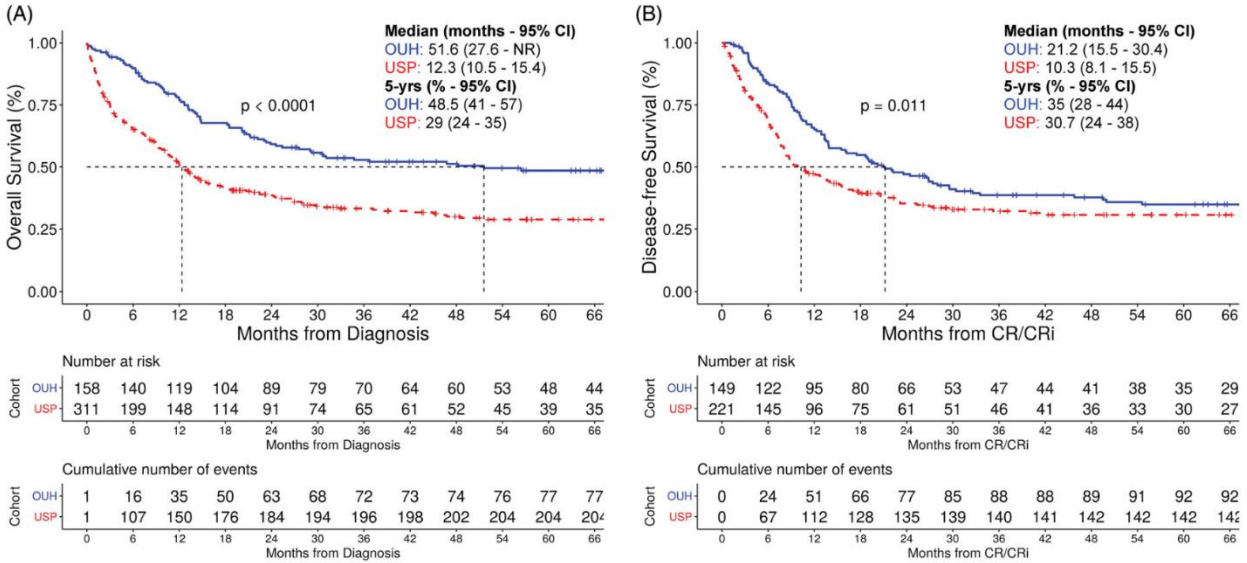
Global Leukemia Academy

Allogeneic Transplantation in LATAM



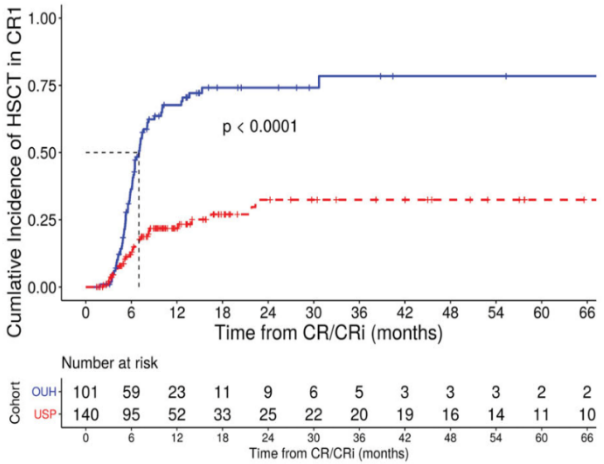
- Smaller number of allo teams per population
- Similar HCT/team rate

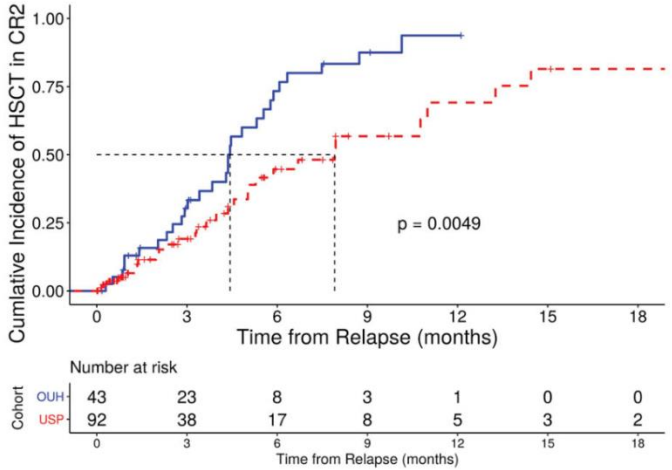
Importance of Allo-HSCT in AML



- Inferior OS and DFS between public centers in São Paulo vs Oxford

Importance of Allo-HSCT in AML



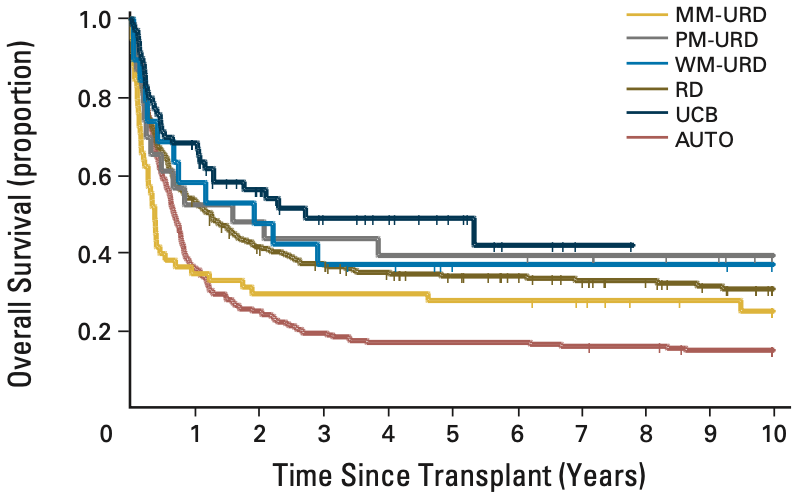


Fewer patients move from diagnosis to HSCT

- Fewer CRs with conventional chemo
- AZA + VEN is not available in public setting
- **23.8 vs 7.2** mo from diagnosis

Allo-SCT in ALL

- Strategy for **high-risk** patients with ALL in **CR1** and for patients in **CR2+**
- Donor type – similar long-term survival
- Haplo with PT-Cy has emerged as a readily available donor source



Tomblyn MB, et al. *J Clin Oncol*. 2009;27(22):3634-3641;
Basquiera AL, et al. *Bone Marrow Transplant*. 2020;55(2):400-408.

Outcomes of ALL in Brazil

Author, Year	Center	N	Regimen	SCT in CR1	Overall Survival
Fogliatto L et al, 2002	HC-UFRGS	42	GMALL 02-84	None	5 yr: 41%
Azevedo I et al, 2014	HEMOPE	41	Hyper-CVAD	Not reported	1 yr: 39%
Portugal R et al, 2015	HU – UFRJ	49	Hyper-CVAD	**4%**	5 yr: 35%
Pinheiro-Junior E et al, 2015	HCFMUSP/ICESP	102	BFM/UCLA	Not reported	4 yr: 30,5%
Silva W et al, 2018	HCFMUSP/ICESP	59	GMALL 07-03	**25%**	5 yr: 24%
Silva W et al, 2020	**Multicenter**	123 – **Ph+**	Chemo + TKI	**21%**	4 yr: 25%
Gurgel L et al, 2021	HUWC - UFC	50	CALGB8811	**30%**	5 yr: 38%
Queiroz Neto M et al, 2022	HC - UFPR	58	St Jude/CALGB 8811	**15%**	10 yr: 23%
Silva W et al, 2022	HCFMUSP/ICESP	104	BFM/Hyper-CVAD/ GRAAPH	**10%**	3 yr: 42.8%
Aguiar T et al, 2022	HEMORIO	104	BFM/Hyper-CVAD	Not reported	3 yr: 25.3%

Preliminary Conclusions – ALL in Brazil

- Allo-HSCT is available to a small subset of patients in public health
  - Low HSCT overall availability
  - More ineligible patients (social issues, more toxicity during chemotherapy, fungal infections, malnutrition)
- Lower availability of TBI
- More toxicity after allo-HSCT
- Public health – lack of monoclonal antibodies – more patients allografted with positive MRD, fewer alternatives for MRD positivity after allo

Personal communication.

Outcomes After Allo-HSCT for ALL

Author, Year	Country	N	Donor	Allo-HSCT in CR1	Overall Survival
Greil C et al, 2020	Germany	180	Related and unrelated	54%	10 yr: 33%
Yeshurun M et al, 2019	CIBMTR (USA among others)	5215	MSD, MUD, UCB	70%	5 yr: 45%
Nagler A et al, 2021	EBMT (Europe)	2304	MSD and Haplo	MSD: 83% Haplo: 67%	MSD: 2 yr 67% Haplo: 2 yr 59%
Brissot E et al, 2020	EBMT (Europe)	615	MUD, MMUD, Haplo, CB	0 (100% in CR2)	2 yr: 38%–47%
Nishiwake S et al, 2013	Japan	1726	Related, unrelated and CB	53%	CR1: 4 yr 65% CR2+: 4 yr 44% Refractory: 4 yr 18%
Basquiera AL et al, 2020	Argentina	236	MSD, MUD, Haplo	53%	2 yr: 54%
Hoon JH et al, 2020	South Korea	440	MSD, MUD, MMUD, CB	100%	5 yr: 57%–65%

ALL HSCT Registry

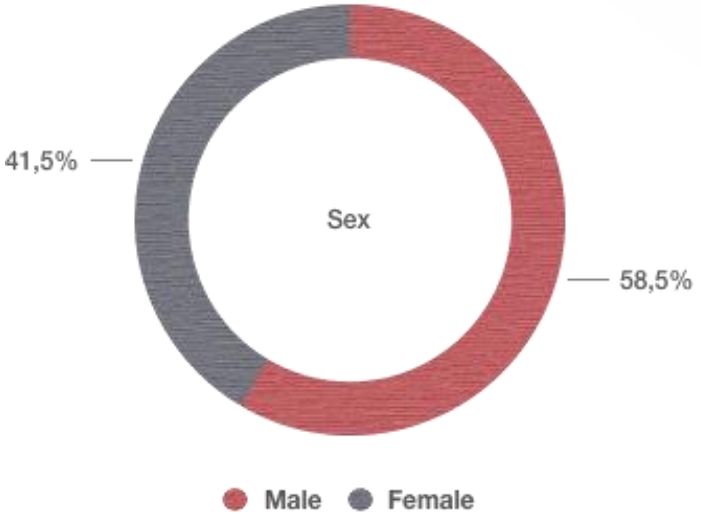
- Retrospective study – 5 centers (HC-FMUSP; HAC-Jaú; HIA; HA; HSL)
- Patients aged ≥16 years in their **first allo-HSCT** for ALL or ambiguous lineage leukemia
- Jan 2007–Dec 2017

Silva WF, et al. *Transplant Cell Ther*. 2022;28(11):763.e1-763.e7.

Patient and Disease Characteristics

N = 275

Median age 31 years (range, 16–65)



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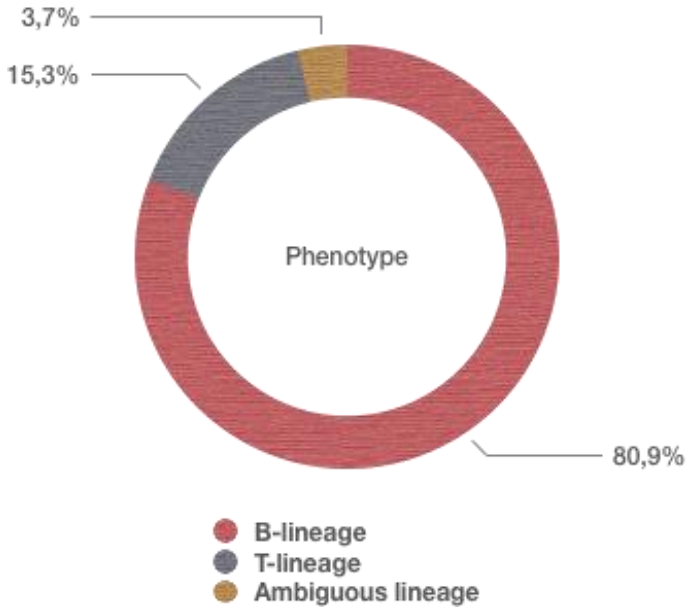
Silva WF, et al. *Transplant Cell Ther*. 2022;28(11):763.e1-763.e7.

Patient and Disease Characteristics

Initial WBC ($\times 10^9$/L) – median (IQR)
9.4 (2.4–50.9)



- Ph-positive ALL: 35%
- *BCR-ABL1* transcript p190: 60%
- Normal karyotype: 52.4%

*Missing: 69.8%.

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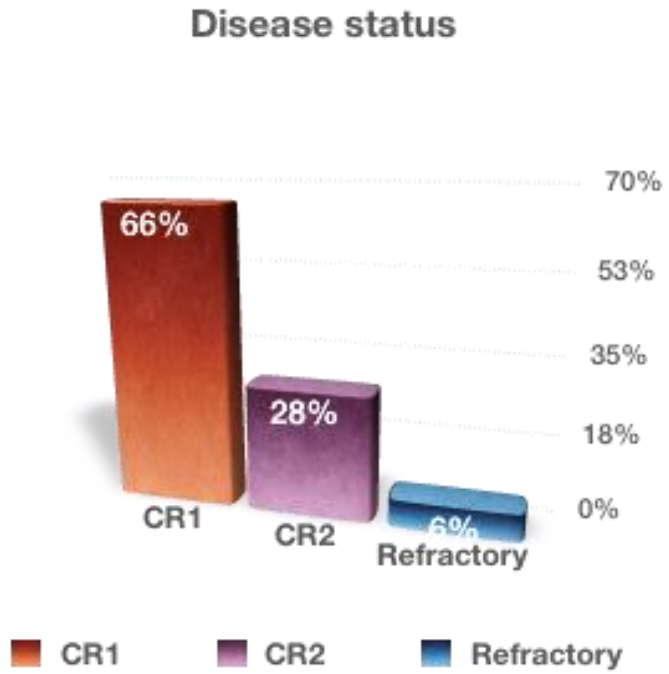
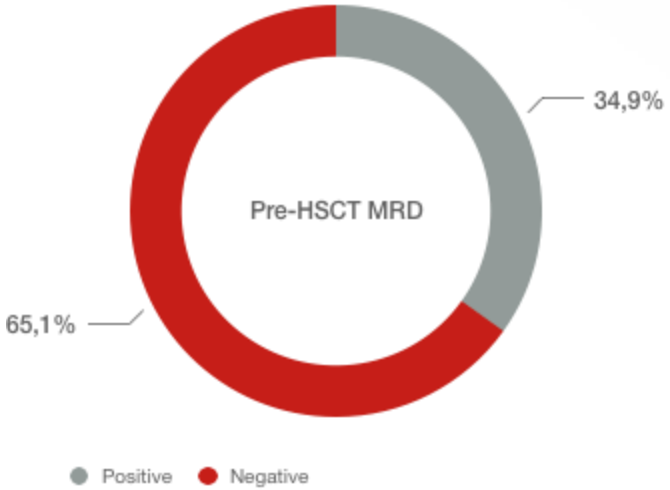
Patient and Disease Characteristics





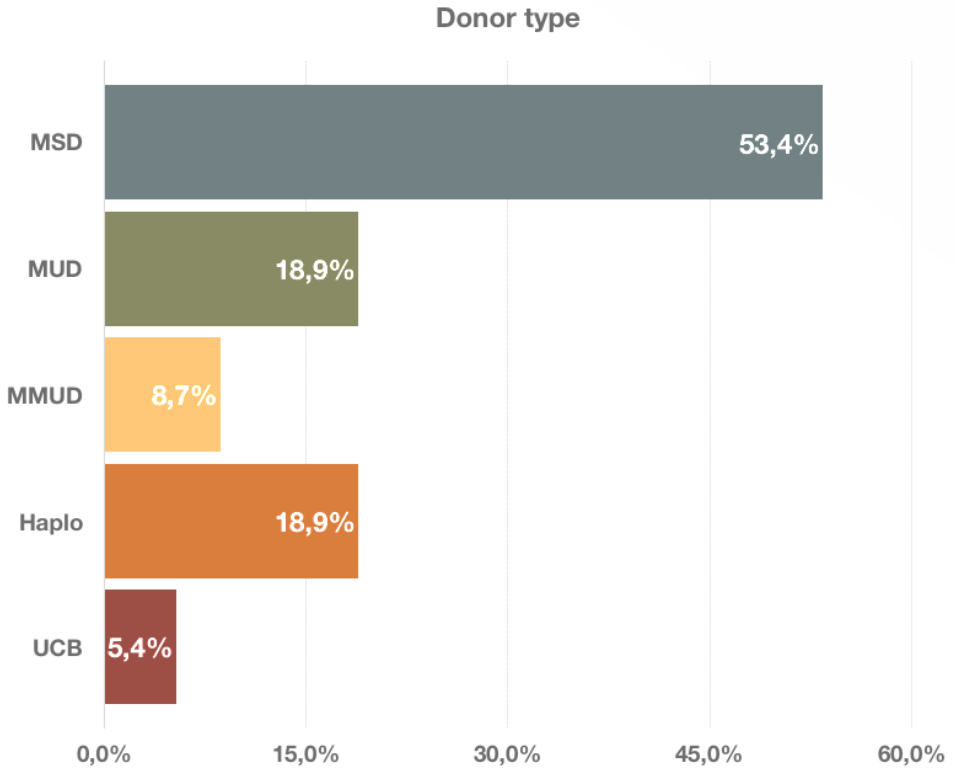
*Missing: 24%.

Silva WF, et al. *Transplant Cell Ther*. 2022;28(11):763.e1-763.e7.

Donor and Transplant Characteristics

- Donor age: 31 years (median)
- Median time to HSCT in CR1: 7.8 months

- Male: 54.1%
- ABO isogroup: 63.6%
- CMV (+/+): 75.3%



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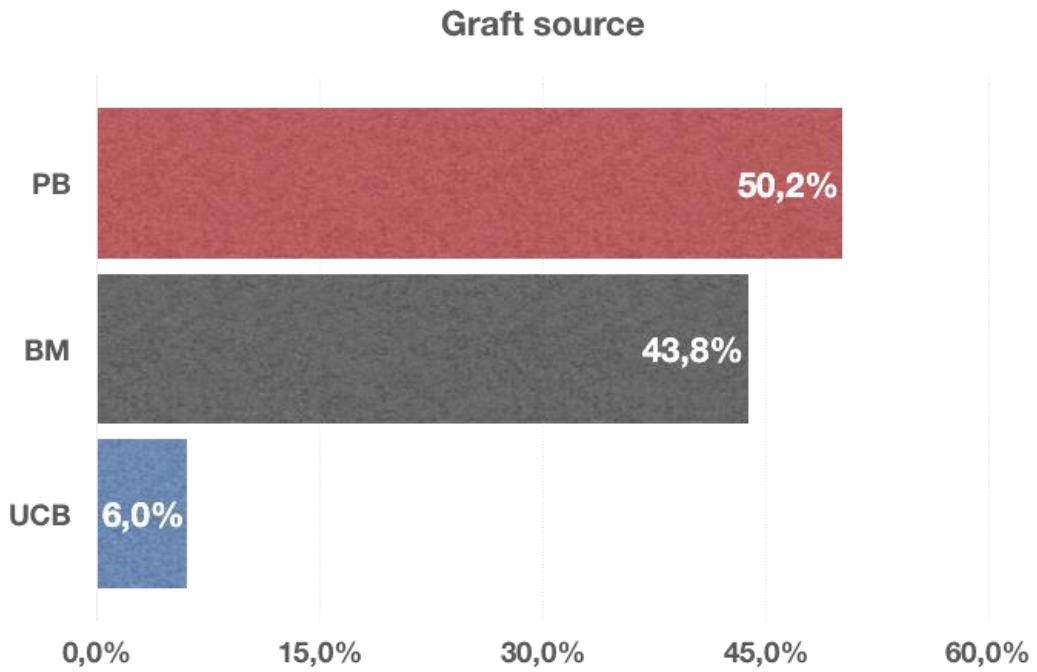
Donor and Transplant Characteristics



No. of infused CD34+ cells ($\times 10^6$/kg) – mean (range)	5.9 (0.15–36)

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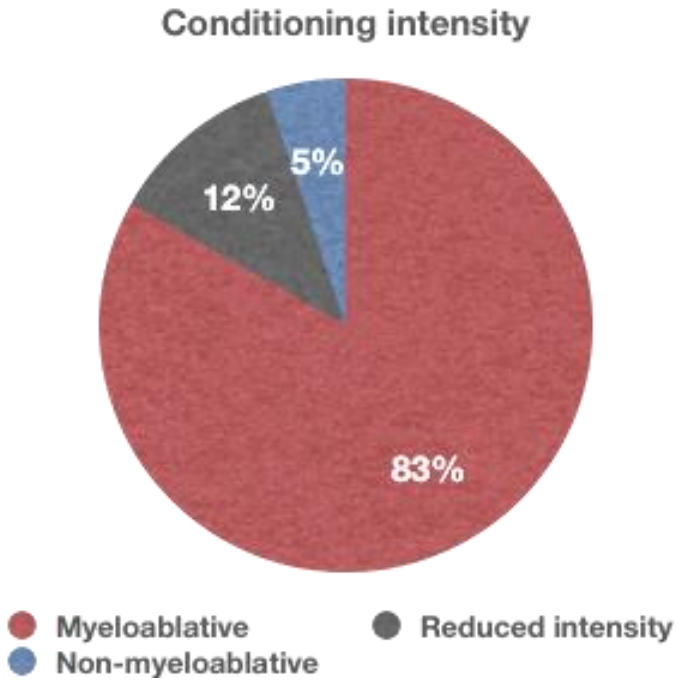
Silva WF, et al. *Transplant Cell Ther*. 2022;28(11):763.e1-763.e7.

Transplant Procedure Characteristics



MAC regimen – n (%)	TBI-based: 150 (67) Bu-based: 73 (33)
RIC regimen – n (%)	TBI-based: 38 (79) Bu-based: 7 (15) Mel-based: 3 (6)

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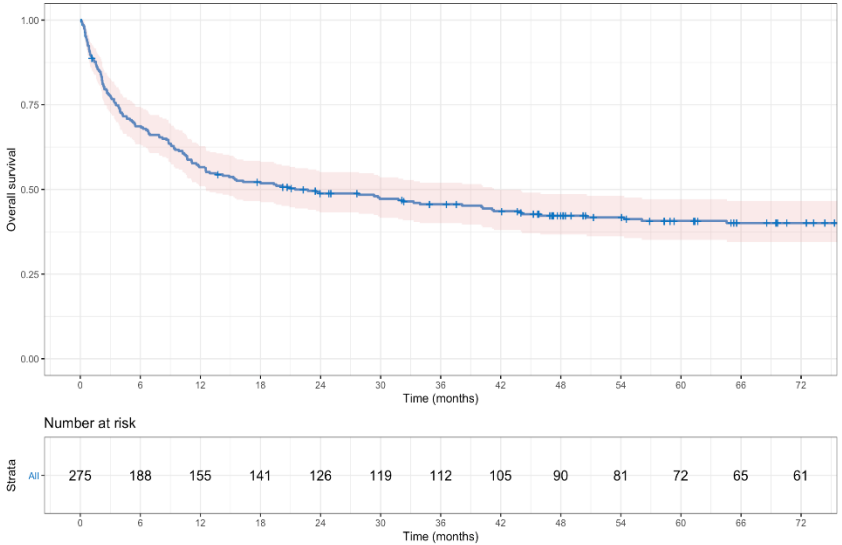
Primary Endpoint

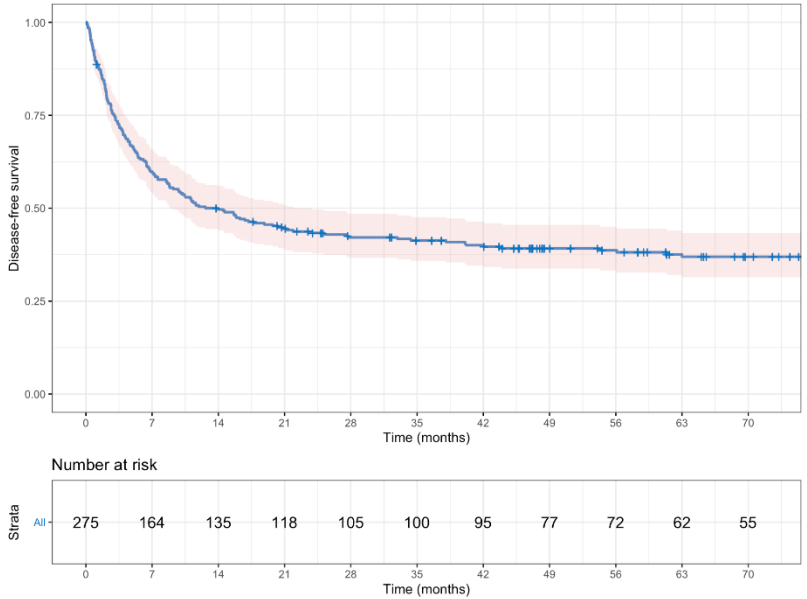
Median follow-up: 6.4 years

Overall survival (OS)



OS: median 21.5 months (95% CI 12.5–41.3)
5-yr OS: 40.7% (95% CI 35.1–47.1)
Death before D+100: 24.4%

Disease-free survival (DFS)



DFS: 11.9 months (95% CI 8.8–21.9)
5-yr DFS: 37.8% (95% CI 32.3–44.1)

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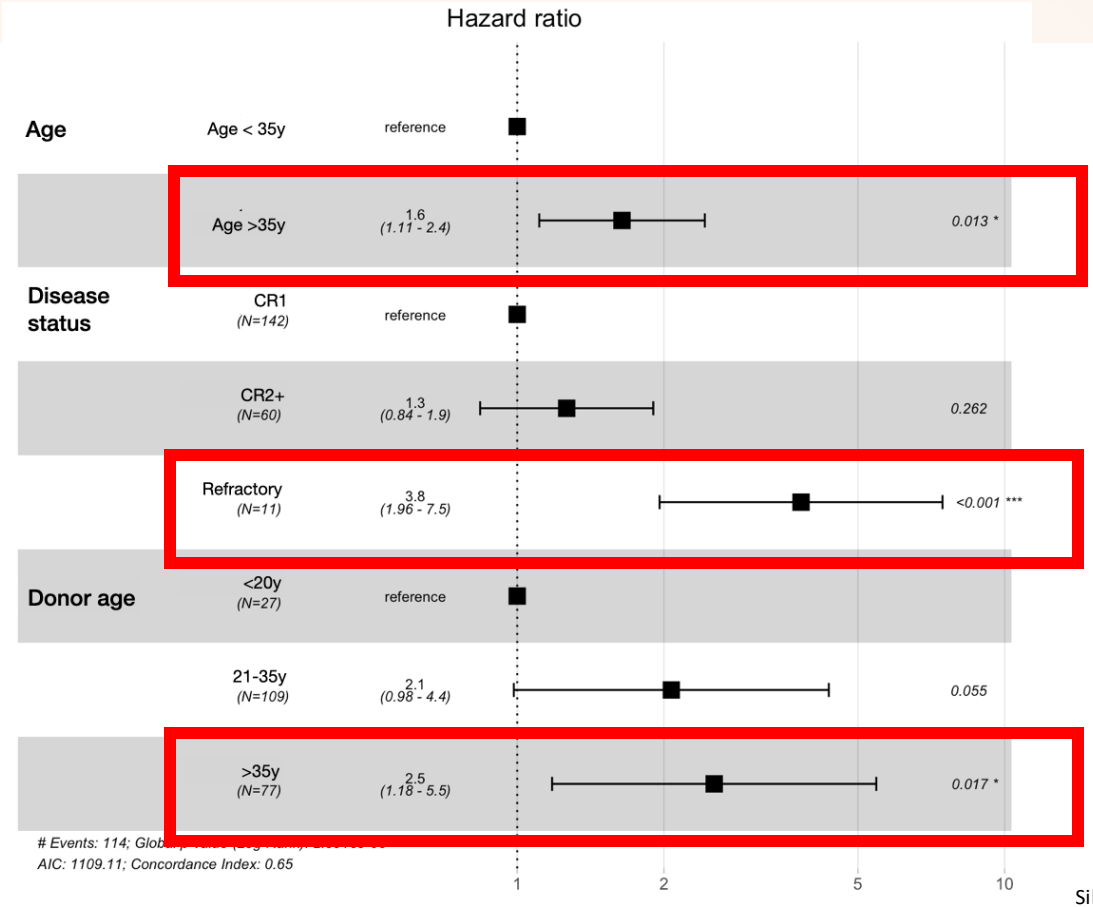
Multivariable Model for OS



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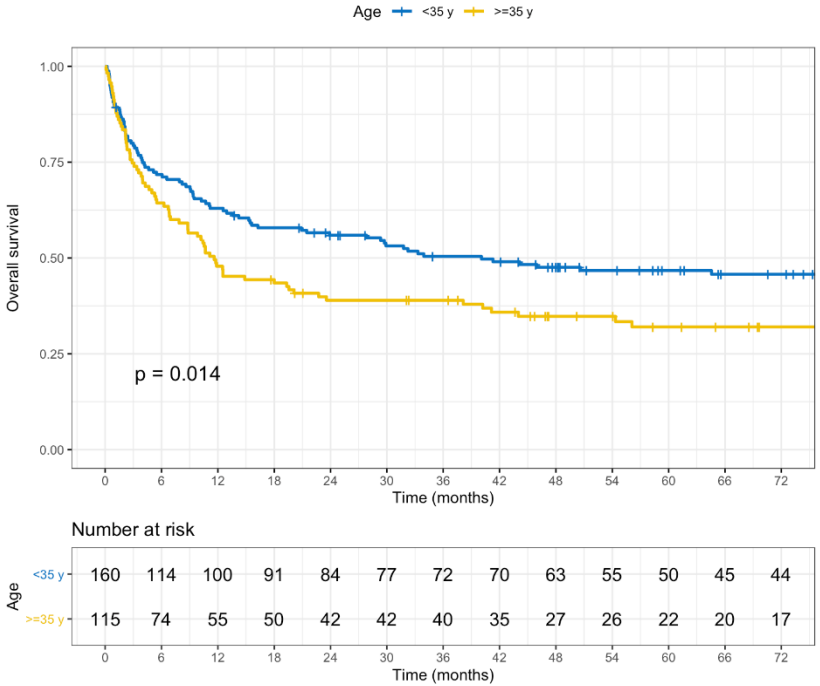
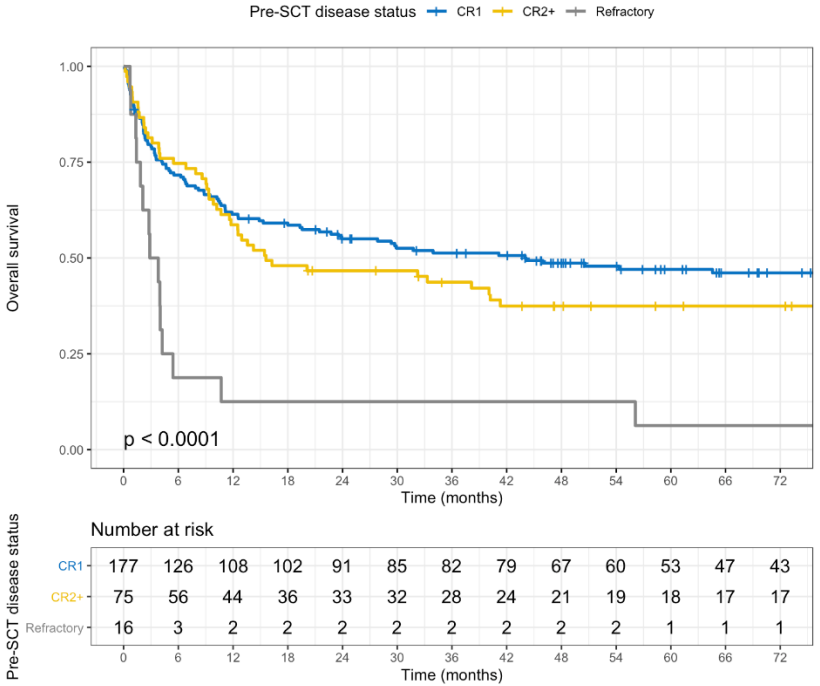
OS Curves





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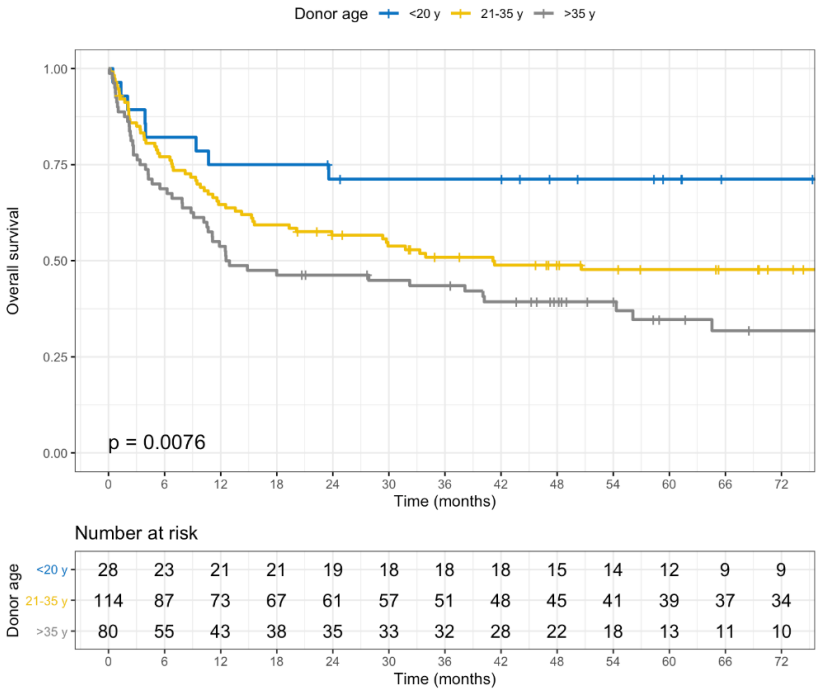
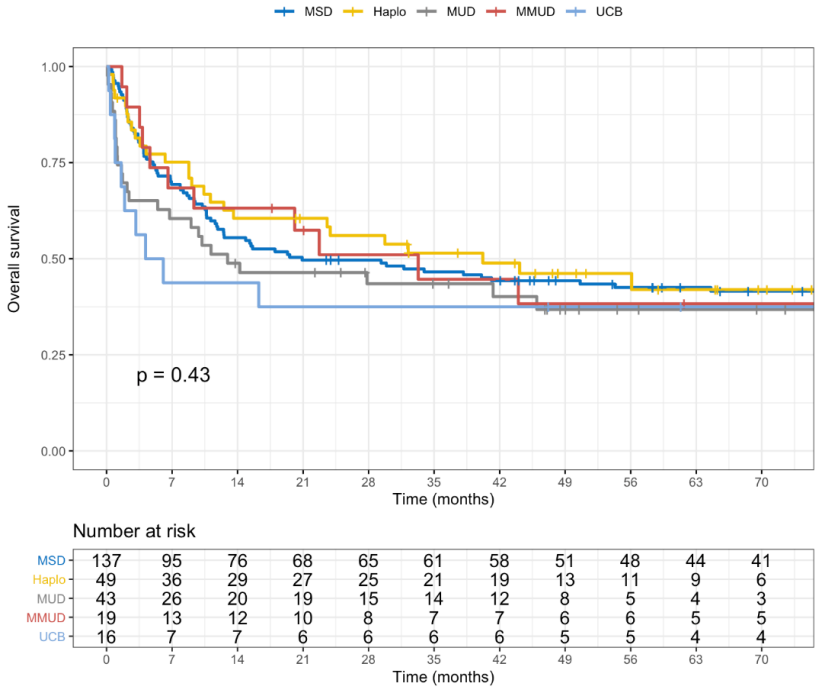
OS Curves





GVHD (only OS): HR 4.2, *P* <.001

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Multivariable Model for DFS

Table 2. Final multivariable model for DFS

Disease-free survival (DFS)	Age:		
	< 35 years	reference	
	≥ 35 years	**1.71 (1.17-2.50)**	**0.01**
	Disease status:		
	CR1	reference	
	CR2+	1.270 (0.85-1.89)	0.24
	Refractory	**4.46 (2.35-8.48)**	**< 0.001**
	Donor age:		
	< 20 years	reference	
	21-35 years	1.91 (0.98-3.74)	0.06
	> 35 years	**2.02 (1.01-4.06)**	**0.05**

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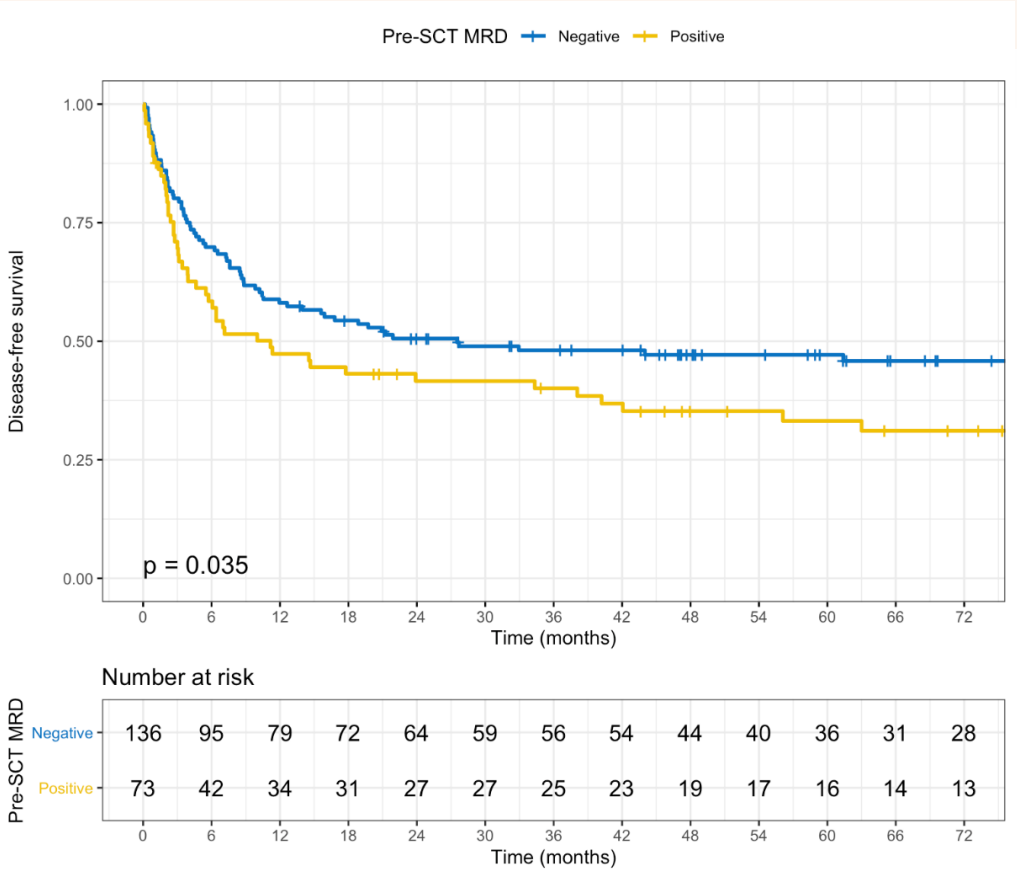
Impact of MRD on DFS



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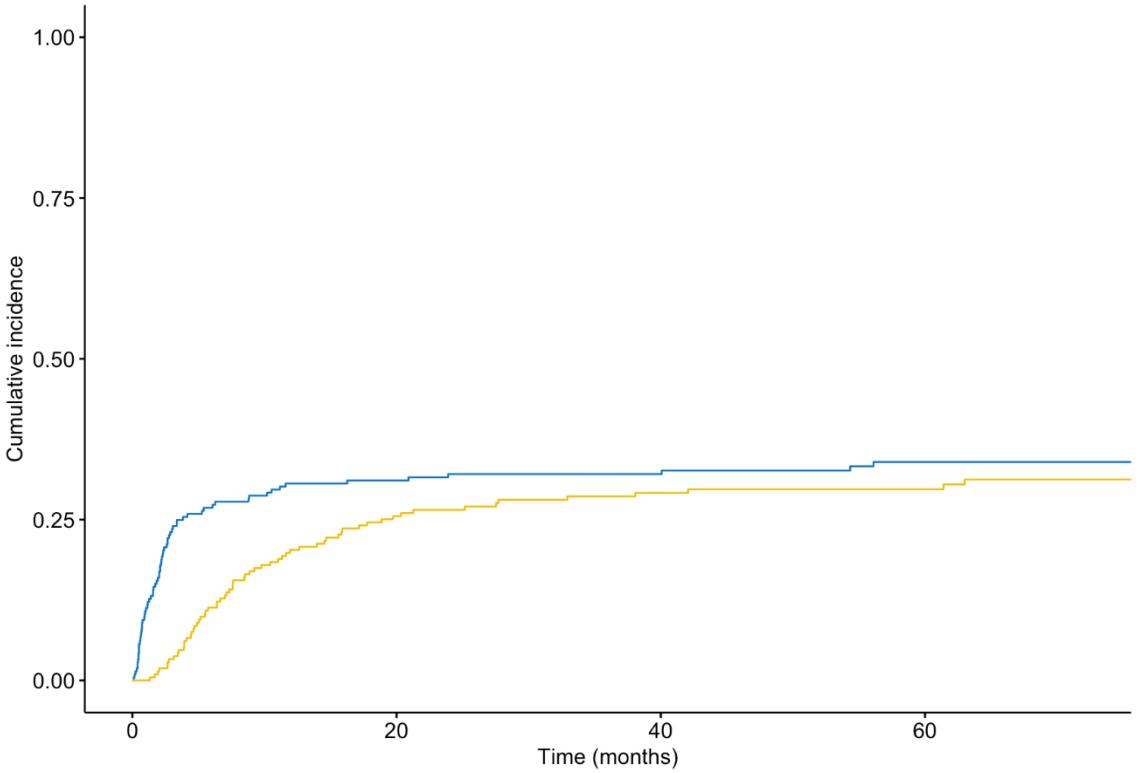
Relapse and NRM



Non-relapse mortality (NRM)[*†]

5 yr: 34.1% (95% CI 28.4–39.8)

*Relapse as competitor.

[†]NRM incidence was 22.6% at D+100.

Cumulative incidence of relapse (CIR)[‡]

5 yr: 28.1% (95% CI 22.9–33.6)

[‡]Death as competitor.

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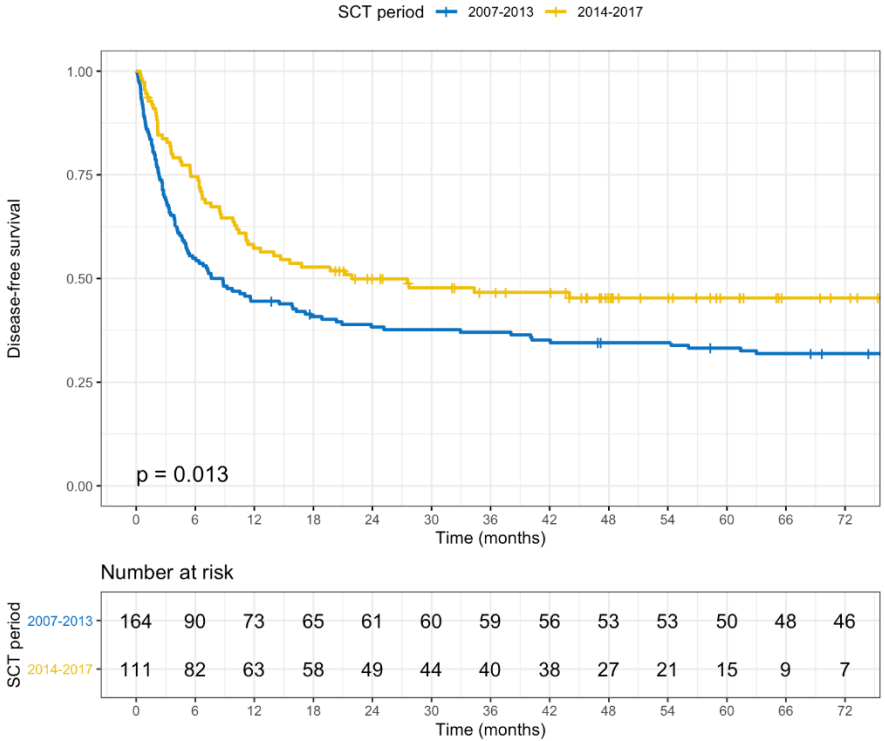
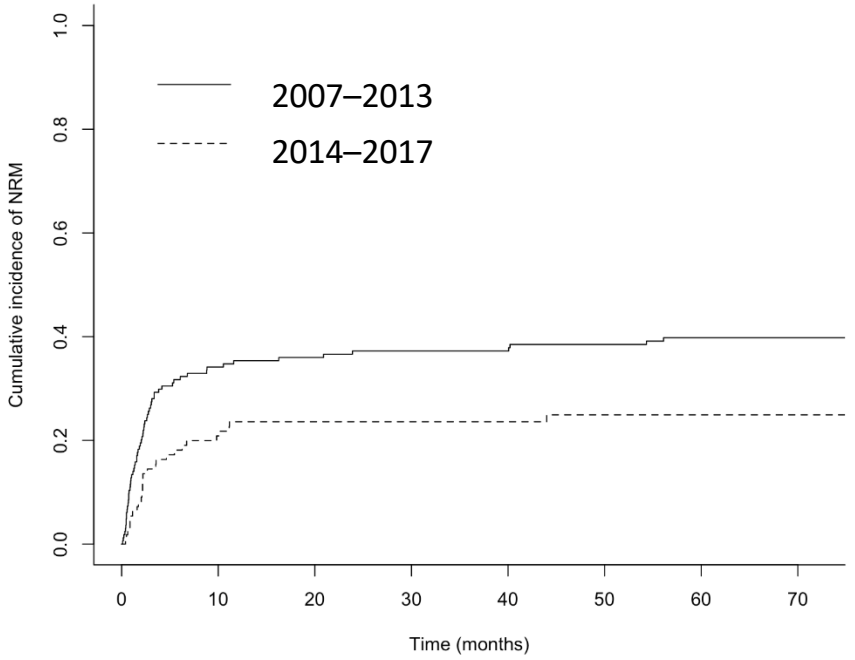
DFS and NRM According to Period





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Multivariable Model for Relapse

Table 3. Final multivariable model for CIR

Cumulative incidence of relapse (CIR)	**CNS disease**	**2.19 (1.08-4.45)**	**0.03**
	Donor type:		
	MSD	reference	
	Haplo	**0.43 (0.21-0.88)**	**0.02**
	MUD	0.51 (0.21-1.27)	0.15
	MMUD	0.47 (0.16-1.35)	0.16
	HSC source:		
	BM	reference	
	PBSC	**0.51 (0.30-0.86)**	**0.01**
	Disease status:		
	CR1	Reference	
	CR2+	**1.76 (1.02-3.05)**	**0.04**
	Refractory	**7.92 (3.25-19.26)**	**<0.001**

*Excluded UCB from analysis.

Silva WF, et al. *Transplant Cell Ther*. 2022;28(11):763.e1-763.e7.

Model for NRM

Table 4. Final multivariable model for NMR

Non-relapse mortality (NMR)	**Age**	**1.04 (1.01-1.06)**	**0.001**
	Disease status:		
	CR1	reference	
	CR2+	1.02 (0.54-1.94)	0.95
	Refractory	**4.24 (1.54-11.66)**	**0.01**
	Donor type:		
	MSD	reference	
	Haplo	1.11 (0.52-2.36)	0.79
	MUD	**3.79 (1.97-7.26)**	**< 0.001**
	MMUD	0.69 (0.16-3.02)	0.63
	UCB	1.88 (0.21-17.21)	0.58
	Donor age	1.02 (0.99-1.05)	0.07

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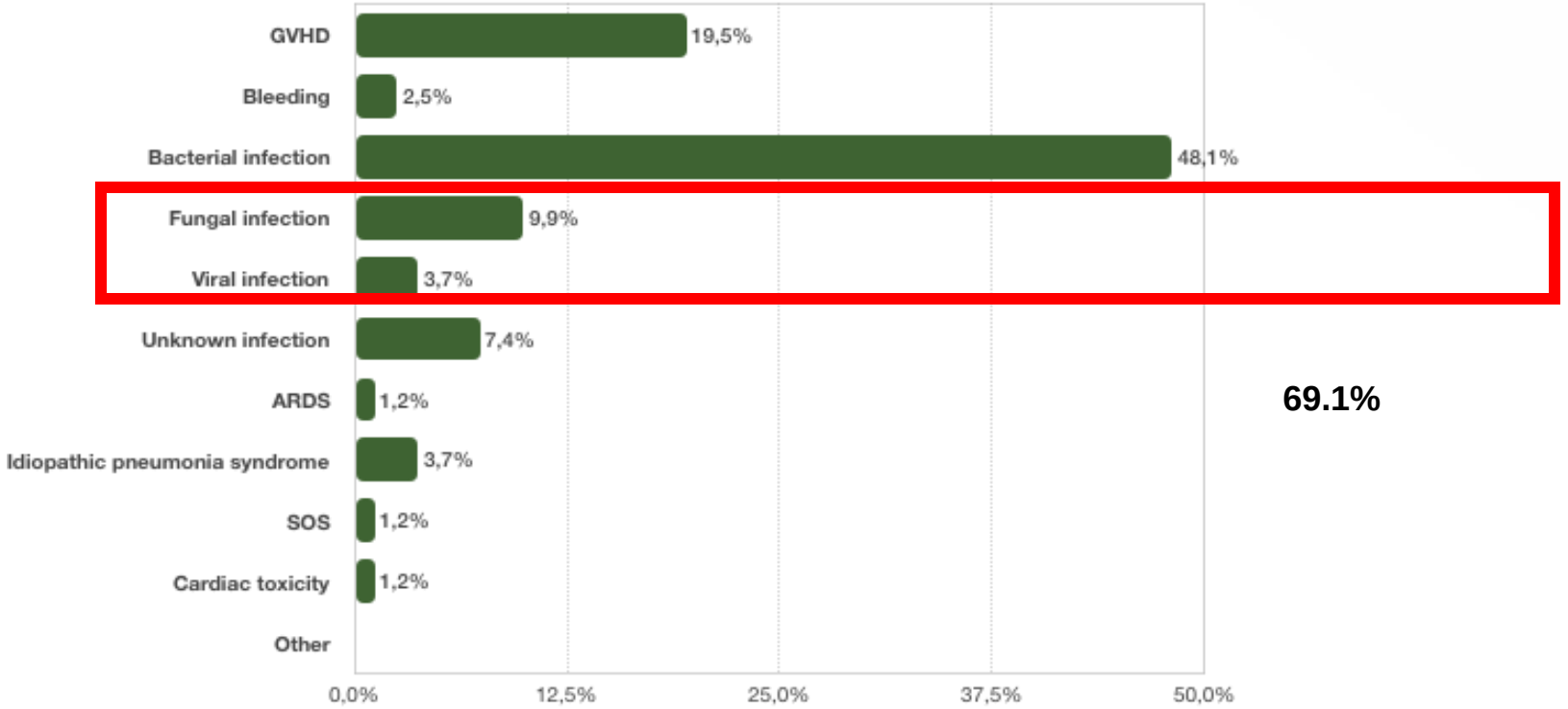
Causes of Death



69.1%

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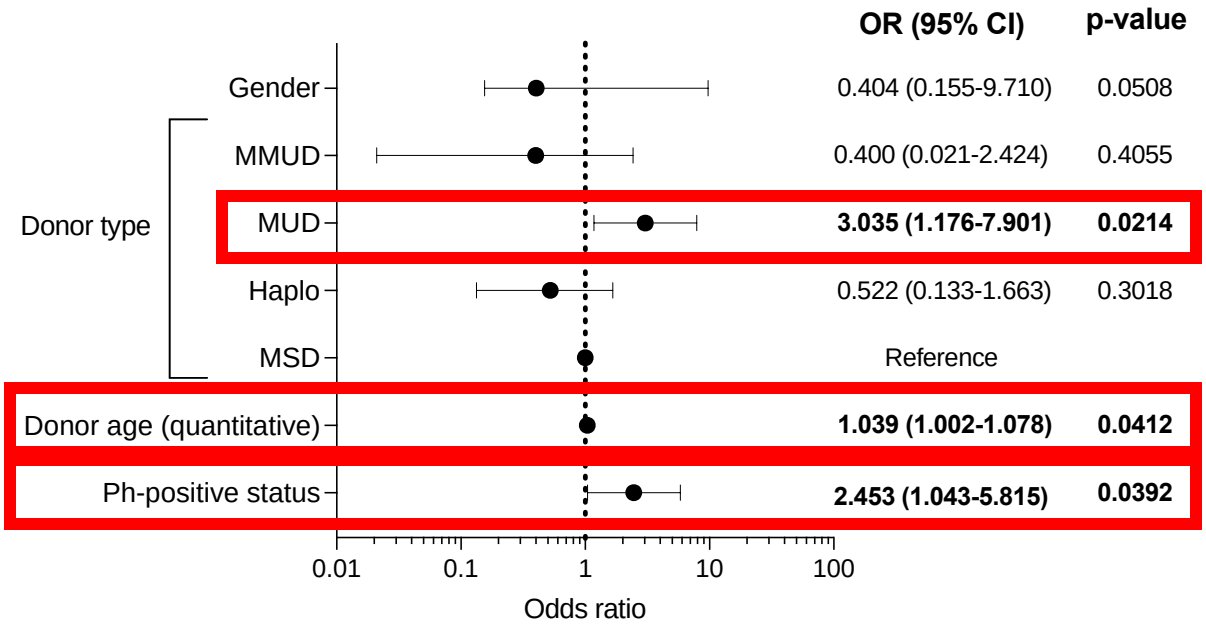
Early Mortality After Allo-HSCT

> EM (before D100): 24.4%



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Cysne D, et al. ASH 2023 (upcoming).

Author	Center/Time	N	CR1	OS	DFS	CIR	NRM	GVHD
Greil et al, 2020	Germany 1995–2018	180	54%	37.6% (5 yr)	34.5% (5 yr)	40% (5 yr)	25.5% (5 yr)	-
Basquiera et al, 2019	Argentina 2008–2017	236	53%	54% (2 yr)	47.6% (2 yr)	29% (2 yr)	24% (2 yr)	A: III–IV: 17%–30% C: 35%–27%
Yeshurun et al, 2018	CIBMTR (CR1, CR2) 2000–2014	5215	70%	45% (5 yr)	40% (5 yr)	32% (5 yr)	29% (5 yr)	A: I–II: 42% III–IV: 23% C: 29%
Yoon et al, 2020	Korea 2005–2015	440	100%	57.2%–65.1% (5 yr)	49.2%–63.1% (5 yr)	7.2%–31.1% (5 yr)	10.9%–29.6% (5 yr)	A: II–IV: 33.1%– 76.9% III–IV: 3.8%–21% C: 14%–72.7%
Present study	**Brazil 2007–2017**	**275**	**66%**	**40.7% (5 yr)**	**37.8% (5 yr)**	**28.1% (5 yr)**	**34.1% (5 yr)**	**A II–IV + C: 58.2%**

Insights

- While OS and DFS were similar to published data, NRM was higher
- There was no impact of the donor type or graft source on survival, whereas haploidentical HSCT was associated with lower CIR (younger haplo >> older MUD?)
- MUD was associated with higher NRM and GVHD rates
- Better selection of patients, use of pediatric protocols, and monoclonal Ab

Limitations

- Retrospective analysis
- Heterogeneity of data
- Prior decade (no monoclonal Ab)

Silva WF, et al. *Transplant Cell Ther*. 2022;28(11):763.e1-763.e7.

Thanks!

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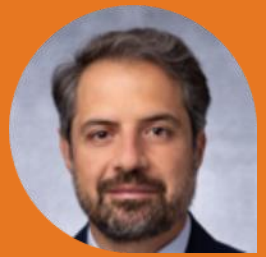
Panel discussion: How treatment in first line influences further therapy approaches in ALL and AML

Elias Jabbour, Naval Daver, and all faculty



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Interactive discussion

How treatment in first line influences further approaches in ALL and AML

1. Will CAR T and bispecifics change the landscape?
2. Role of HSCT (revisited) – is it still confirmed?
3. What does the future look like?

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

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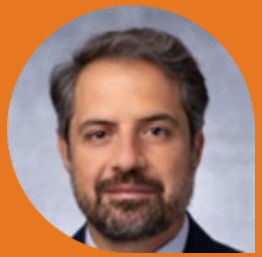
ARS questions

Elias Jabbour



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Question 3 [REPEATED]

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. CAR T approaches are active beyond second line in Ph– ALL

Question 4 [REPEATED]

The prognosis of R/R AML patients depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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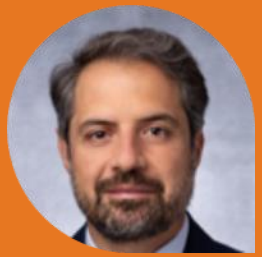
Session close

Elias Jabbour



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Thank you!

- Thank you to our sponsors, expert presenters, and to you for your participation
- Please complete the **evaluation** 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!

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