Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

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

June 19–20, 2024 – Latin America

Meeting sponsors AMGEN rigel

APTITUDE HEALTH®

Global Leukemia Academy

Welcome to Day 2

Naval Daver

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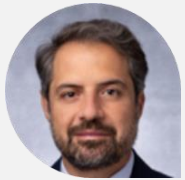
Meet the Faculty

CO-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

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

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

Fabio Santos, MD, PhD
Hospital Israelita Albert Einstein, 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 as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring acute leukemias
- Gain insights into antibodies and bispecifics in ALL: What are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies in acute leukemias
- Review promising novel and emerging therapies in acute leukemias
- Explore regional challenges in the treatment of acute leukemias across LATAM

Day 2: Virtual Plenary Sessions

Thursday, June 20, 2024
5.00 PM – 8.00 PM UTC -5 (Houston)
7.00 PM – 10.00 PM UTC -3 (Brasilia/Buenos Aires)

Time (UTC -3)	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	Long-term safety considerations for leukemias (focus on ALL)	Jae Park
7.50 PM – 8.10 PM	Current and future role of transplantation in acute leukemias in LATAM	Phillip Scheinberg
8.10 PM – 8.20 PM	Break	
8.20 PM – 8.40 PM	Current treatment options for relapsed AML in adult and elderly patients	Fabio Santos
8.40 PM – 9.10 PM	AML case-based panel discussion • Case AML: young high-risk (8 min + 5-min discussion) • Case AML: elderly (10 min) (8 min + 5-min discussion)	Fabio Santos (moderator) • Luana Nóbrega da Costa, MD • Carolina Perrone, MD Panelists: All faculty
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	Naval Daver and all faculty
9.50 PM – 10.00 PM	Session close	Naval Daver

Question 1

What age group is considered elderly for patients with AML?

A. ≥50 years
B. ≥55 years
C. ≥60 years
D. ≥65 years
E. ≥70 years

Question 2

How do you assess 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 + chemotherapy is active in both front line and salvage for ALL

B. Kinase inhibitors can be combined with other therapy modalities in Ph-positive ALL

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

D. There are no effective consolidation treatments for patients who remain MRD positive after induction therapy

Question 4

The prognosis of patients with R/R AML 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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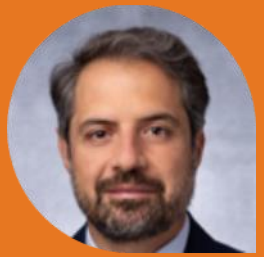
Current treatment options for relapsed ALL in adult and elderly patients

Elias Jabbour



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Adults With R/R Acute Lymphocytic Leukemia in 2024: Immunotherapies and Sequencing of CD19-Targeted Therapies

Elias Jabbour, MD

Department of Leukemia

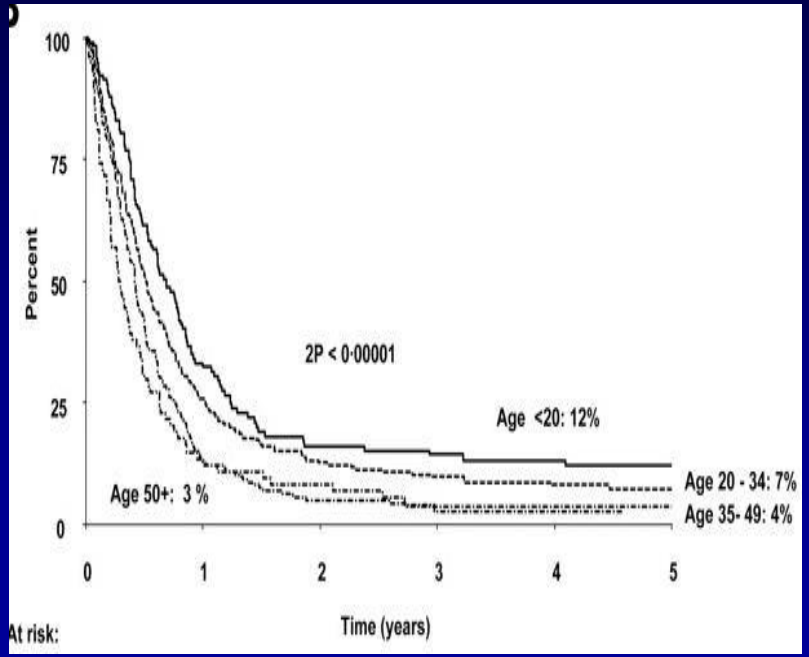
The University of Texas MD Anderson Cancer Center, Houston, USA

Summer 2024

ALL – Historical Survival Rates After First Relapse

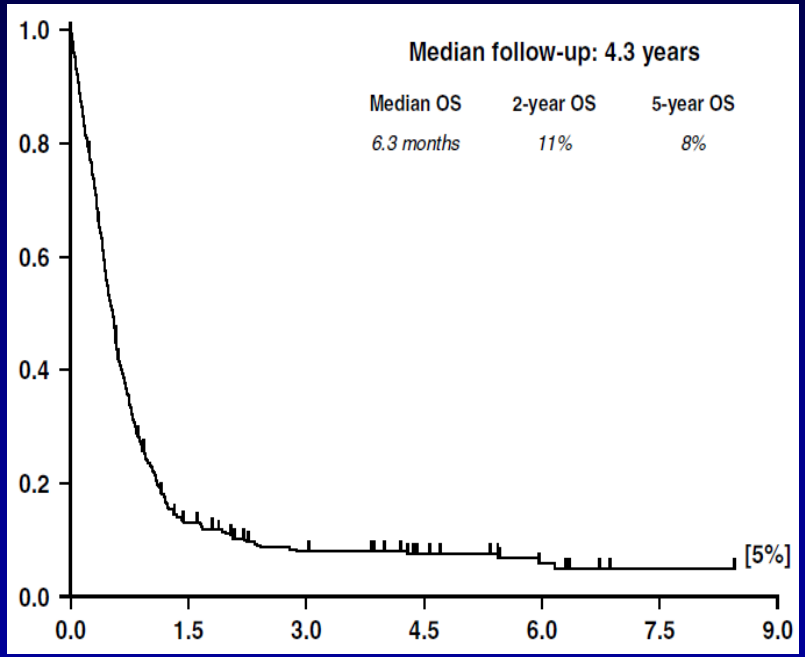
MRC UKALL2/ ECOG2993 Study (n = 609)[1]

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



LALA-94 Study (n = 421)[2]

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



1. Fielding AK, et al. *Blood*. 2007;109:944-950; 2. Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

Historical Results in R/R ALL

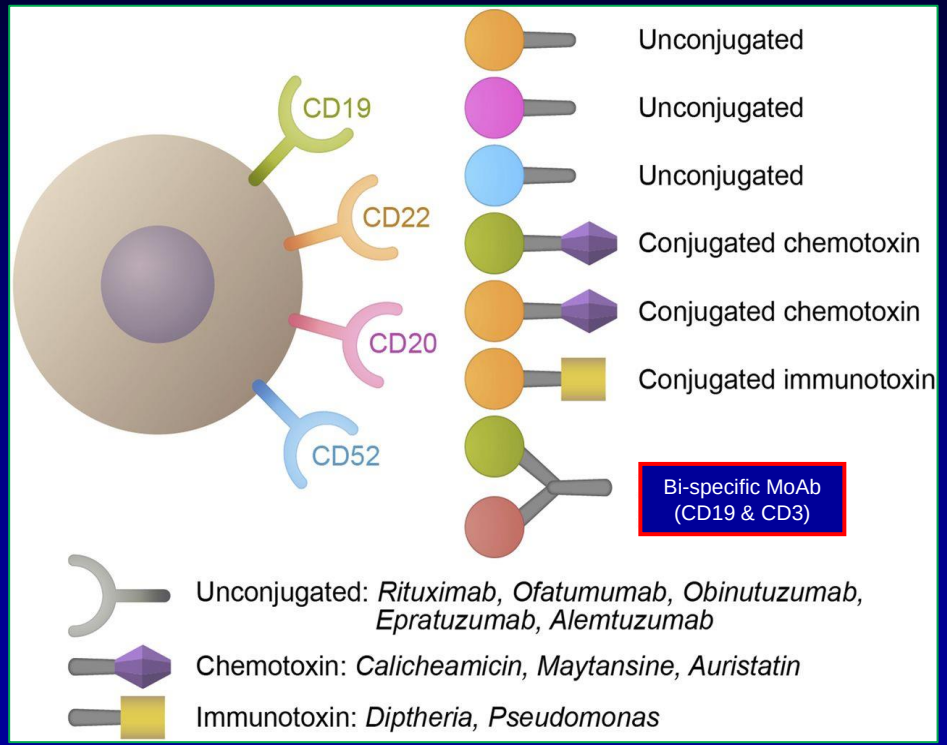
- Poor prognosis in R/R ALL Tx with standard of care (SOC) chemotherapy

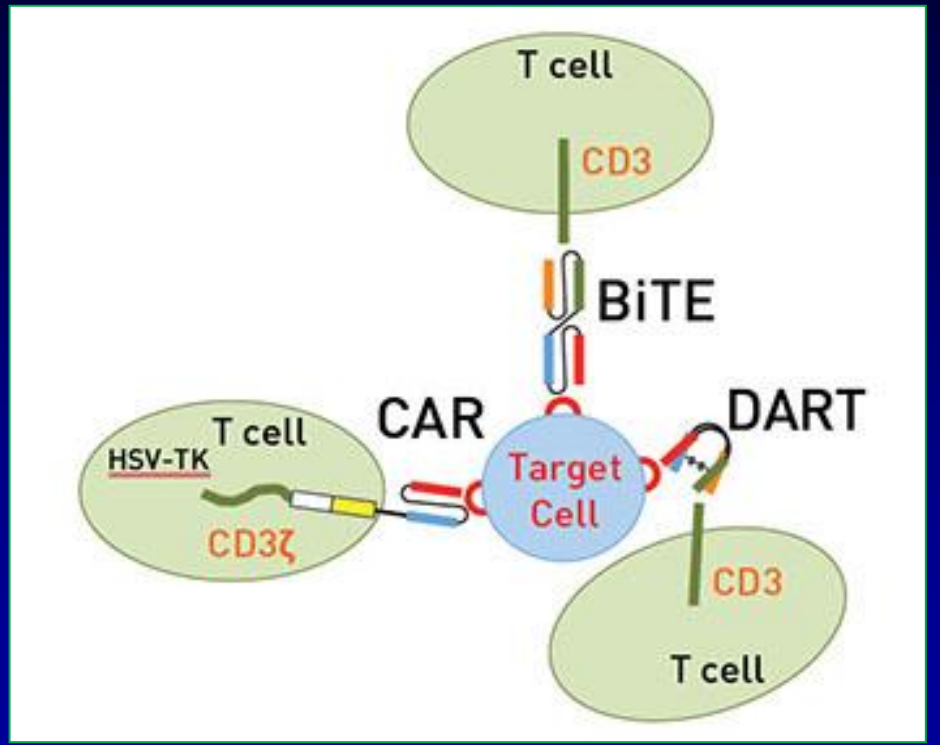
Rate (95% CI)	No Prior Salvage (S1)	One Prior Salvage (S2)	≥2 Prior Salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.7	3.4	2.9

Gökbuget N, et al. *Haematologica.* 2016;101:1524-1533.

Immuno-Oncology in ALL

- **Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR T cells**



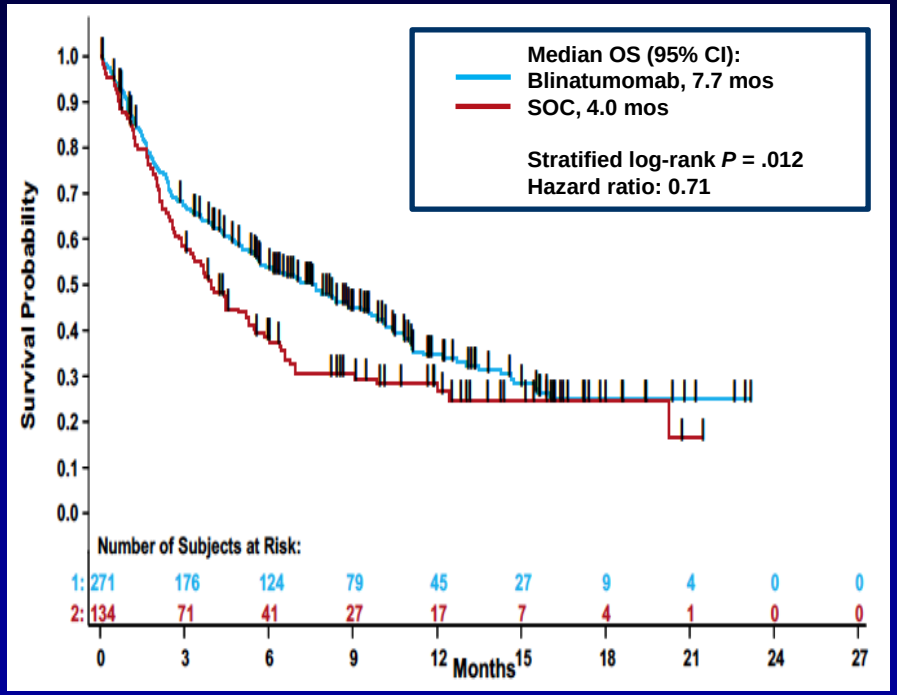


Jabbour E, et al. *Blood.* 2015;125:4010-4016.

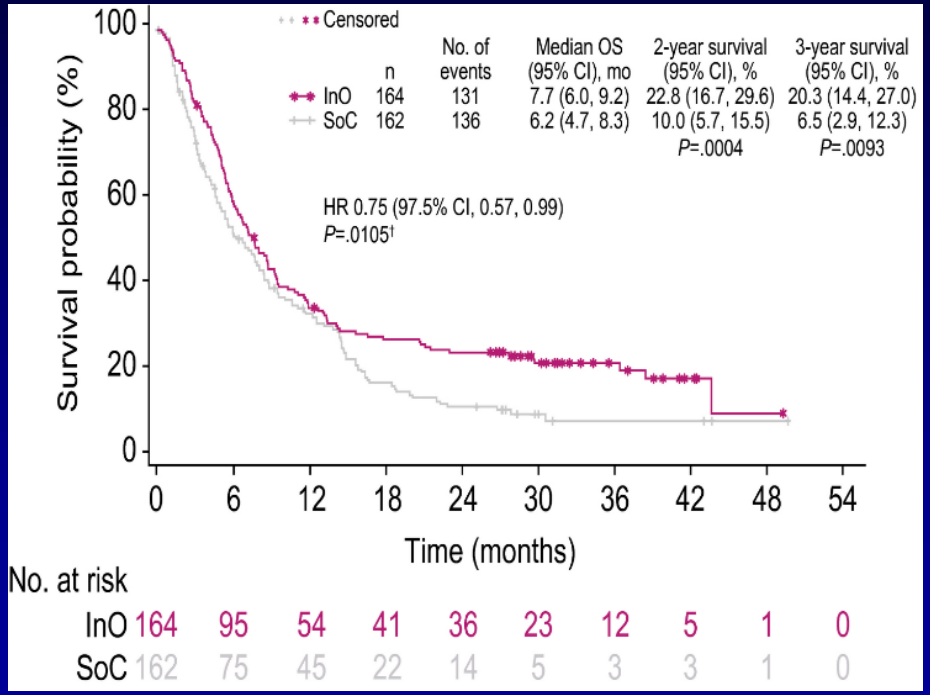
Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

- **Marrow CR**

Blina vs SOC: 44% vs 25%[1]

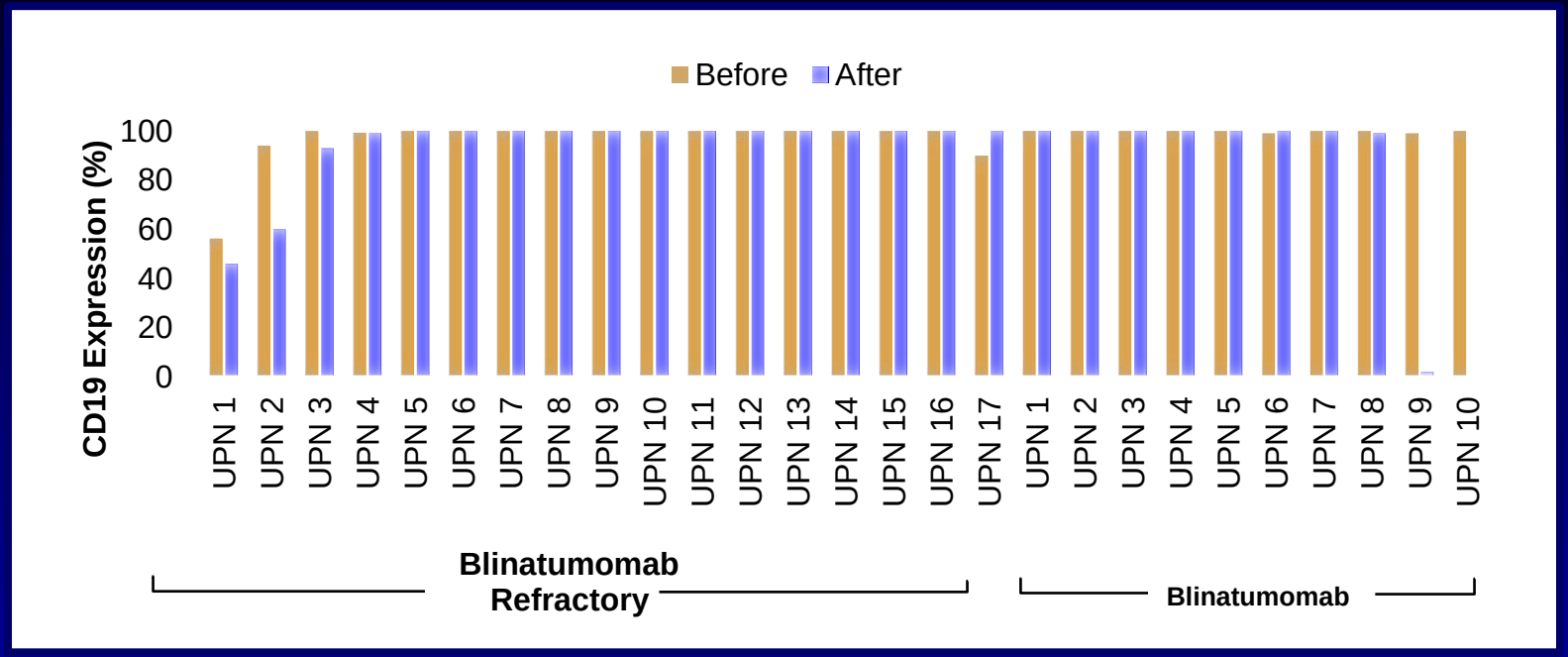


Ino vs SOC: 74% vs 31%[2,3]



1. Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847; 2. Kantarjian H, et al. *N Engl J Med.* 2016;375:740; 3. Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

CD19 (%) Expression Before and After Blinatumomab Therapy

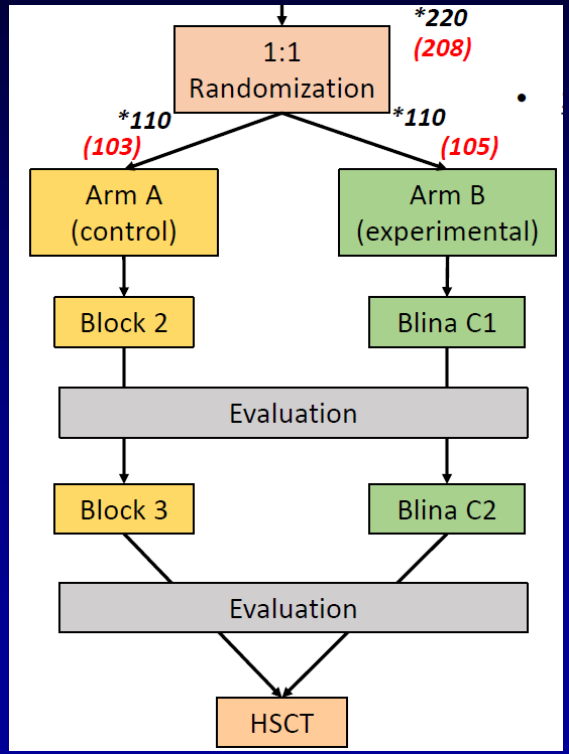


- **61 patients evaluated for immunophenotype; 56 (92%) had CD19-positive disease**
  - 5 (8%) had ALL recurrence with CD19-negative disease
  - 2 patients experienced progression with lower CD19-positive disease

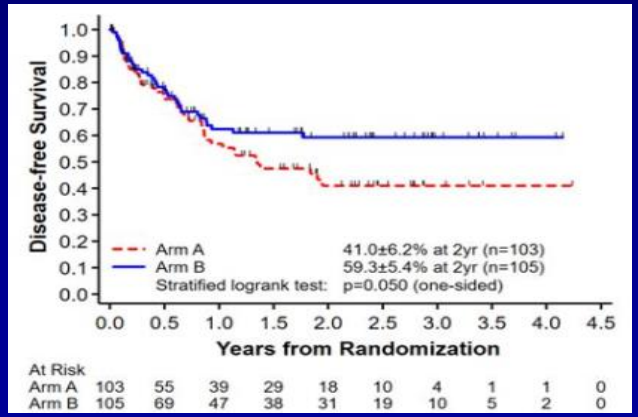
Jabbour E, et al. *Am J Hematol.* 2018;93:371-374.

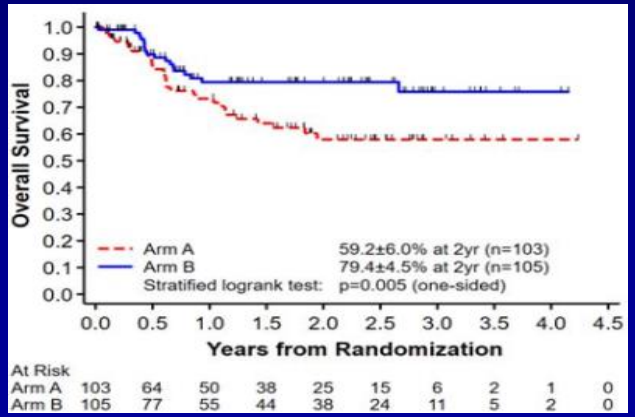
Phase III Study of Blinatumomab vs ChemoRx in Children/AYA in Salvage 1

- 208 pts HR/IR randomized 1:1 to blina (n = 105) vs chemoRx (n = 103) post Block 1 reinduction



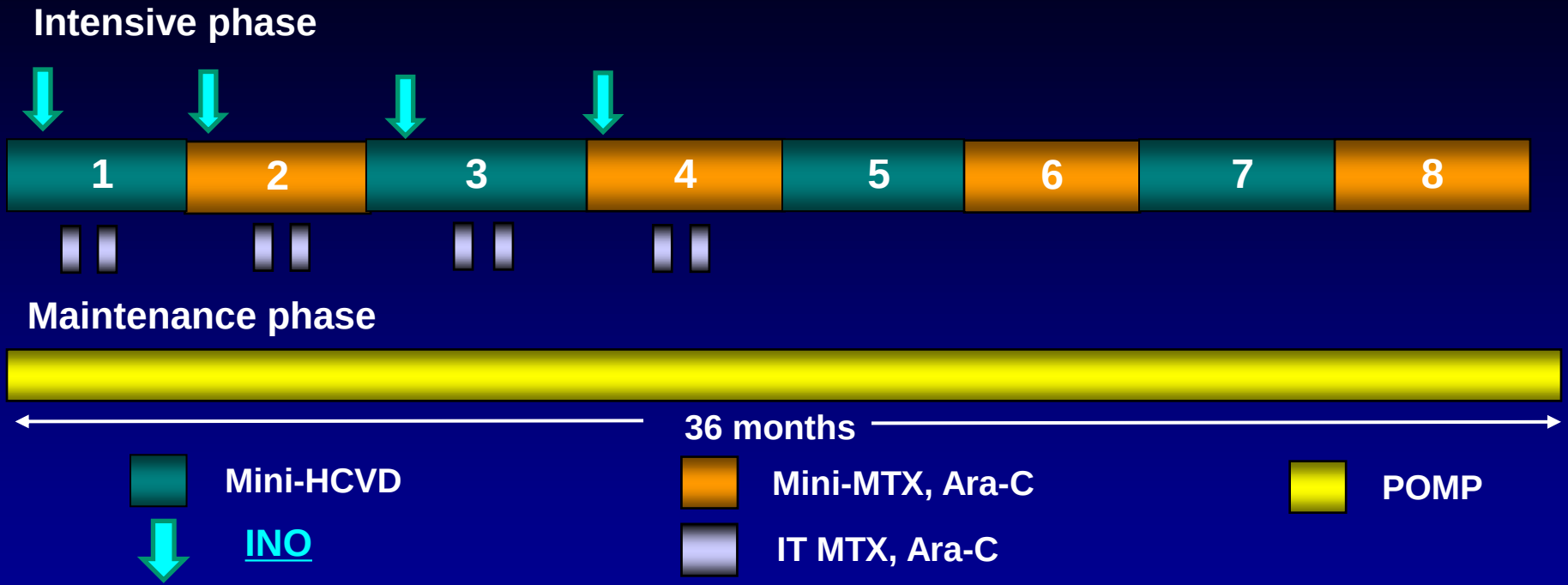
Parameter	Blina	Chemo	*P* Value
2-yr DFS, %	59	41	.05
2-yr OS, %	79	59	.005
SCT, %	70	43	<.001
MRD clearance, %	75	32	<.001





Brown PA, et al. *JAMA*. 2021;325:833-842; Brown PA, et al. ASH 2019. Abstract LBA-1 and oral presentation.

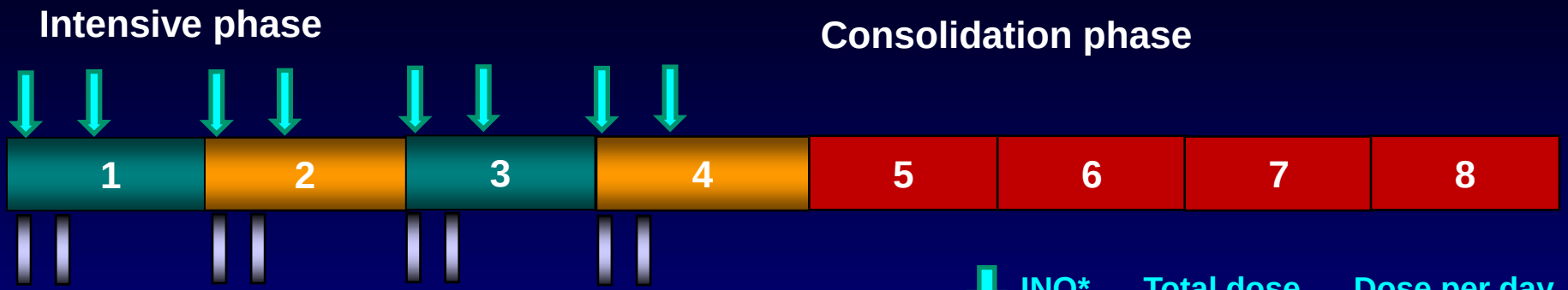
Mini-HCVD + INO ± Blina in R/R B-ALL: Original Design (Pts #1–67)

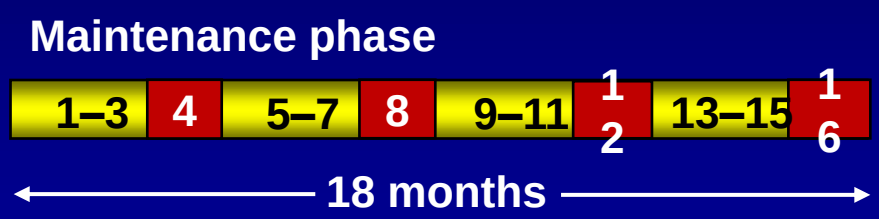


INO	First 6 pts	7 to 34	35+
C1 (mg/m^2)	1.3	1.8	1.3
C2–4 (mg/m^2)	0.8	1.3	1.0

Short N, et al. EHA 2023; Abstract S119 and oral presentation.

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

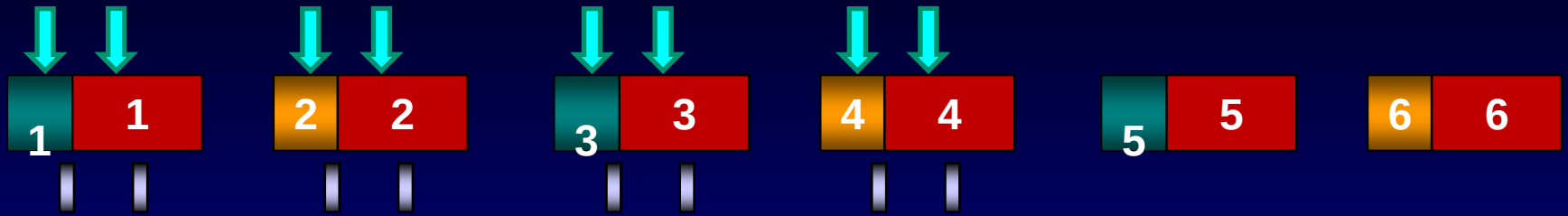
Blinatumomab

IT MTX, Ara-C

POMP

Short N, et al. EHA 2023; Abstract S119 and oral presentation.

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



Maintenance phase

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

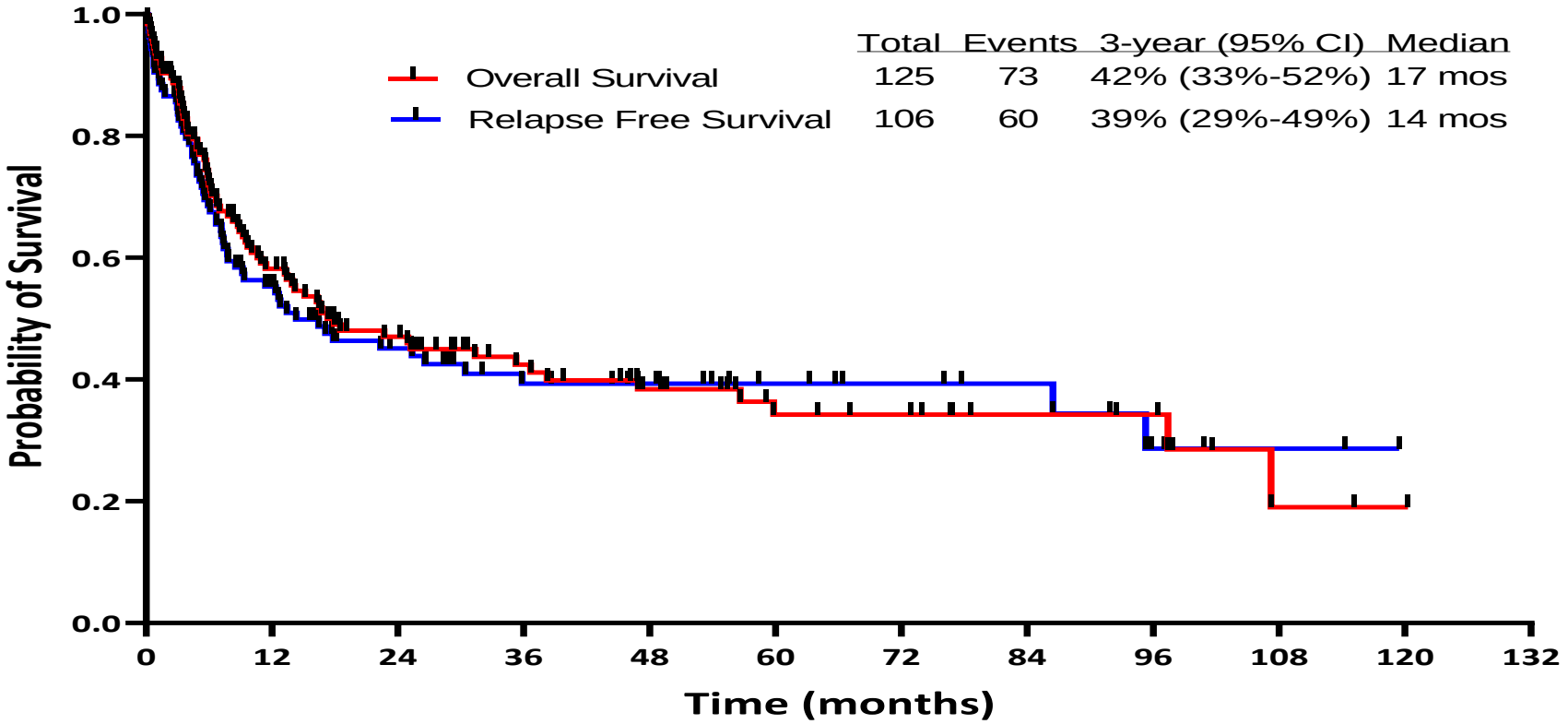
Short N, et al. EHA 2023; Abstract S119 and oral presentation.

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)

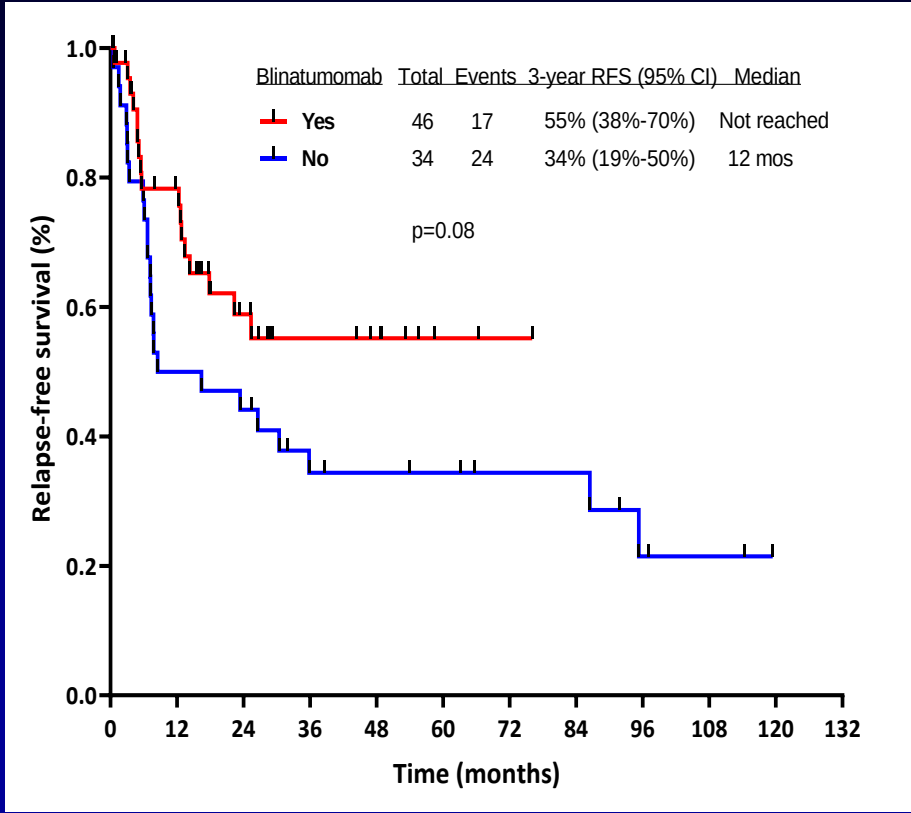
Short N, et al. EHA 2023; Abstract S119 and oral presentation.

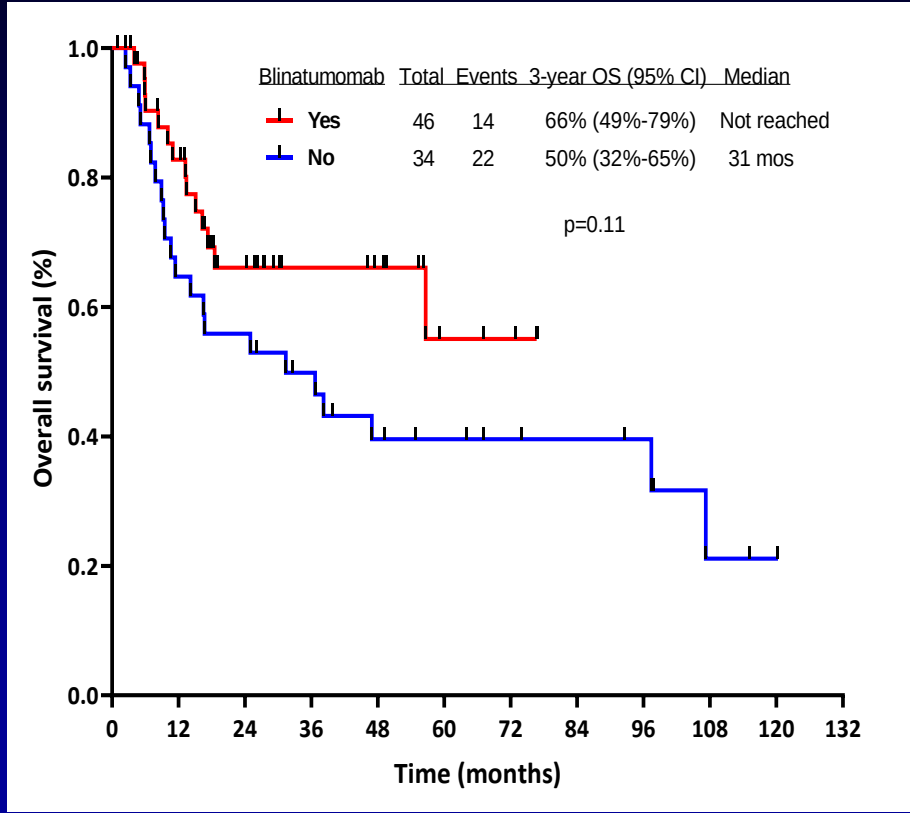
Mini-HCVD + INO ± Blina in R/R B-ALL: RFS and OS (Entire Cohort)



Short N, et al. EHA 2023; Abstract S119 and oral presentation.

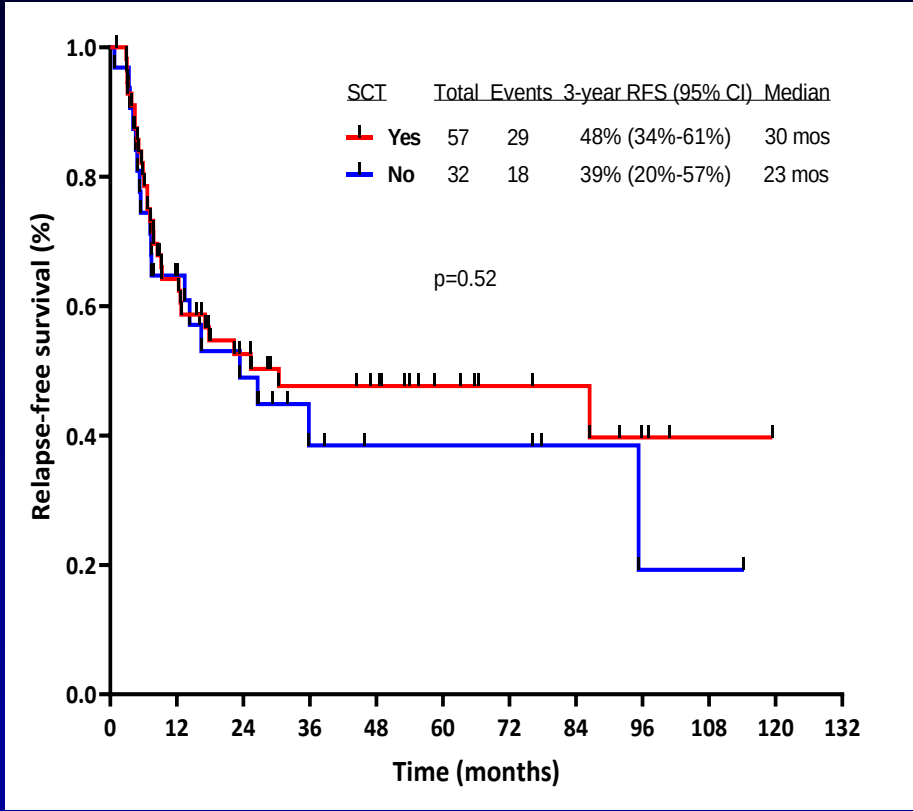
Mini-HCVD + INO ± Blina in R/R B-ALL: OS and RFS by Receipt of Blinatumomab (Salvage 1 Only)

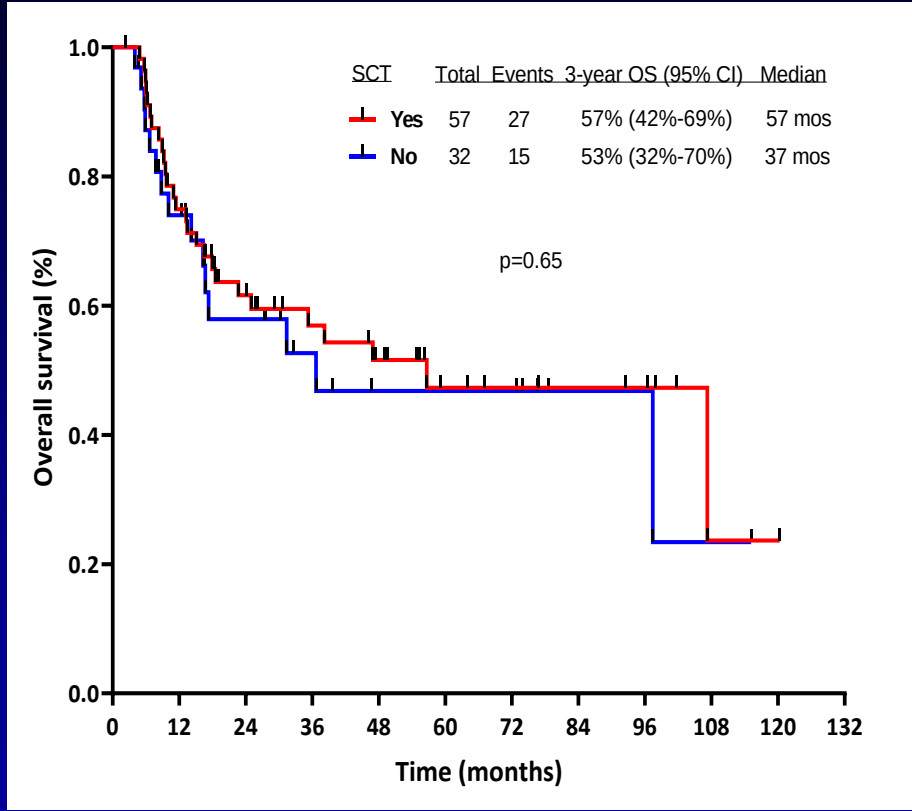




Short N, et al. EHA 2023; Abstract S119 and oral presentation.

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

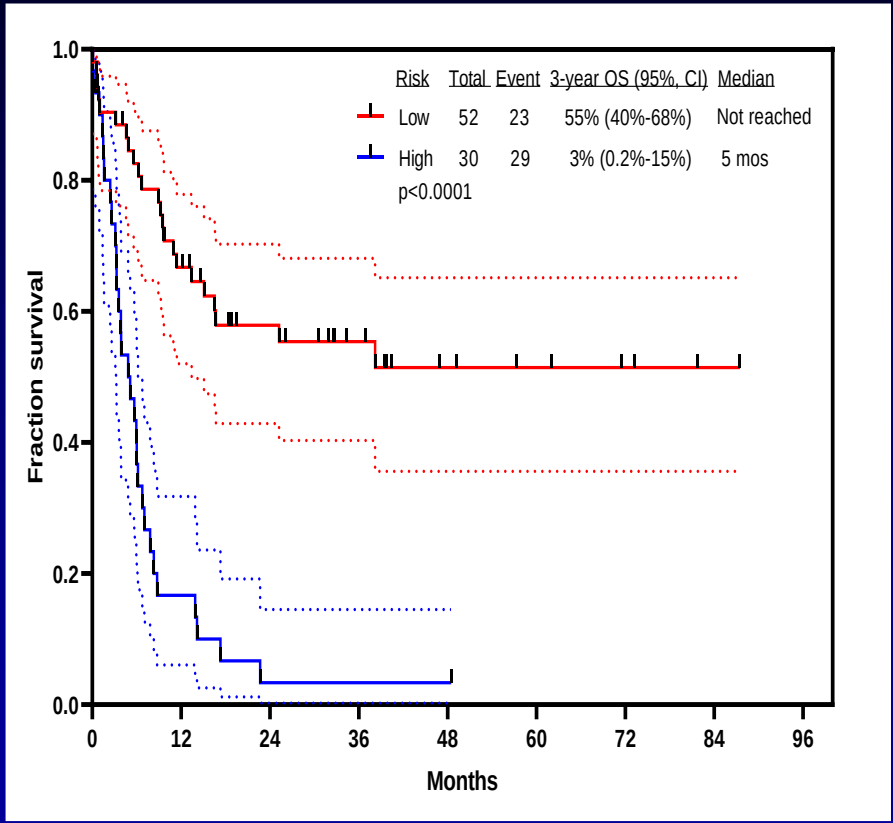




Short N, et al. EHA 2023; Abstract S119 and oral presentation.

Model: mHCVD + INO ± Blina in R/R ALL – a Prognostic Model for Survival

Variable	Risk Classification	
	Low*	High**
% CD22	≥70%	<70%
Cytogenetic	Diploid, complex, others	11q23 rearrangements Ho-Tr



*Low risk required all low-risk criteria.
**High risk required any one of high-risk criteria.

Sasaki Y, et al. *Blood*. 2020;136(suppl 1):abstract 1899.

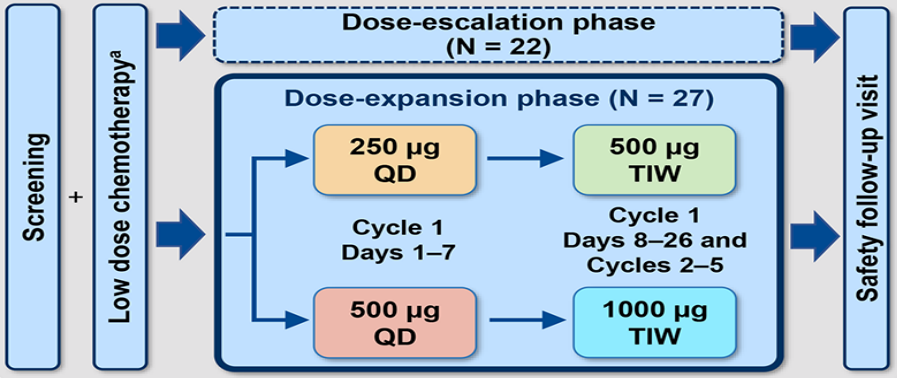
Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia

Results from the expansion phase of a phase 1b trial

Objective

To assess the efficacy and safety of subcutaneous blinatumomab in heavily pretreated adults with R/R B-ALL at two doses

Study Schema



Results

Efficacy

250 µg QD/500 µg TIW (N = 14)
- CR/CRh: 85.7%
- MRD-neg CR/CRh: 75%

500 µg QD/1000 µg TIW (N = 13)
- CR/CRh: 92.3%
- MRD-neg CR/CRh: 100%

Dosing regimen 500 µg QD/1000 µg TIW demonstrated higher MRD-negative CR/CRh within 2 cycles (100%) compared with dosing regimen 250 µg QD/500 µg TIW (75%)

Safety

250 µg QD/500 µg TIW (N = 14)
- Grade ≥3 CRS[b]: 21.4%
- Grade ≥3 NE[b]: 42.9%

500 µg QD/1000 µg TIW (N = 13)
- Grade ≥3 CRS[b]: 23.1%
- Grade ≥3 NE[b]: 23.1%

- SC injections were well tolerated
- No treatment-related grade 4 CRS or NE

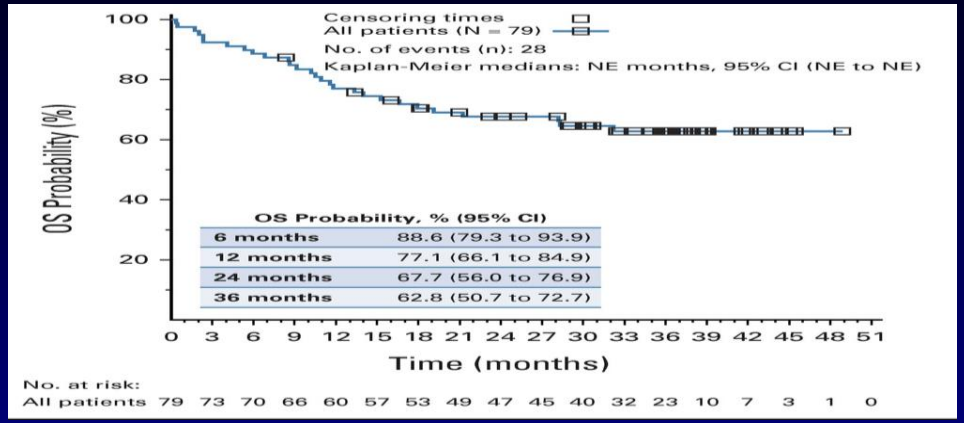
Conclusion

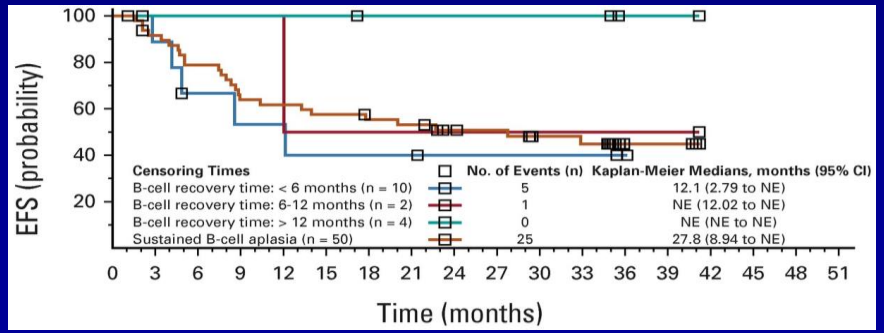
Treatment with single agent SC blinatumomab resulted in a high CR rate, high MRD-negativity rate, and an acceptable safety profile in heavily pretreated adults with R/R B-ALL

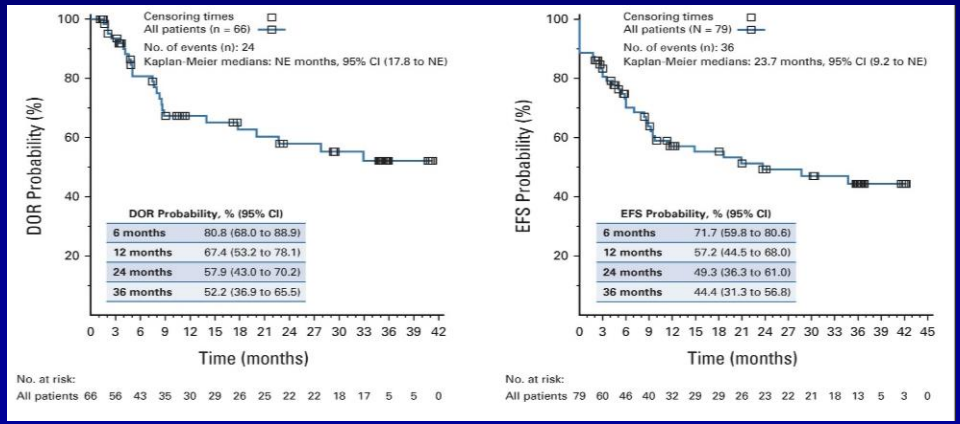
Jabbour E, et al. *Am J Hematol.* 2024;99(4):586-595.

3-Year Update of Tisagenlecleucel in R/R ALL

- 97 pts ≤26 yrs old enrolled
  - 79 (81%) received tisa
- Median age 11 yrs (3–24)
- Median prior Tx 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%
- Grade 3/4 AE 29%







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

Brexucabtagene Autoleucel (CD19 CAR T) in R/R ALL (ZUMA)

- 78 pts Rx with brexu-cel. Median FU 54 mos
- CR/CRi 57/78 = 73%

ALL Subset	No	Median OS (mos)	% 4-yr OS
Total	78	25.6	40
Prior Rx			
1	15	60.4	57
2+	63	25.4	36
Prior blina			
Yes	38	15.9	55
No	40	60.4	24
Later allo SCT			
Yes	14	36.3	-
No	43	60.4	-

Oluwole. *J Clin Oncol.* 2024;24:S6531.

Toxicities of Brexu-Cel in R/R ALL: ROCCA Results

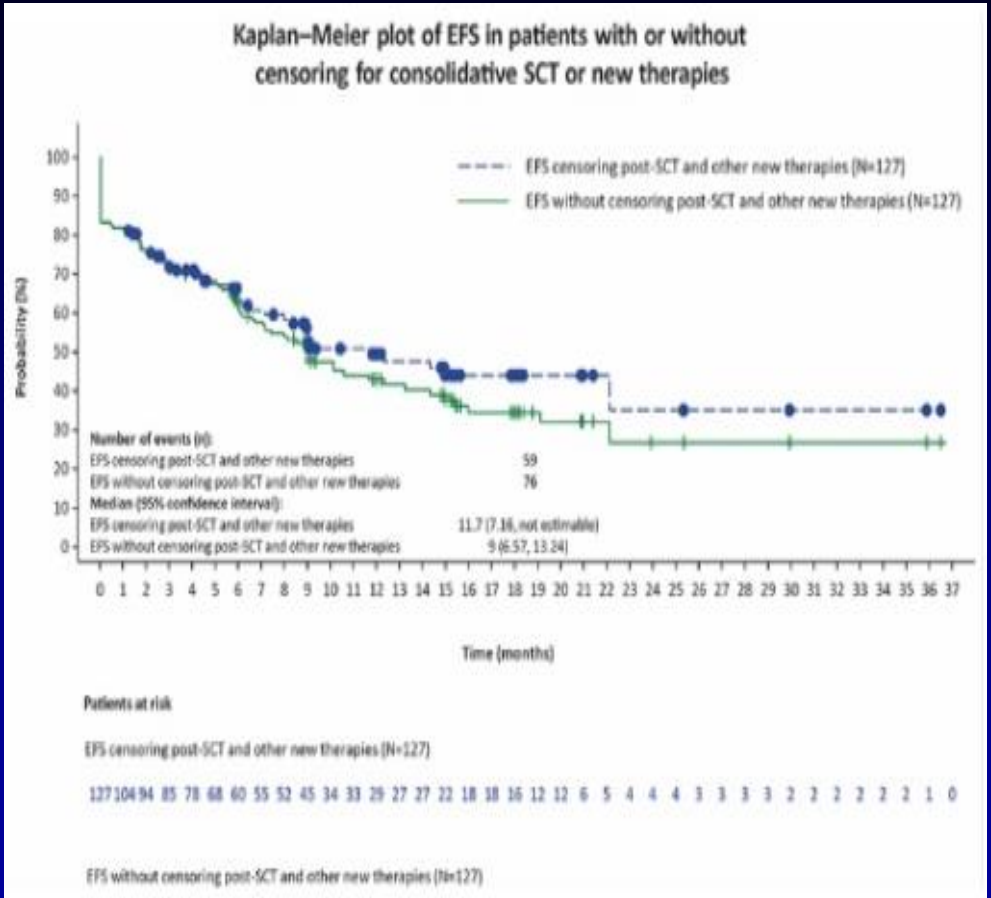
- Retrospective analysis of adults (N = 152) with R/R B-ALL receiving commercial brexu-cel
- Grade 3 CRS higher in ZUMA-3 than seen in the ROCCA dataset, but ICANS rates were comparable
- Grade 3+ CRS showed a numerical increase in patients with active disease at apheresis (>5% marrow blasts and/or EMD); OR: 2.35, 95% CI: 0.69–8.0, *P* = .17
- Grade 3+ ICANS more likely in pts with active disease at apheresis; OR: 2.63, 95% CI: 1.28–5.38, *P* = .008

Factor	ROCCA	ZUMA-3
Patients infused, n	152	55
Any CRS	82%	89%
Grade ≥3 CRS	9%	24%
Time to onset, days	5 (0–14)	–
Any ICANS	56%	60%
Grade ≥3 ICANS	31%	25%
Time to onset, days	7 (0–21)	–
Early death by day 28, n (%)	9 (6)	–

Kopmar NE, et al. ASH 2023. Abstract 522 and oral presentation.

Obecaptagene Autoleucel (OBE-CEL) in Adult R/R ALL (FELIX)

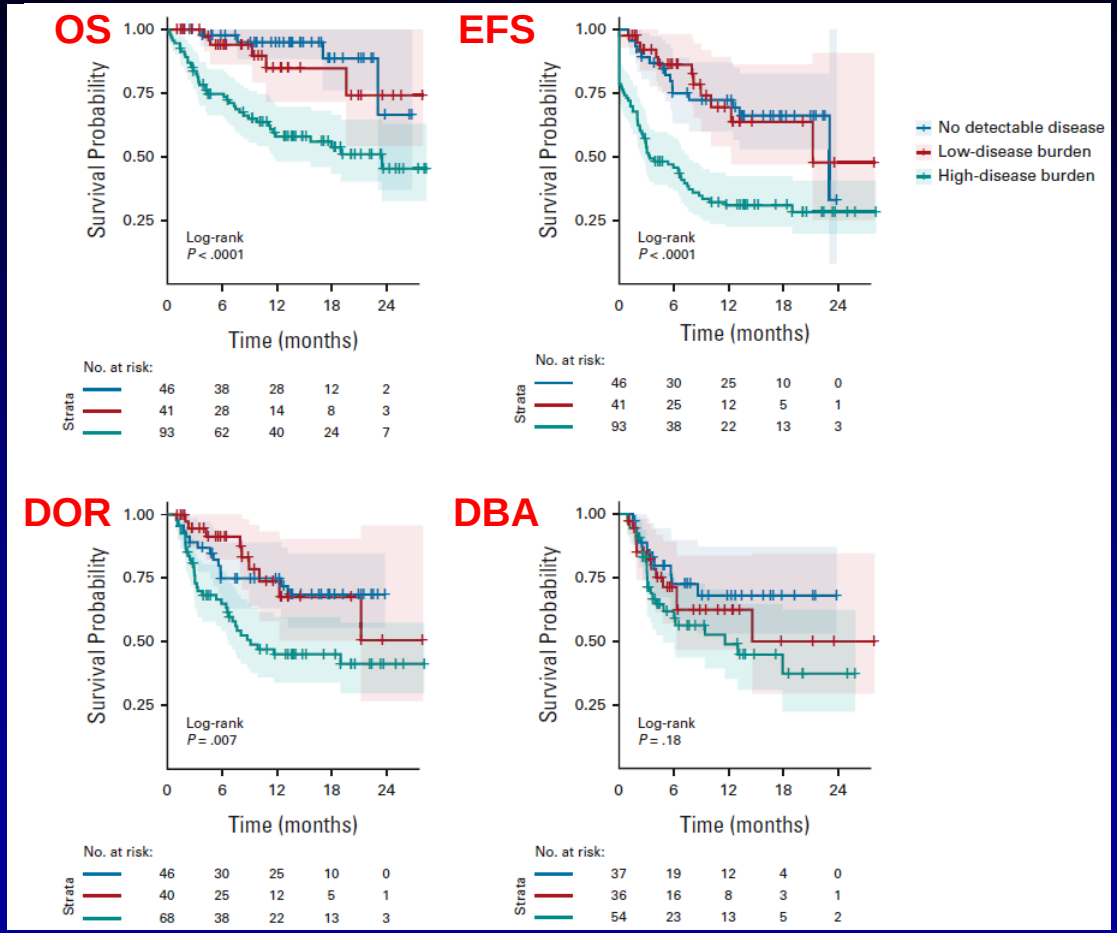
- AUTO 1 fast off-rate CD19 binder CAR T
- 153 enrolled, 127 (83%) infused. Median age 47 yrs
- Prior blina 42%, ino 31%, allo SCT 44%
- cCR-CRi 99/127 = 78% (99/153 = 65%). 19/77 allo SCT
- Loss of CAR T = HR 2.9
- 12-mos EFS 49%, 12-mos OS 61%



Jabbour E, et al. *J Clin Oncol.* 2024;24:S6504; Roddie et al. *HemaSphere.* 2024;8:S114.

Real-World CAR Consortium and Disease Burden

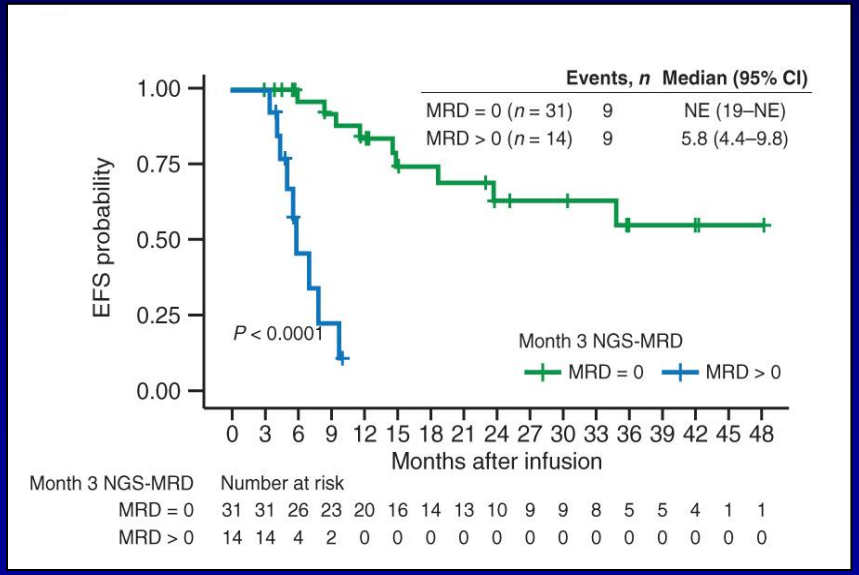
- 200 pts (185 pts infused)
- Median age: 12 yrs (0–26 yrs)
- CR: 85%
- Disease burden
  - HBD: n = 94 (51%)
  - LBD: n = 41 (22%)
  - ND: n = 46 (25%)
- Survival outcomes
  - 12-mo EFS: 50%
  - 12 mo OS: 72%
- Safety
  - G3 CRS: 21% (35% in HBD)
  - G3 NE: 7% (9% in HBD)

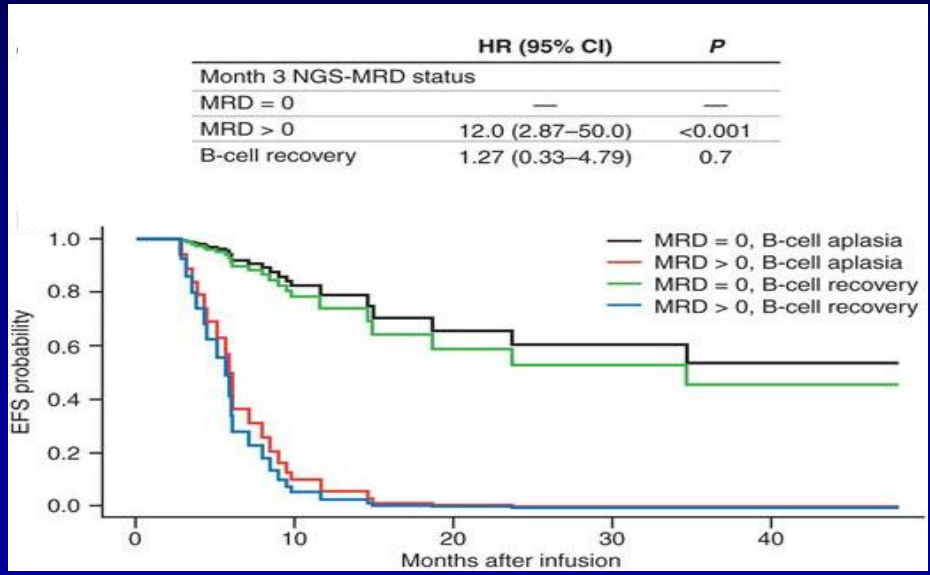


Schultz LM, et al. *J Clin Oncol*. 2022;40(9):945-955.

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

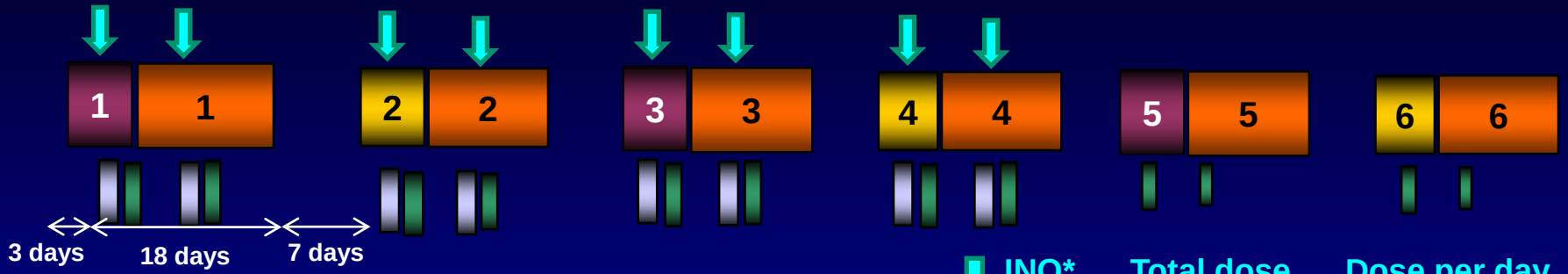




Pulsipher MA, et al. *Blood Cancer Discov.* 2022;3(1):66-81.

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

Induction phase: C1–C6



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

Consolidation phase

CAR T Consolidation

Mini-HCVD

Mini-MTX, Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

ALL 2024: Conclusions

- Significant improvements across all ALL categories
- Incorporation of Blina-InO in FL therapy highly effective and improves survival
- Early eradication of MRD predicts best overall survival
- Antibody-based Txs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather, complementary (together)
- Future of ALL Tx
  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

Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX
Email: ejabbour@mdanderson.org
Cell: 001.713.498.2929

Global Leukemia Academy

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

Jae Park

APTITUDE HEALTH®

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 Mlynarski, 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

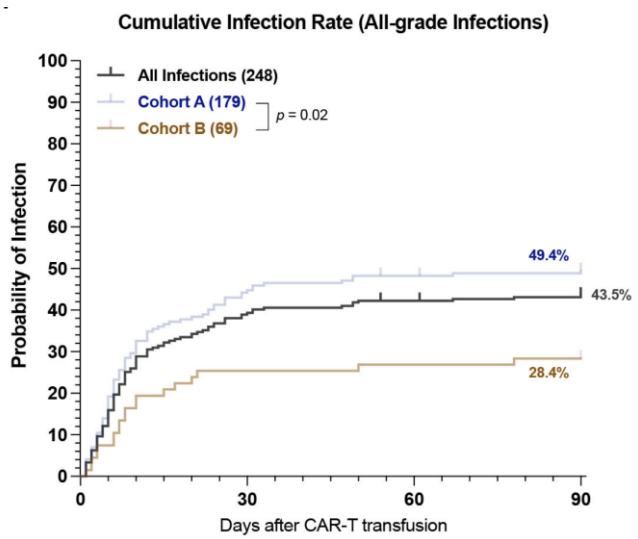
	HSCT vs CHT	Male vs Female	Aged ≤55 Yr vs >55 Yr
ECOG 0–1	<.0001		.02
Skin	<.0001	.02	
Lung	<.0001		
Cardiac	.03		.02
GI system	.02		
Neurologic	.002	.02	
Kidney/liver	<.0001		
Endocrine	.001		
Eye	<.0001		.04
Infection	.0001	.01	
Fatigue	.007		
Sec. malignancies			.03

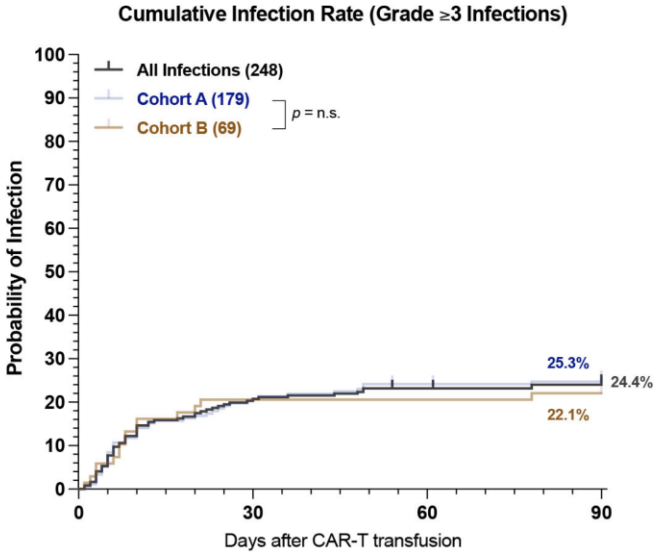
Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

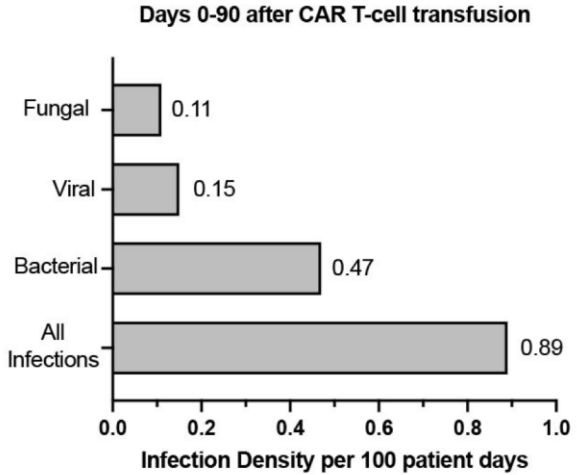
Remarks

- 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

Infections After CAR T-Cell Therapy Are Common and Associated With Increased Mortality

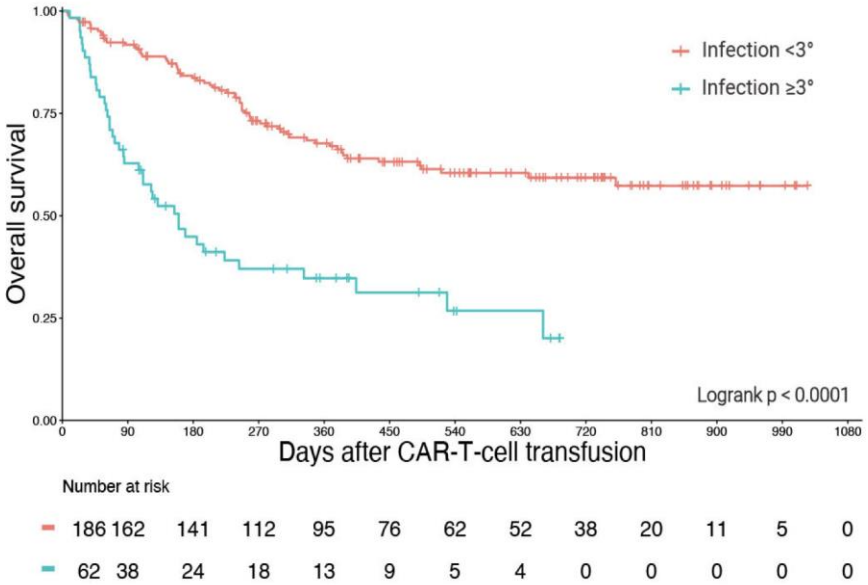






Rajeski K, et al. *J Immunother Cancer.* 2022;10(5):e004475.

Infections After CAR T-Cell Therapy Are Common and Associated With Increased Mortality

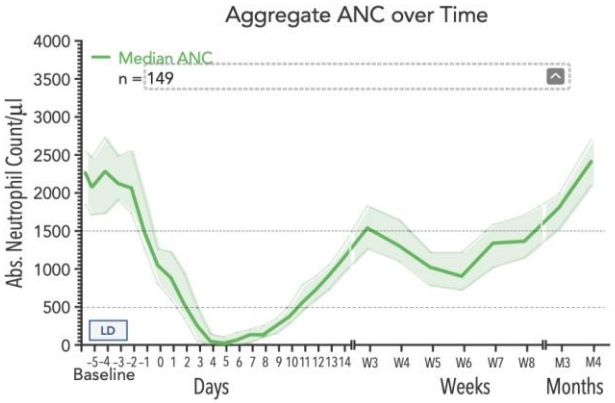


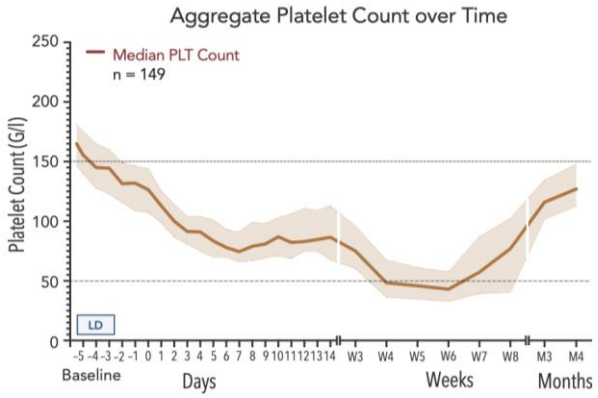
Etiologies of infections are multifactorial

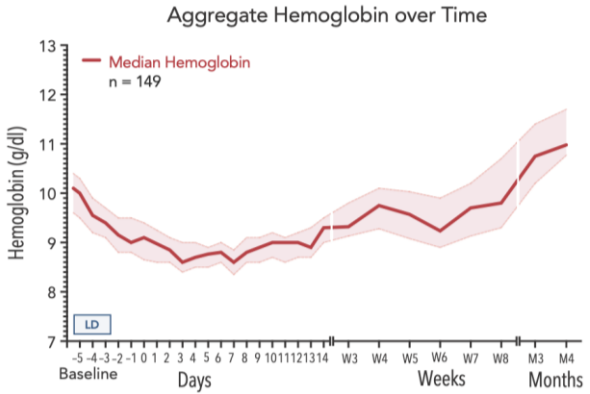
- Lymphodepleting chemotherapy
- Pre-existing disease and prior chemotherapies
- Baseline cytopenia
- Prolonged post-treatment cytopenia
- Persistent disease following CAR T

Rajeski K, et al. *J Immunother Cancer.* 2022;10(5):e004475.

Cytopenia After CAR T-Cell Therapy Can Be Prolonged





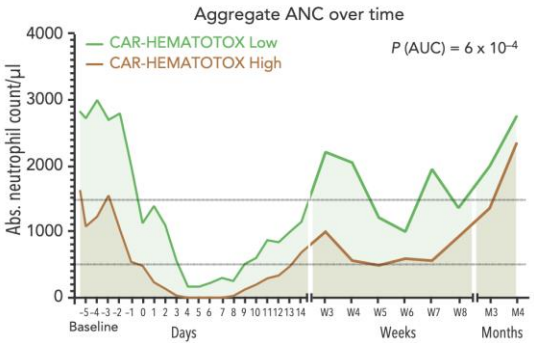


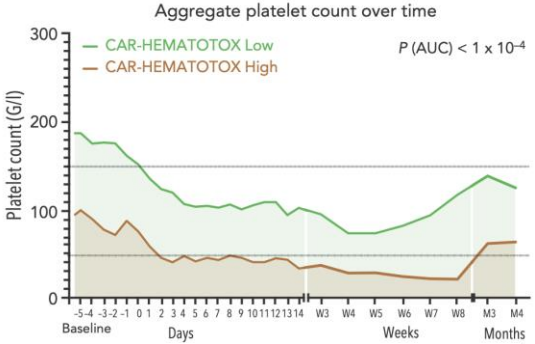
CAR-HEMATOTOX Score

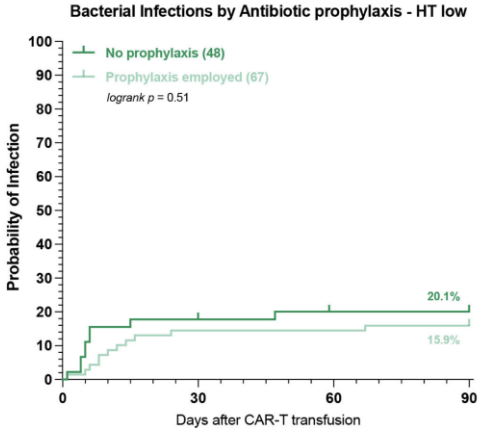
Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1	**High: ≥ 2**		

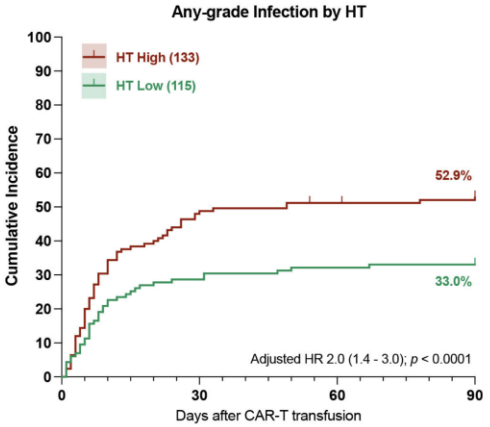
Rajeski K, et al. *Blood.* 2021;138(24):2499-2513.

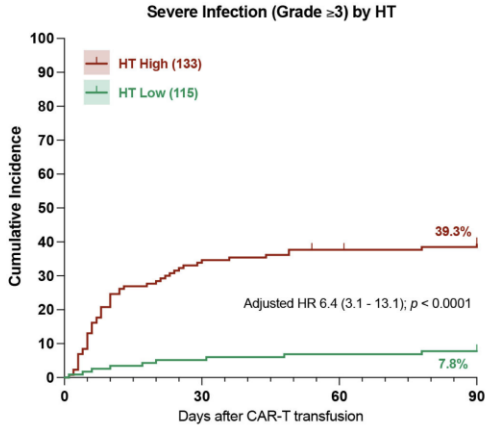
CAR-HEMATOTOX Score Can Predict High-Risk Patients for Cytopenia and Infections

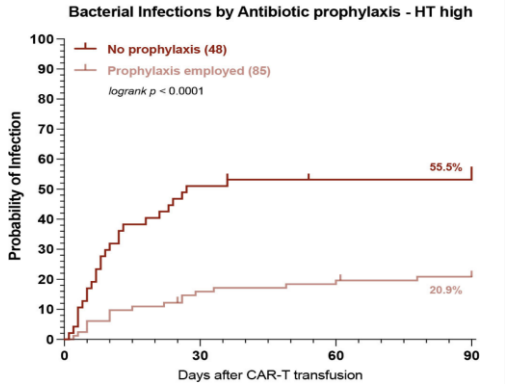












Rajeski K, et al. *J Immunother Cancer.* 2022;10(5):e004475; Rajeski K, et al. *Blood.* 2021;138(24):2499-2513.

Global Leukemia Academy

Current and future role of transplantation in acute leukemias in LATAM

Phillip Scheinberg

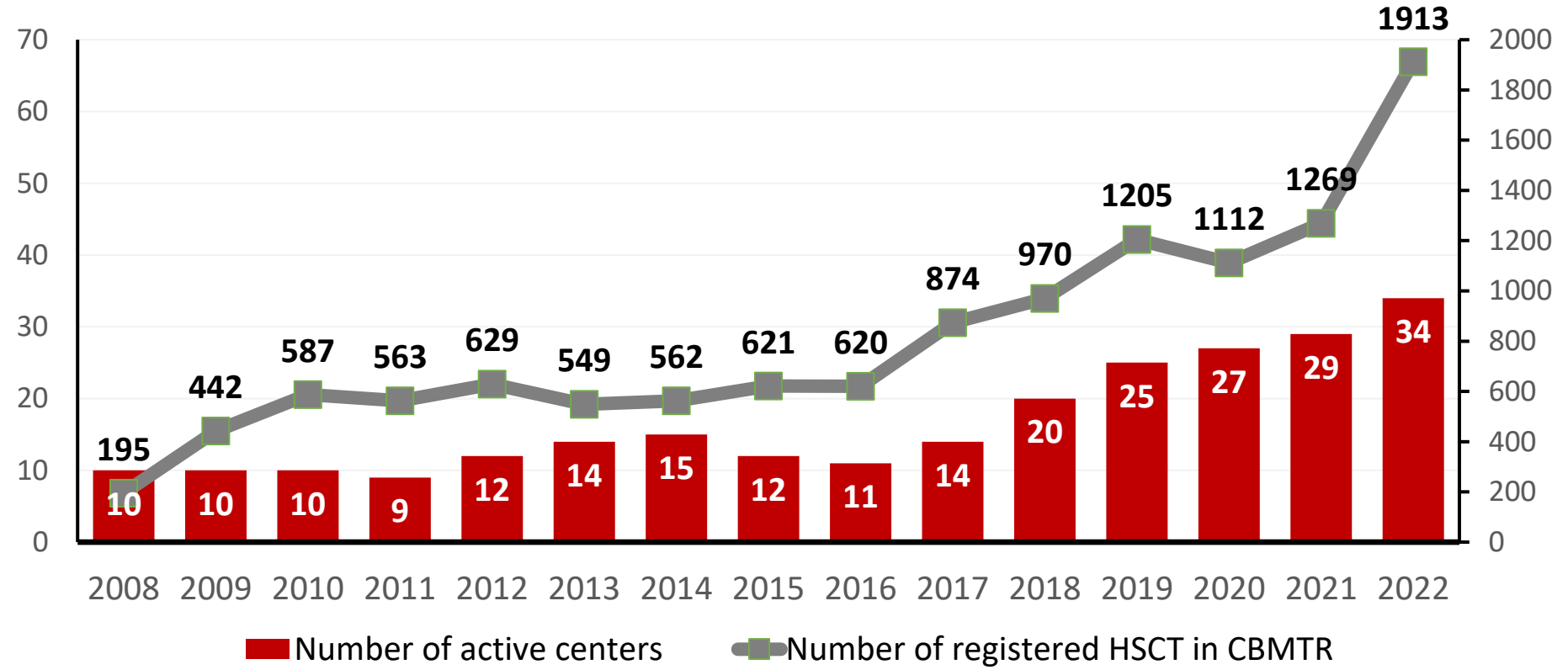
APTITUDE HEALTH®

Disclosures

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

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

Number of Brazilian active centers at the CIBMTR, and HSCT registered (2008-2022)



Source: Data Back to Center July/2023

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

GD BRASIL
GERENTES DE DADOS TCTH - BRASIL

SBTMO
SOCIEDADE BRASILEIRA DE TERAPIA CELULAR E TRANSPLANTE DE MEDULA ÓSSEA

Dados Registro brasileiro SBTMO/CIBMTR

Dados TCTH no Brasil (2012-2023)

Fonte: CIBMTR – Data Back to Center
https://portal.cibmtr.org/Pages/default.aspx

Resultados

- ✓Entre 2012-2023 foram registrados 12.416 Transplantes
- ✓Centros participantes: 44
- ✓Análise descritiva de dados demográficos
- ✓Gráficos gerados pelo Power BI desktop
- ✓Sobrevida global estimada pelo método de Kaplan-Meier utilizando o programa R (Comparação entre grupos pelo teste de Log-rank)

Critérios de exclusão – Dados faltantes

Total de transplantes: 12.416

Critérios exclusão – Dados sem informação	N
Tipo de transplante (Alogênico/Autólogo)	60
Tipo de doador Alogênico	16
Diagnóstico primário	105
Fonte de células	5
Total TCTH analisados	**12.230**

Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

44

Centros participantes

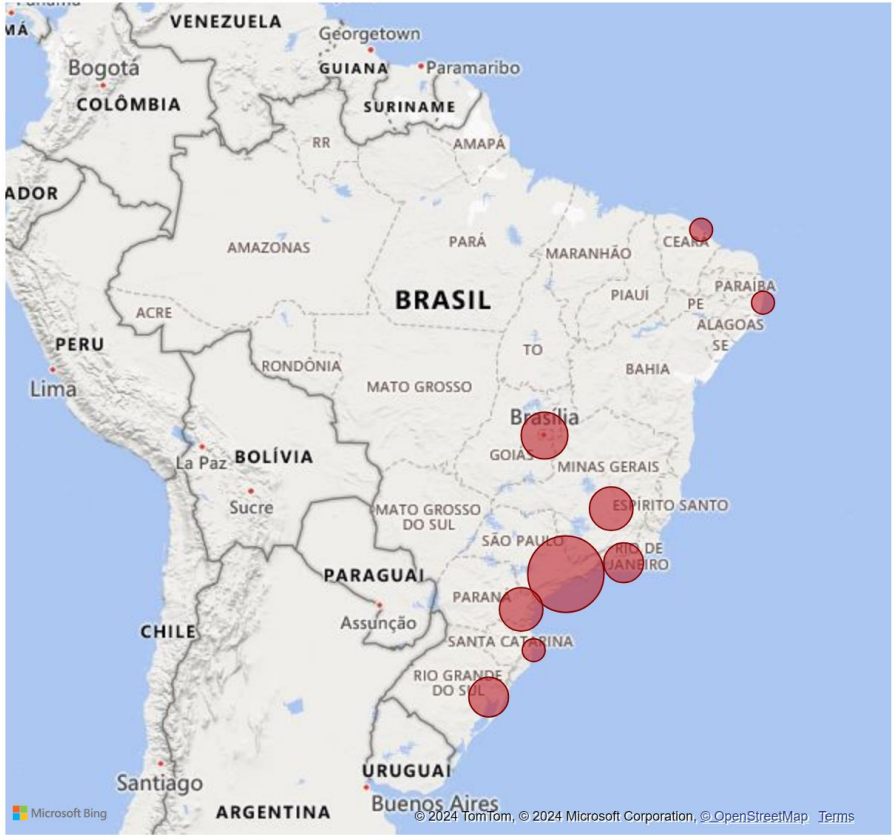
Center Name
A.C. Camargo Cancer Center
Albert Einstein Hospital
Associação Hospitalar Moinhos de Vento
Bio Sana's Serviços Médicos
Bio Sana's São Camilo
Centro De Pesquisa Clinica Hospital 9 De Julho
Centro de Pesquisas Oncológicas Dr. Alfredo Daura Jorge (CEPON)
Complexo Hospitalar de Niterói
CTMO-HCFMUSP
Fundação Faculdade Regional de Medicina de São José do Rio Preto (FUNFARME)
Fundação Pio XII - Hospital de Câncer de Barretos
Hospital Amaral Carvalho
Hospital Brasília
Hospital da Criança de Brasília José Alencar
Hospital das Clínicas - Faculdade de Medicina de Botucatu, UNESP
Hospital de Clínicas - UFPR
Hospital de Clínicas de Porto Alegre
Hospital DF Star
Hospital Erasto Gaertner
Hospital Leforte Liberdade
Hospital Mãe de Deus
Hospital Monte Sinai

Center Name
Hospital Nossa Senhora das Graças - IP
Hospital Pequeno Príncipe
Hospital Samaritano
Hospital São Camilo - Mooca
Hospital São Camilo - Pompéia
Hospital São Camilo - Santana
Hospital Sírio Libanês
Hospital Sírio Libanês em Brasília
Hospital Universitário Clementino Fraga Filho, Univ. Fed. RJ
Hospital Universitario da Universidade Federal de Juiz de Fora
Hospital Universitário Walter Cantídio/UFC
Instituto da Criança - Hospital das Clínicas da Faculdade de Medicina Universidade de São Paulo
Instituto de Cardiologia do Distrito Federal - Unidade de TMO Pietro Albuquerque
Instituto de Oncologia Pediátrica - GRAACC
Instituto Nacional de Câncer
Natal Hospital Center
Real e Benemérita Sociedade de Beneficiência Portuguesa de São Paulo
Real Hospital Português
Santa Casa de Montes Claros
UFMG Hospital das Clínicas Servico de Transplante de Medula Óssea
UNICAMP - HEMOCENTRO
Universidade Federal de São Paulo - Hospital São Paulo

Localização dos centros participantes (2012-2023)

44

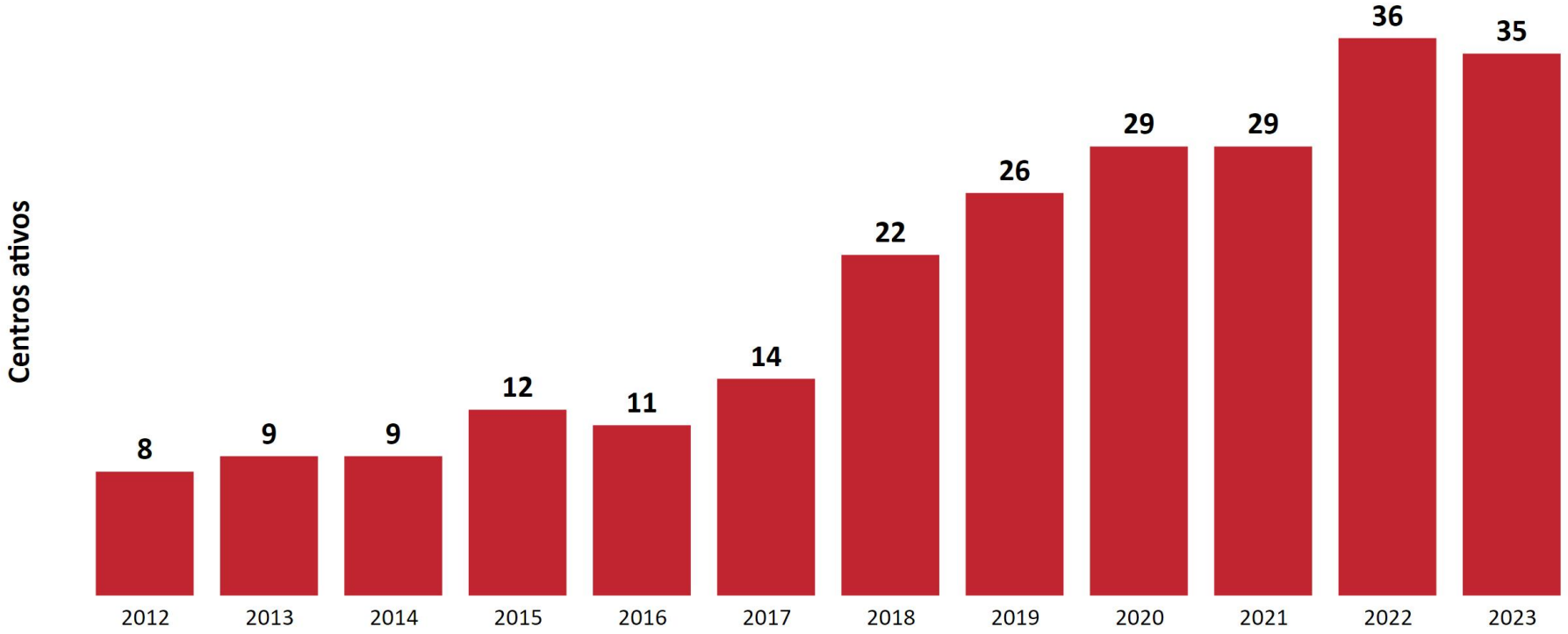
Centros TMO



Estado	Centros TMO
SP	21
DF	5
MG	4
PR	4
RJ	3
RS	3
CE	1
PE	1
RN	1
SC	1
Total	**44**

Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

Número de centros brasileiros ativos no CIBMTR por ano

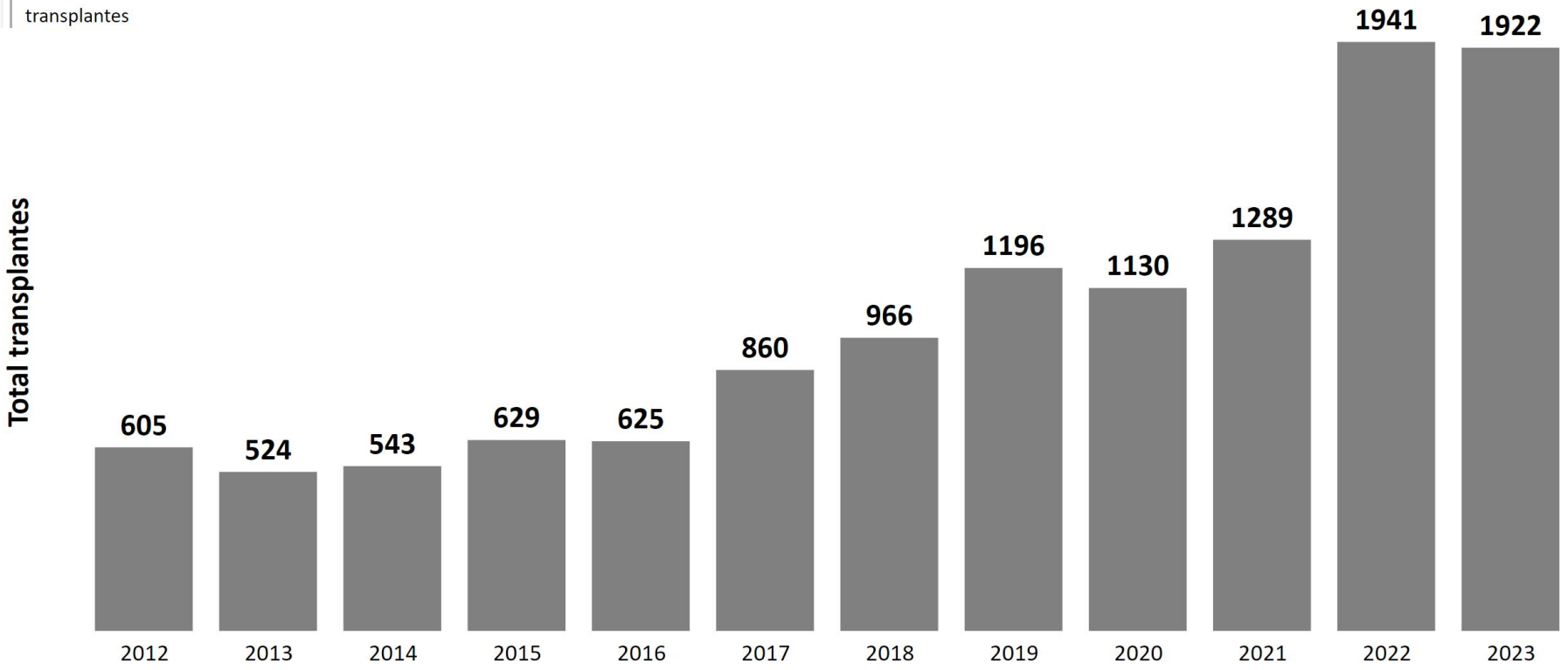


Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

Total de transplantes realizados no Brasil e registrados no CIBMTR

12230

transplantes

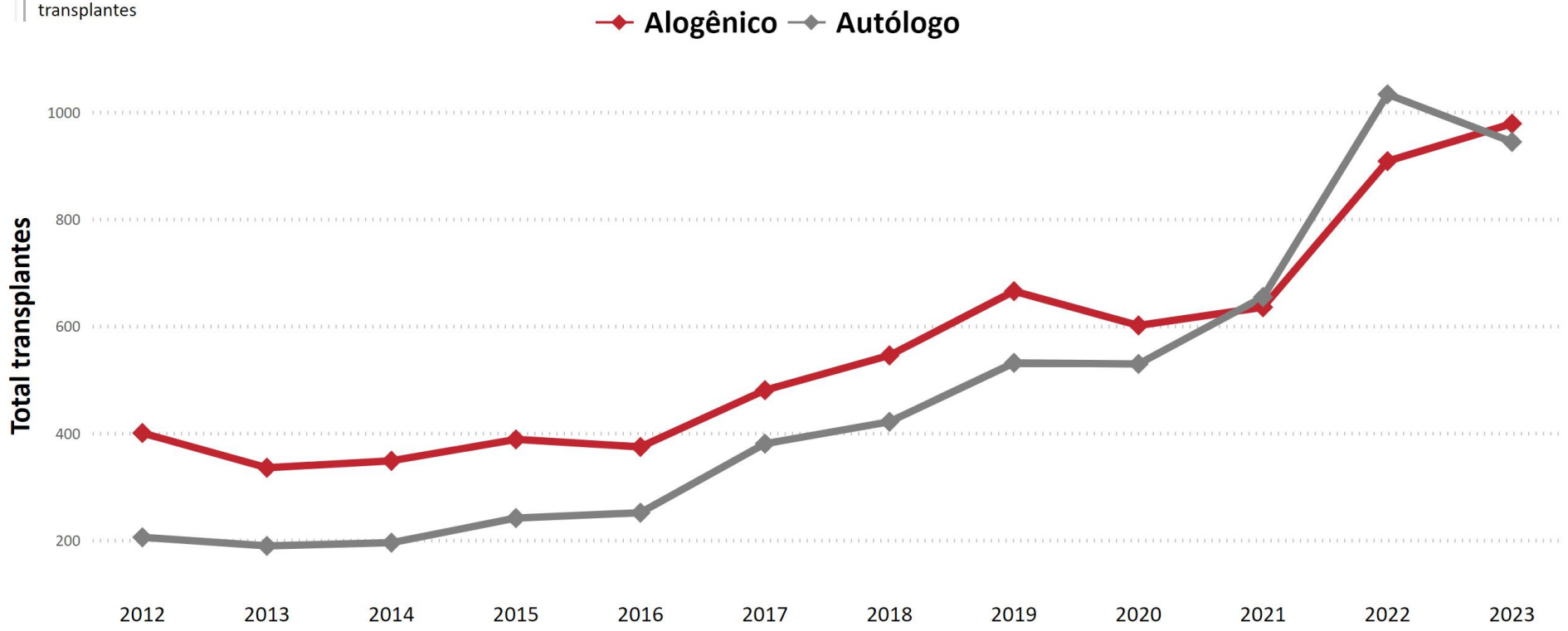


Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

Total de transplantes realizados no Brasil e registrados no CIBMTR

12230

transplantes

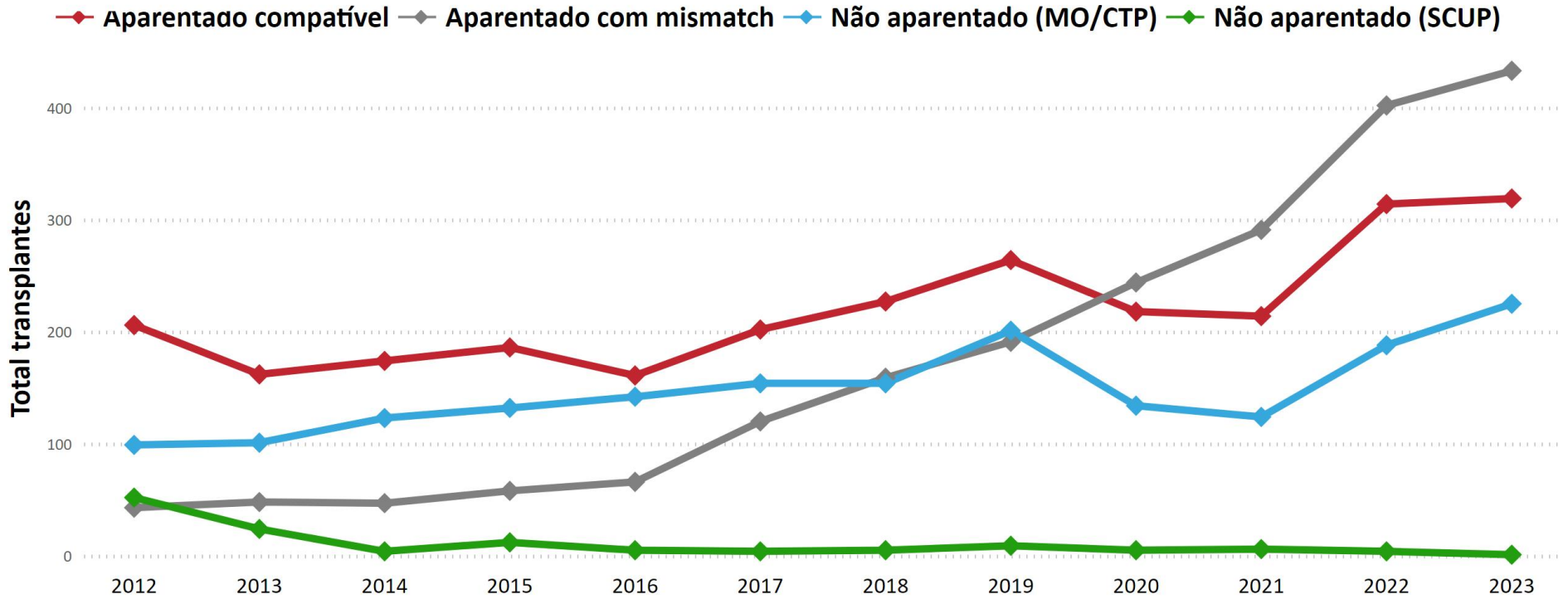


JBMTCT. 2024;5(1).

TCTH Alogênicos realizados no Brasil por tipo de doador

6657

transplantes

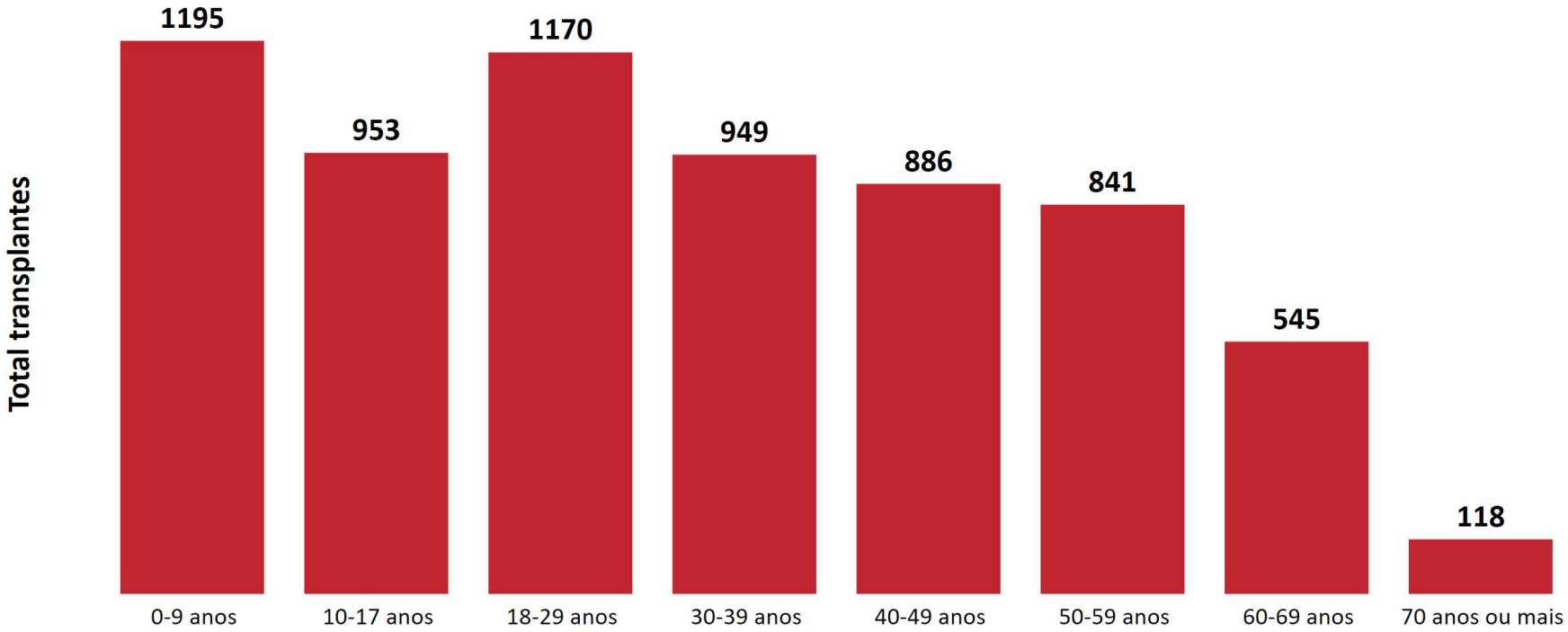


JBMTCT. 2024;5(1).

TCTH Alogênico por faixa de idade

6657

transplantes

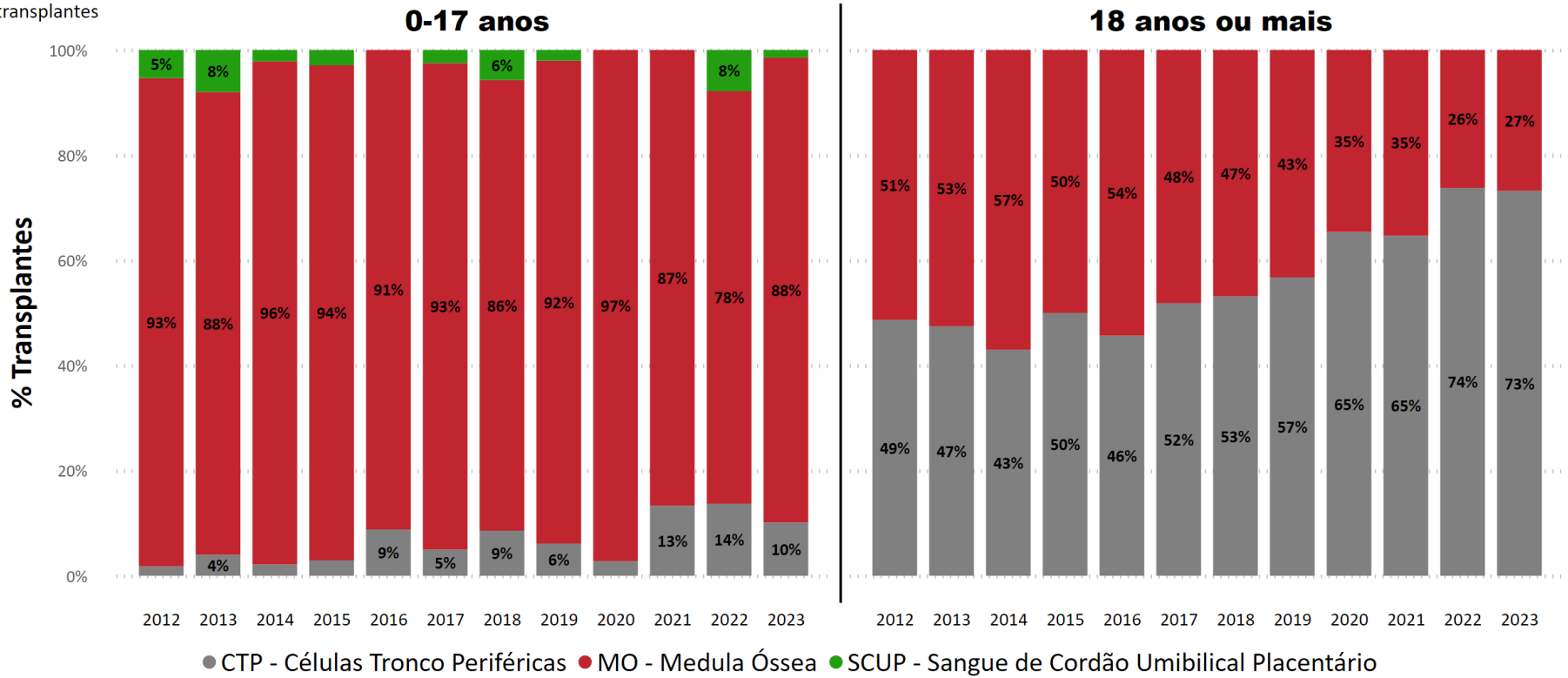


JBMTCT. 2024;5(1).

TCTH Alogênico aparentado compatível por fonte de células

2647

transplantes

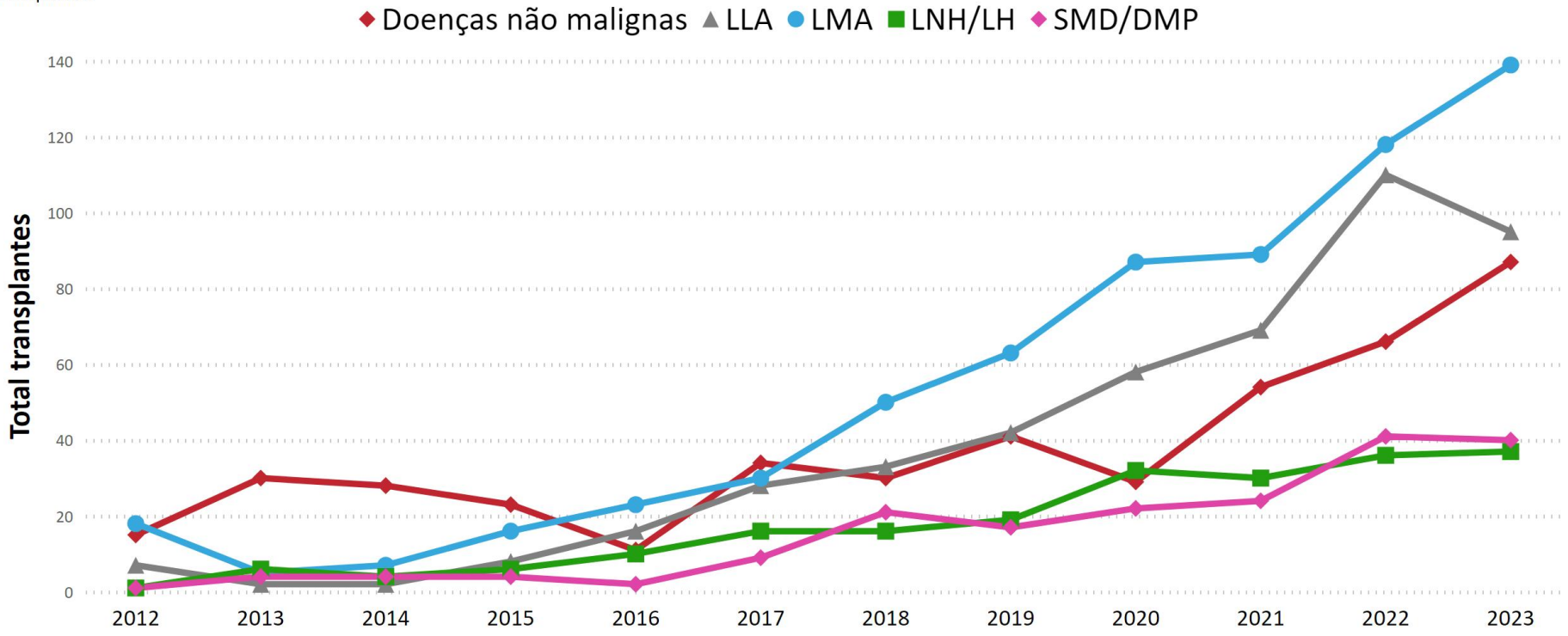


JBMTCT. 2024;5(1).

TCTH Alogênico aparentado com mismatch por diagnóstico

1965

transplantes*



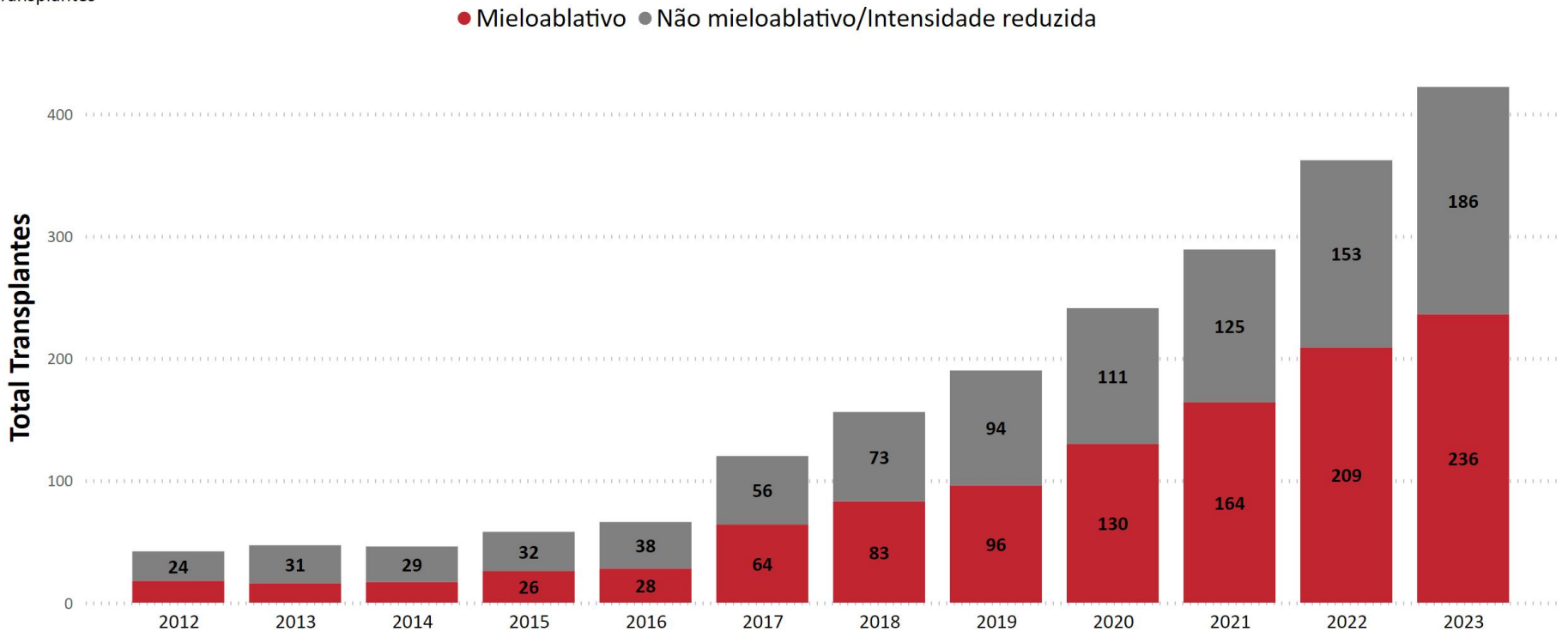
JBMTCT. 2024;5(1).

**Principais diagnósticos transplantados*

TCTH Alogênico aparentado com mismatch por condicionamento

2102

transplantes



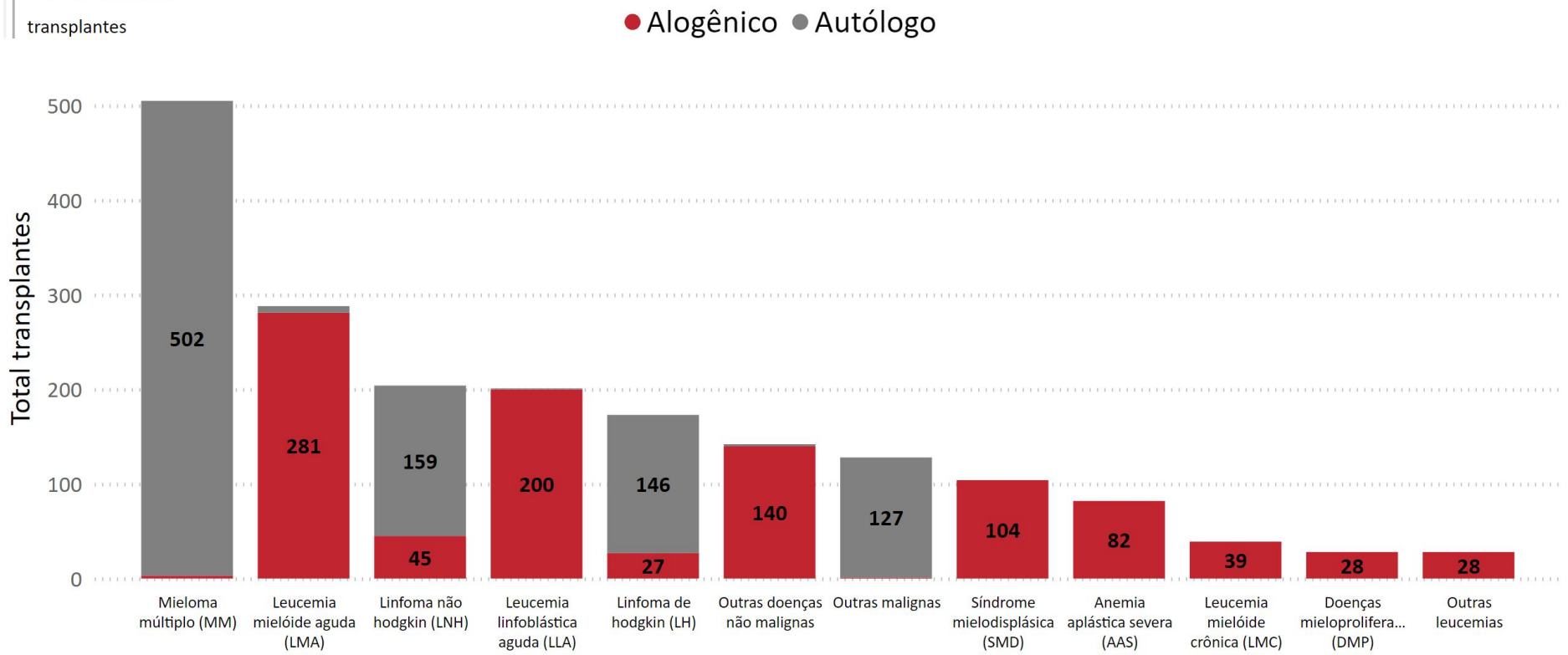
JBMTCT. 2024;5(1).

**63 transplantes sem informações sobre o tipo de condicionamento*

Indicações para TCTH no Brasil, 2023

1922

transplantes

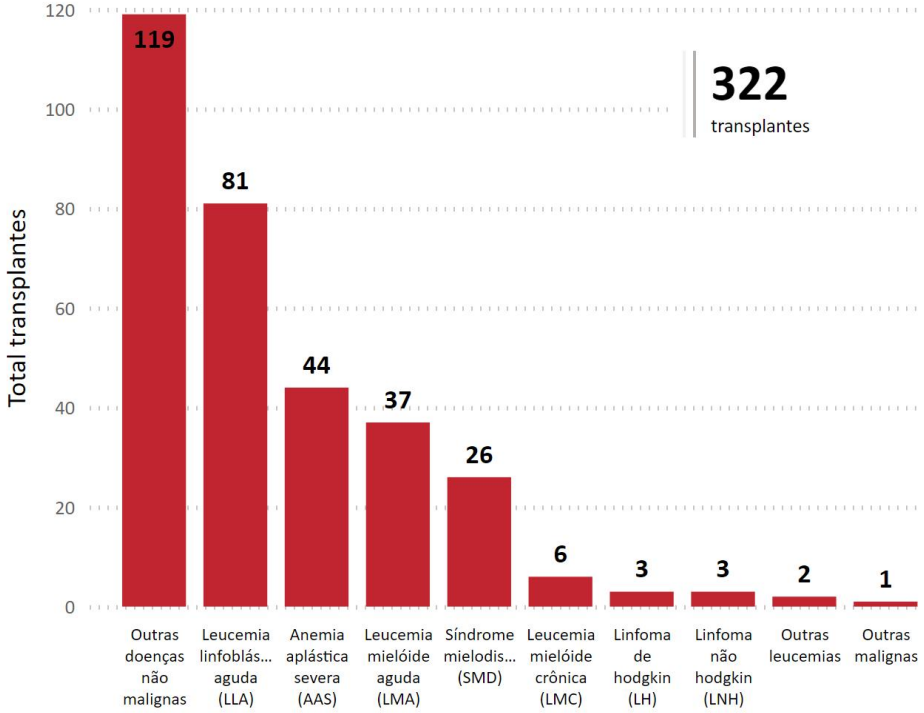


Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

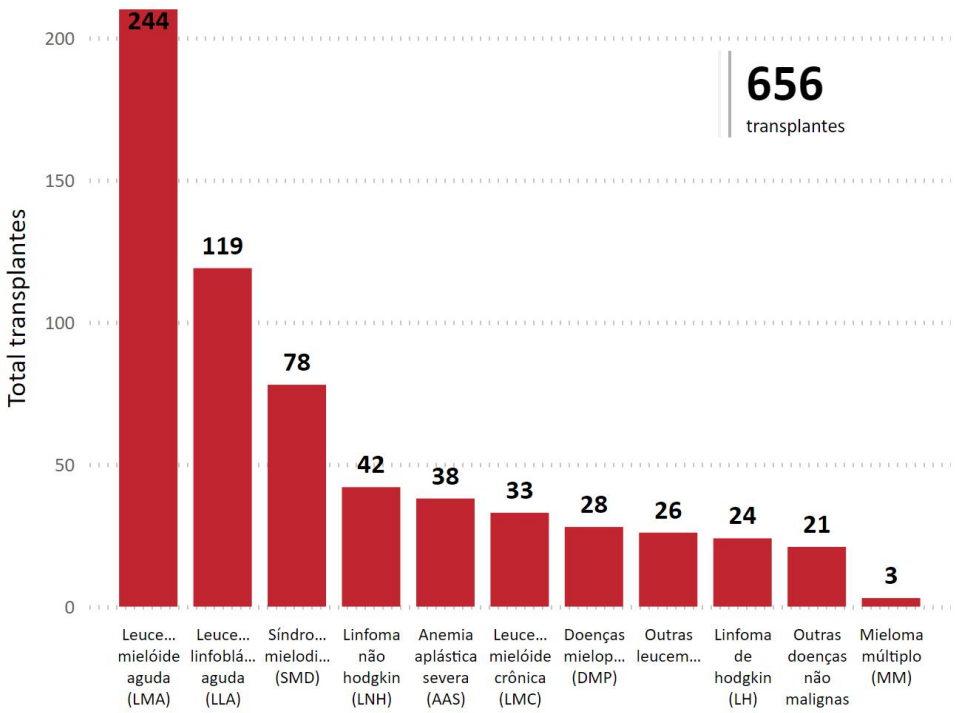
Indicações para TCTH Alogênico no Brasil, 2023

978
transplantes

0 - 17 anos



18 anos ou mais

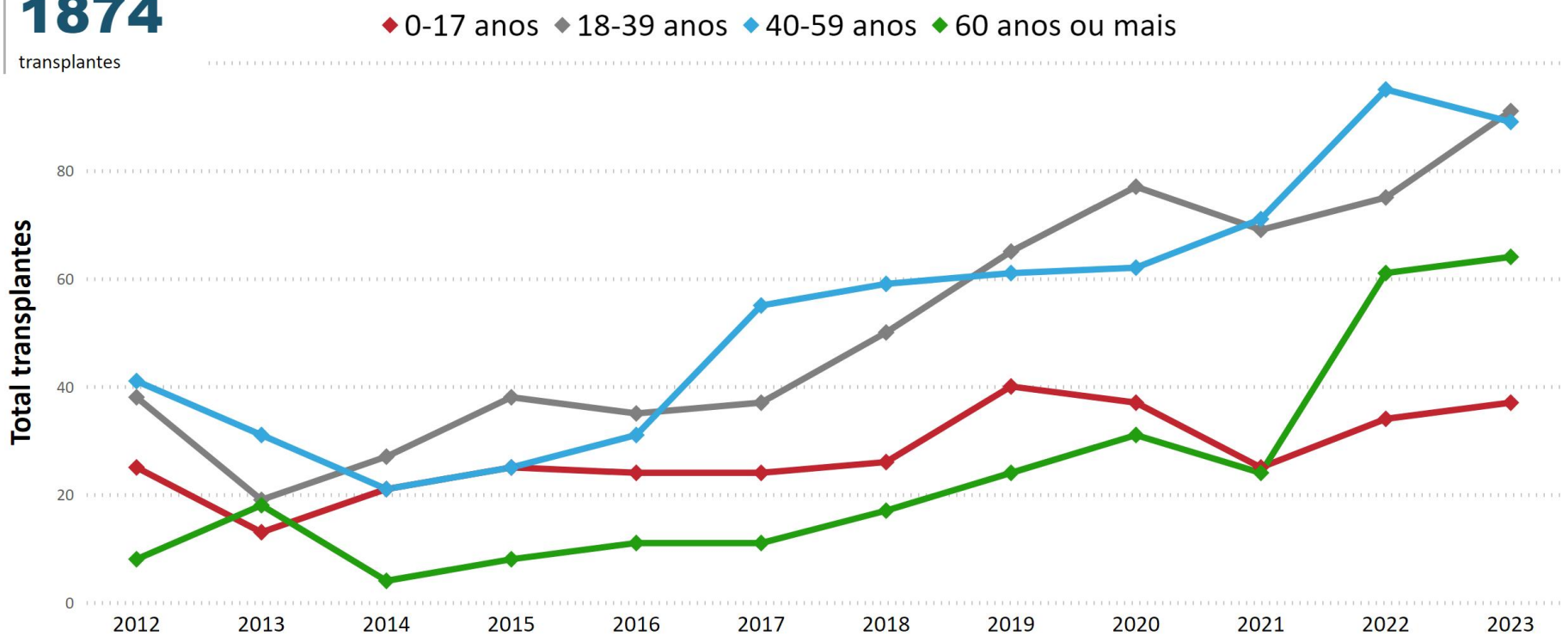


SBTMO CIBMTR GD BRASIL

JBMTCT. 2024;5(1).

Tendência no TCTH Alogênico para Leucemia Mieloide Aguda (LMA) pela idade do receptor

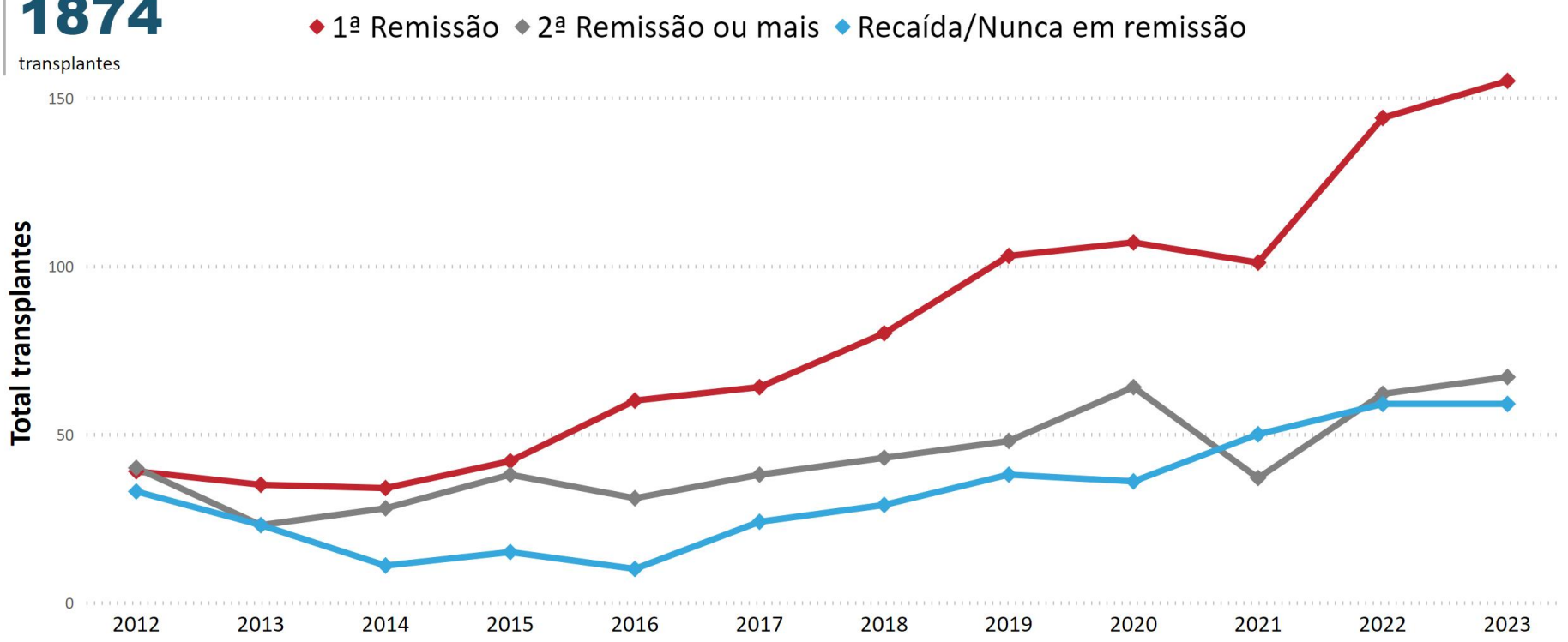
1874
transplantes



JBMTCT. 2024;5(1).

Tendência no TCTH Alogênico para Leucemia Mieloide Aguda (LMA) pelo status da doença pré transplante

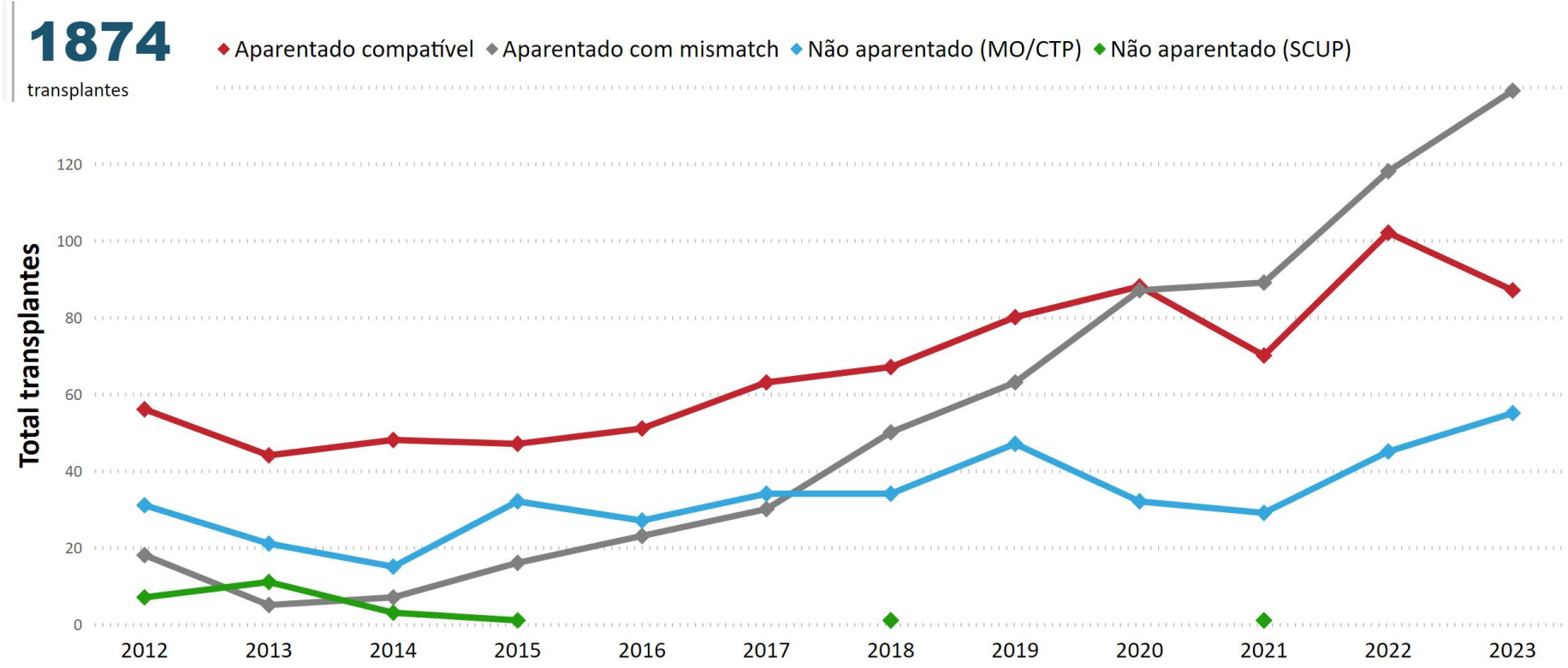
1874
transplantes



JBMTCT. 2024;5(1).

**4 transplantes sem informações sobre o status da doença*

Tendência no TCTH Alogênico para Leucemia Mieloide Aguda (LMA) por tipo de doador

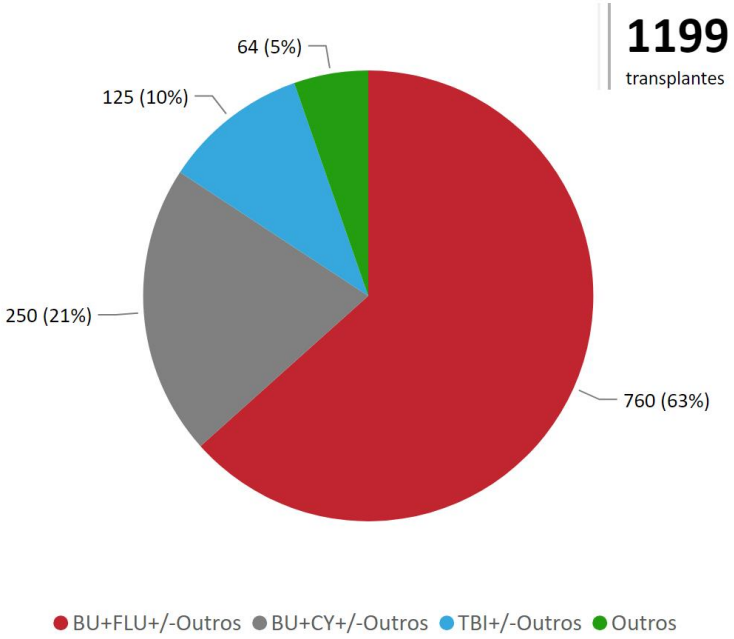


JBMTCT. 2024;5(1).

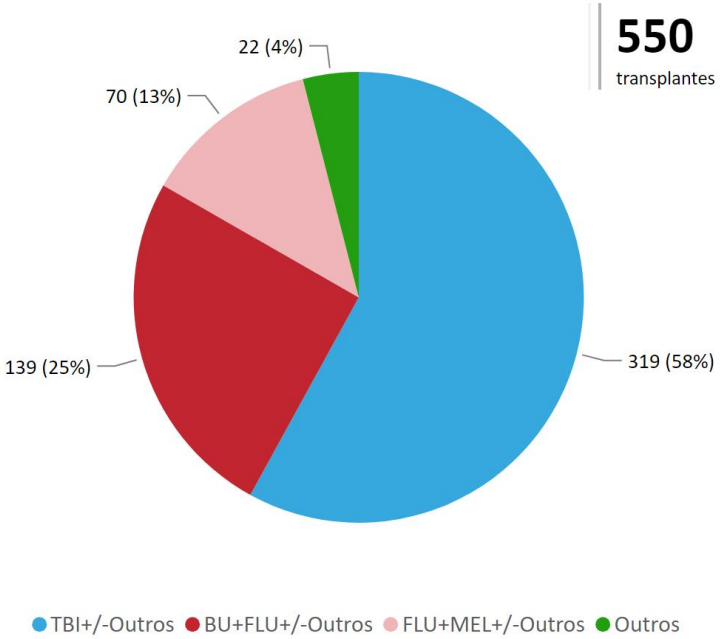
Principais condicionamentos para Leucemia Mieloide Aguda (LMA) no TCTH Alogênico

1874
transplantes*

Mieloablativo



Não Mieloablativo/Intensidade reduzida

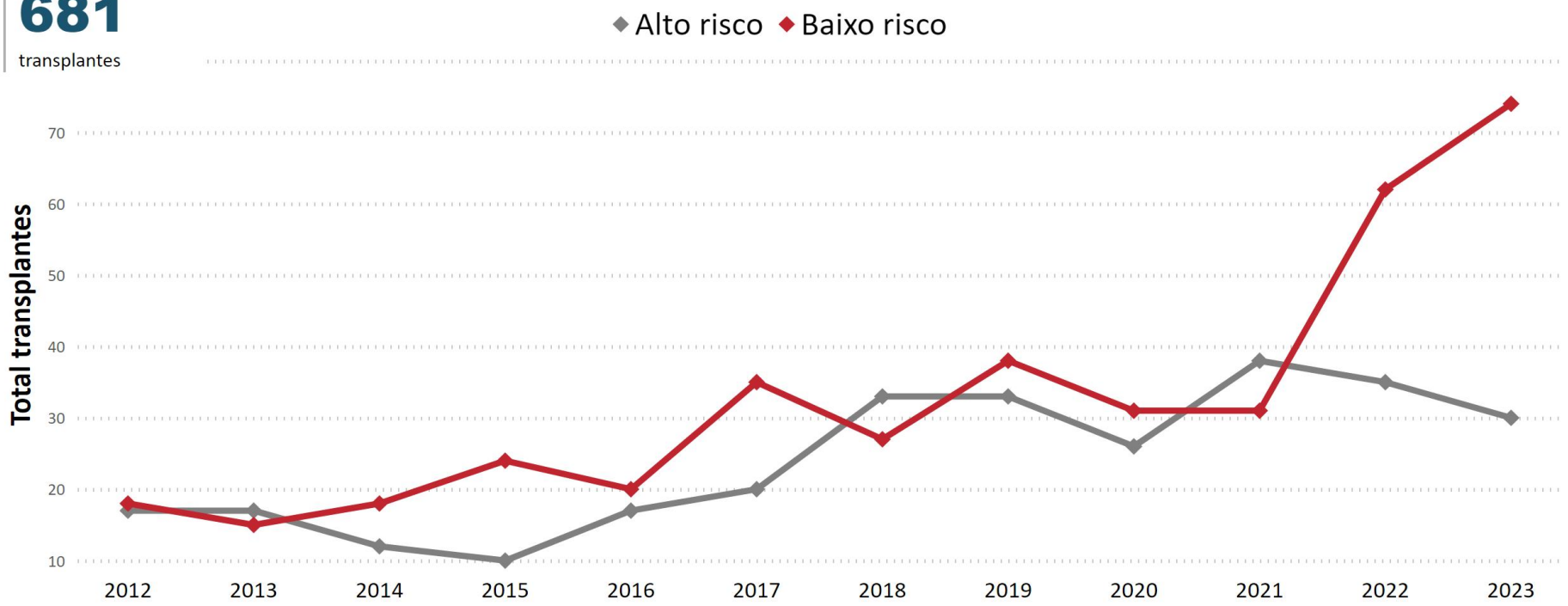


Bu: Bussulfano, Flu: Fludarabina, Cy: Ciclofosfamida, TBI: Irradiação corpórea total, Mel: Melfalano
**125 transplantes sem informações sobre condicionamento*

JBMTCT. 2024;5(1).

Tendência no TCTH Alogênico para Síndromes Mielodisplásicas (SMD) pelo estágio da doença pré transplante

681
transplantes



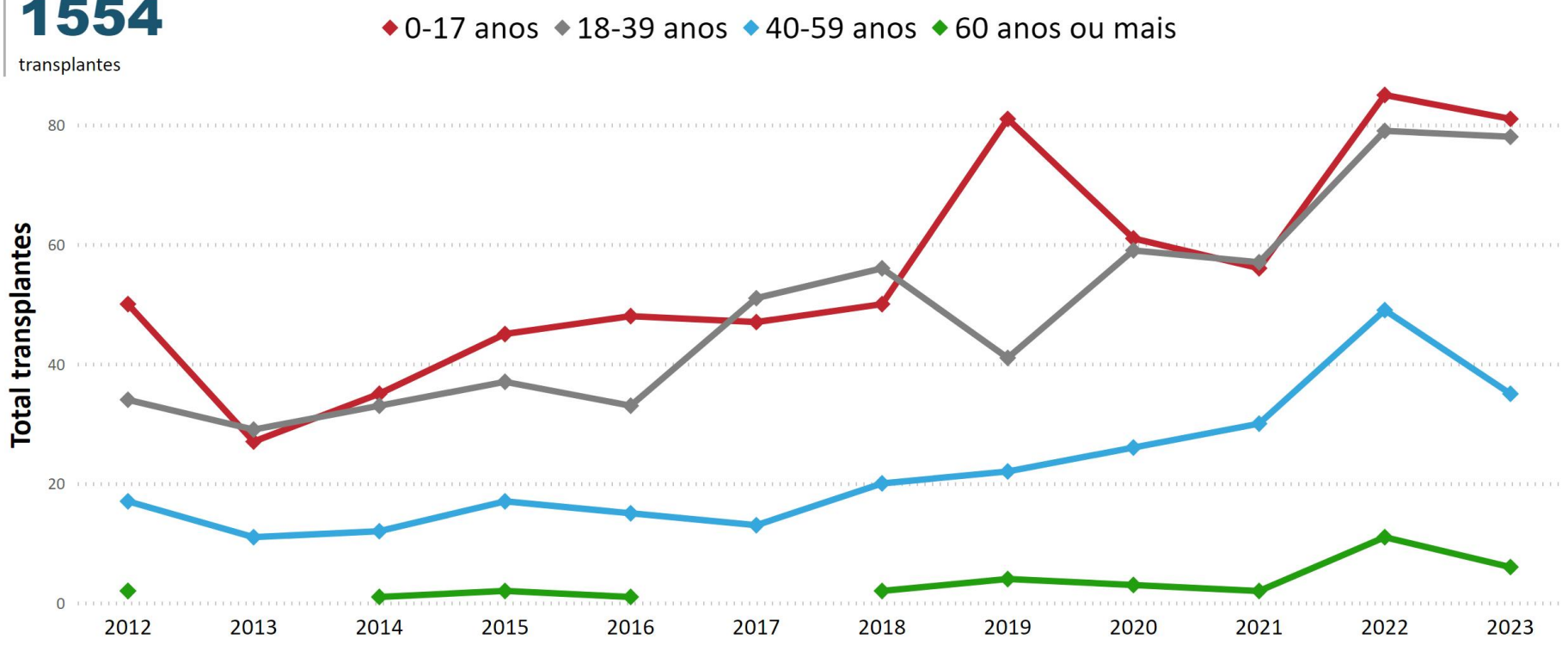
Baixo risco: Anemia refratária (AR) ou Anemia refratária com sideroblastos em anel (ARSA), Citopenia refratária com displasia multilinhagem (CRDM), SMD com del((5q) isolada

Alto risco: Anemia refratária com excesso de blastos (AREB) ou Leucemia Mielomonocítica Crônica (LMMC)

JBMTCT. 2024;5(1).

Tendência no TCTH Alogênico para Leucemia Linfoblástica Aguda (LLA) pela idade do receptor

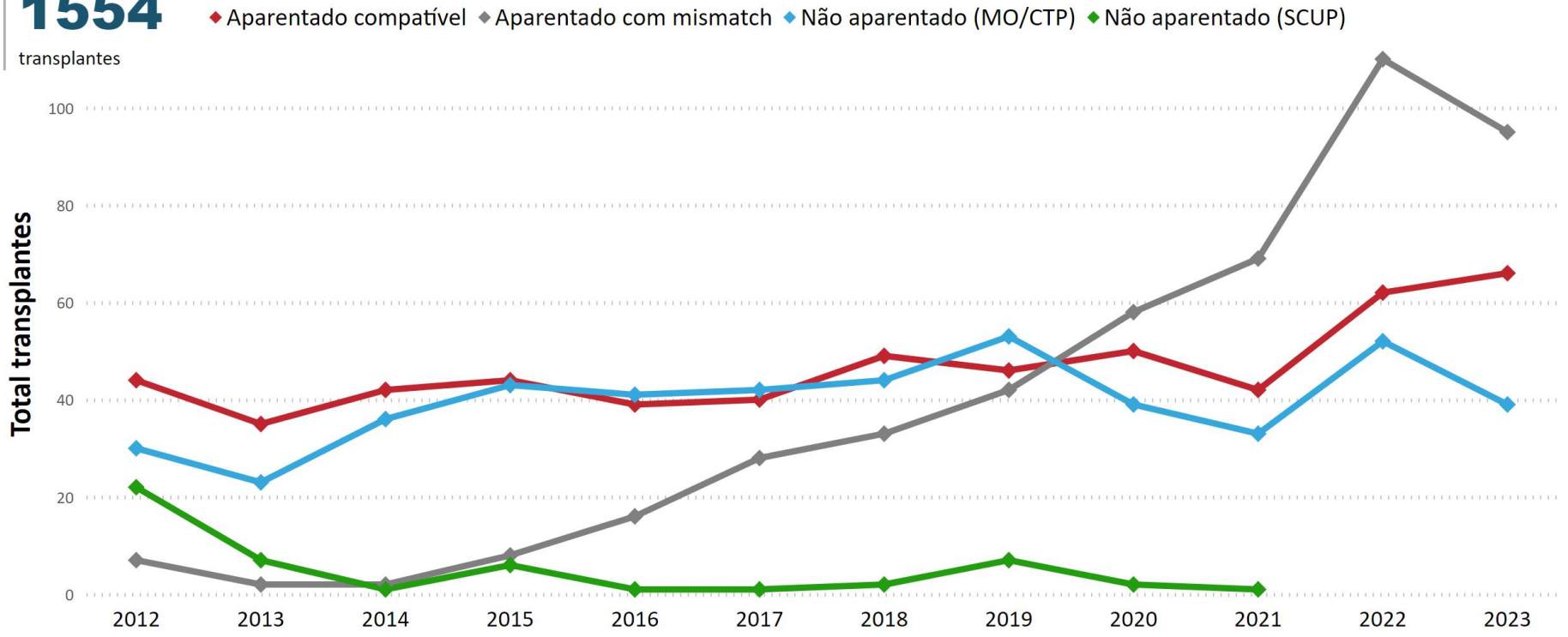
1554
transplantes



JBMTCT. 2024;5(1).

Tendência no TCTH Alogênico para Leucemia Linfoblástica Aguda (LLA) por tipo de doador

1554
transplantes

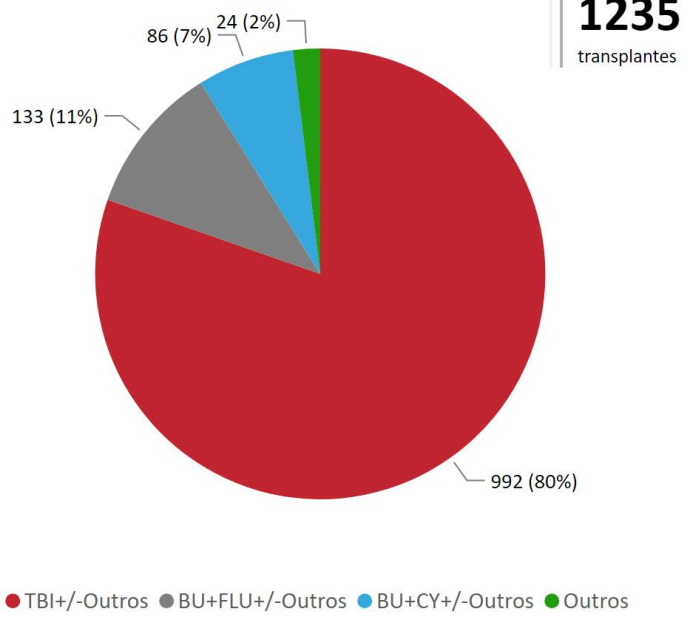


JBMTCT. 2024;5(1).

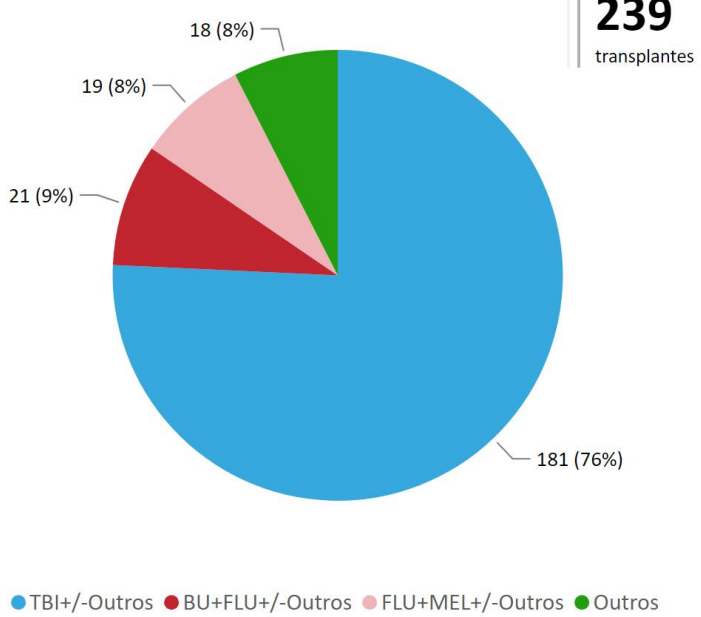
Principais condicionamentos para Leucemia Linfoblástica Aguda (LLA) no TCTH Alogênico

1554
transplantes

Mieloablativo



Não Mieloablativo/Intensidade reduzida



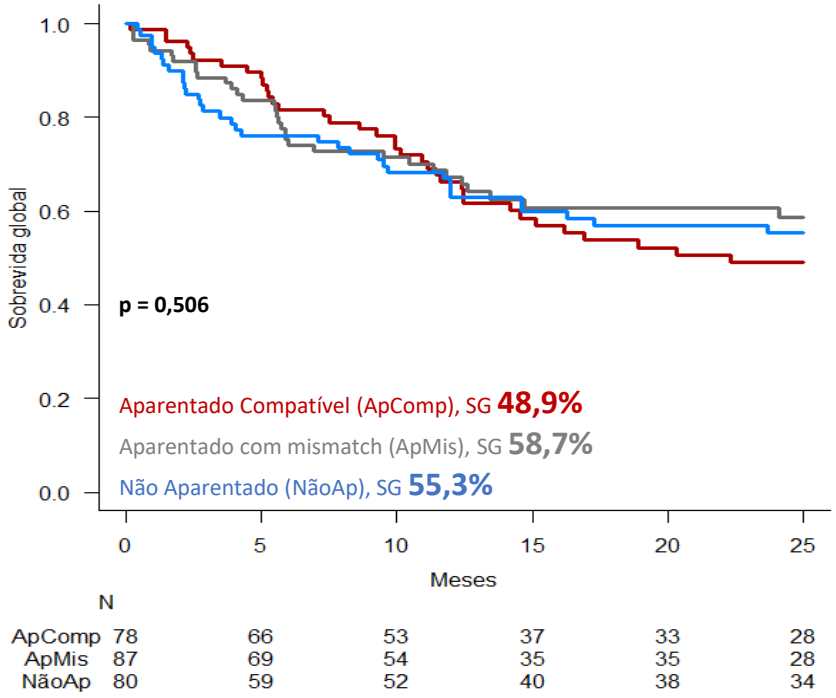
Bu: Bussulfano, Flu: Fludarabina, Cy: Ciclofosfamida, TBI: Irradiação corpórea total, Mel: Melfalano
**80 transplantes sem informações sobre condicionamento*

JBMTCT. 2024;5(1).

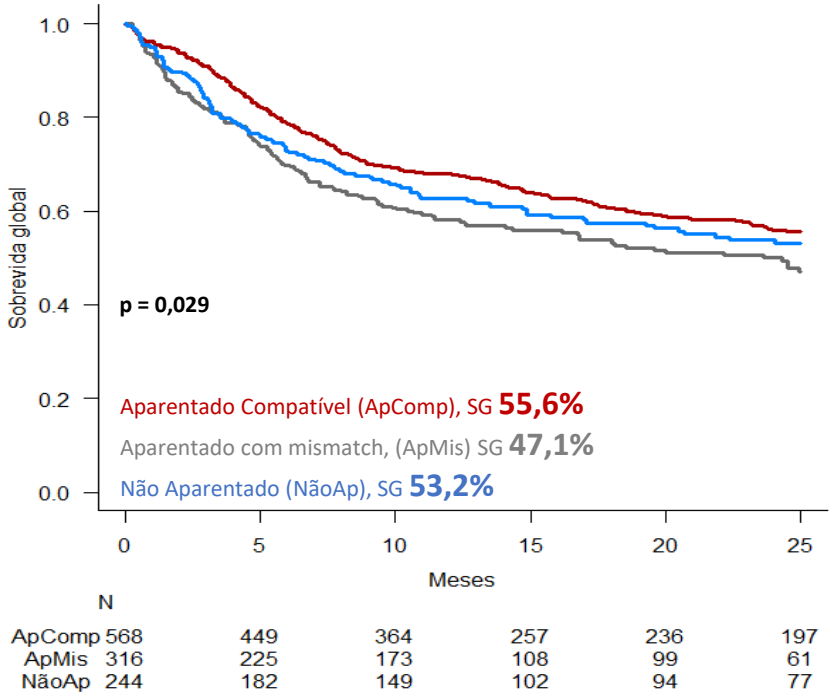
Leucemia mieloide aguda (LMA) – TCTH alogênico

Sobrevida global por **tipo de doador** após 1º TCTH (n=1.373)

0-17 anos (n=245)



18 anos ou mais (n=1.128)

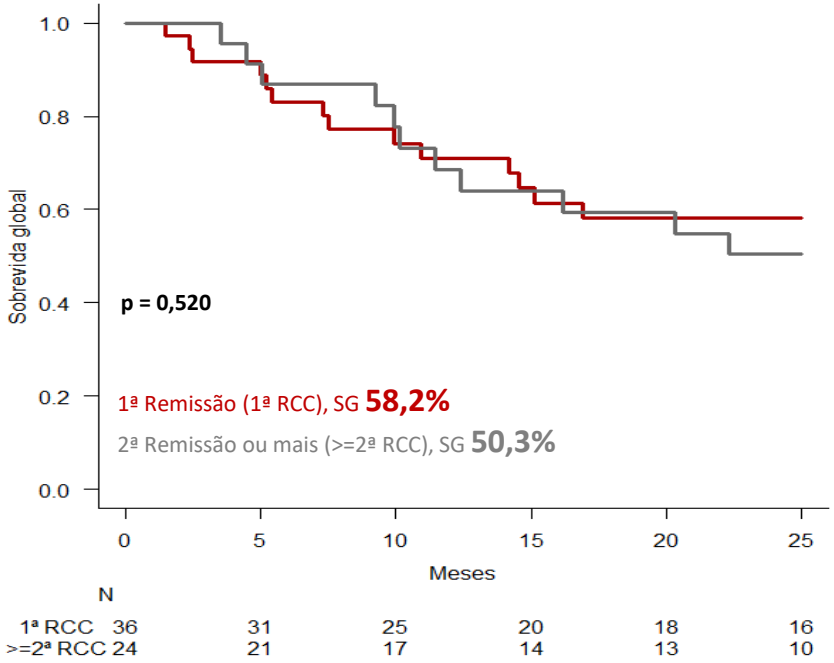


Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

Leucemia mieloide aguda (LMA) – Alogênico **aparentado compatível**

Sobrevida global por **status da doença** após 1º TCTH (n=646)

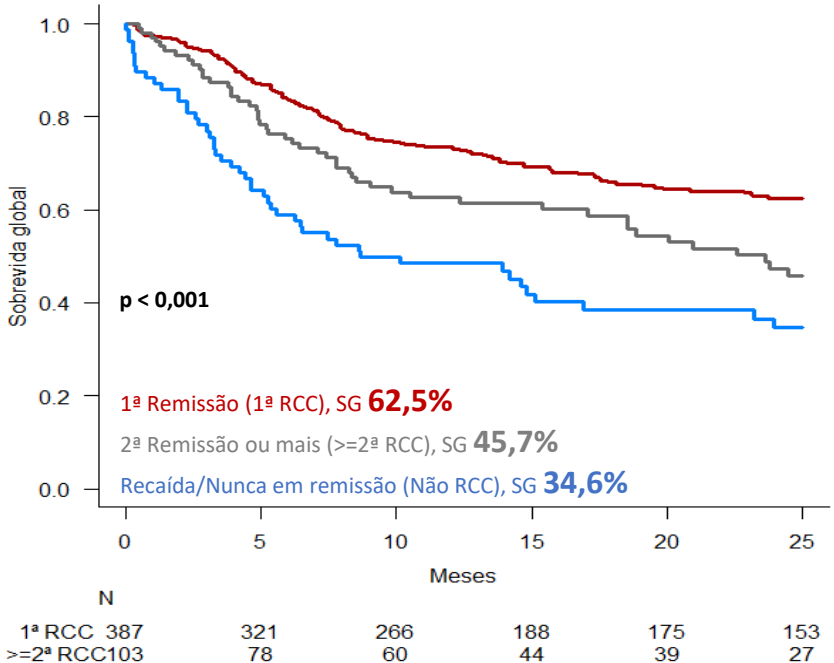
0-17 anos (n=78)



N					
1ª RCC 36	31	25	20	18	16
>=2ª RCC 24	21	17	14	13	10

***NãoRCC: (N=18)*

18 anos ou mais (n=568)



N					
1ª RCC 387	321	266	188	175	153
>=2ª RCC103	78	60	44	39	27
NãoRCC 78	50	38	25	22	17

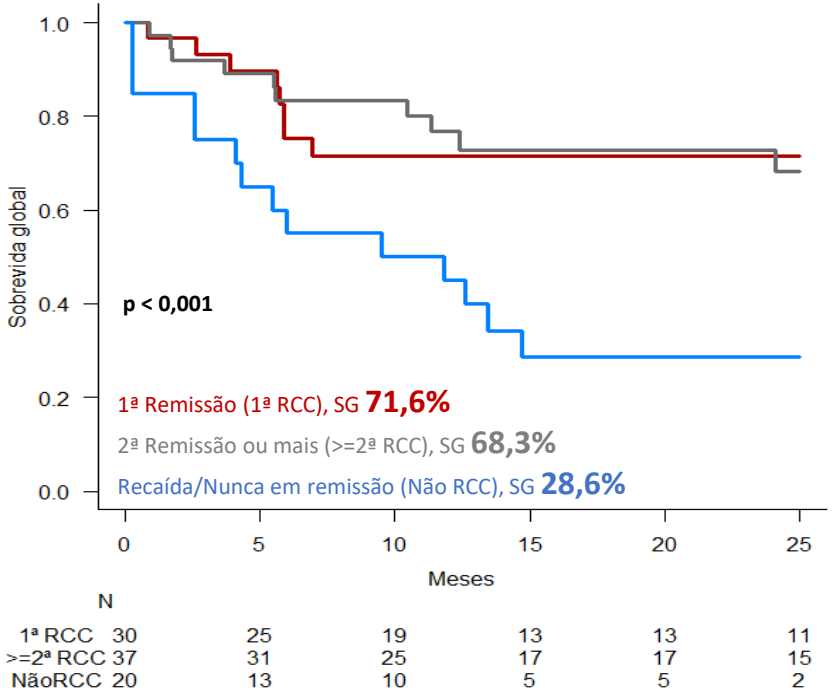
***Grupos com menos de 20 pacientes não serão apresentados no gráfico*

JBMTCT. 2024;5(1).

Leucemia mieloide aguda (LMA) – Alogênico **aparentado com mismatch**

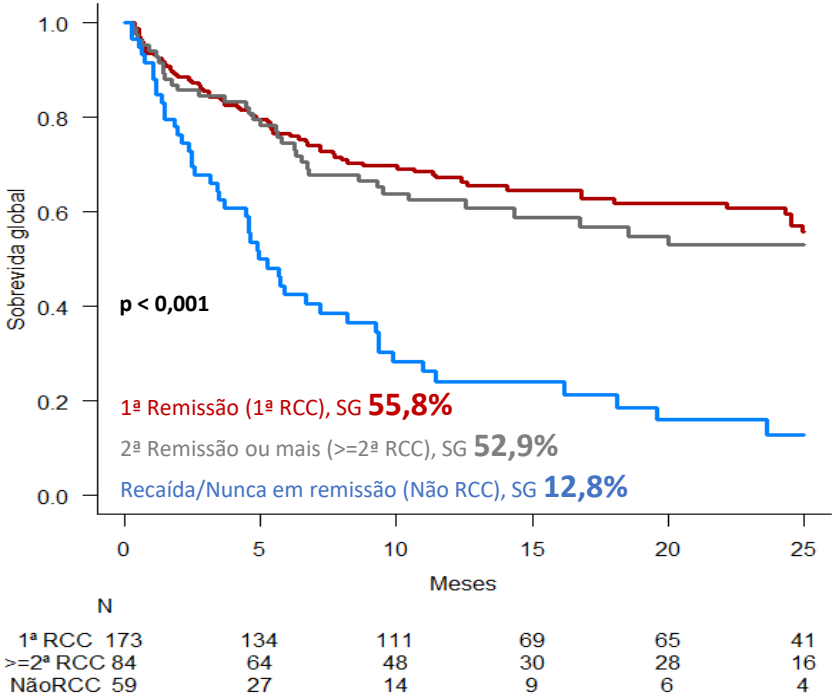
Sobrevida global por **status da doença** após 1º TCTH (n=403)

0-17 anos (n=87)



N					
1ª RCC 30	25	19	13	13	11
>=2ª RCC 37	31	25	17	17	15
NãoRCC 20	13	10	5	5	2

18 anos ou mais (n=316)



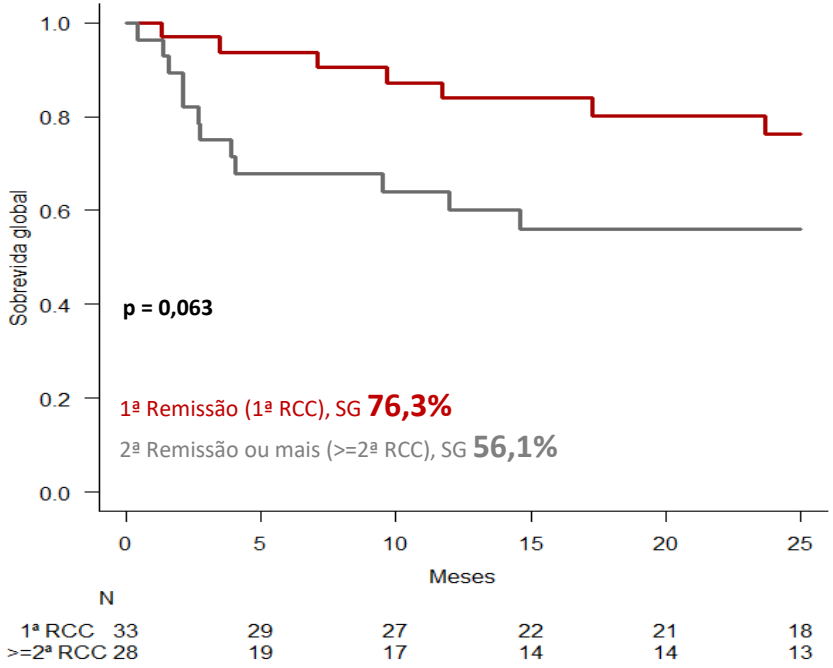
N					
1ª RCC 173	134	111	69	65	41
>=2ª RCC 84	64	48	30	28	16
NãoRCC 59	27	14	9	6	4

JBMTCT. 2024;5(1).

Leucemia mieloide aguda (LMA) – Alogênico **não aparentado**

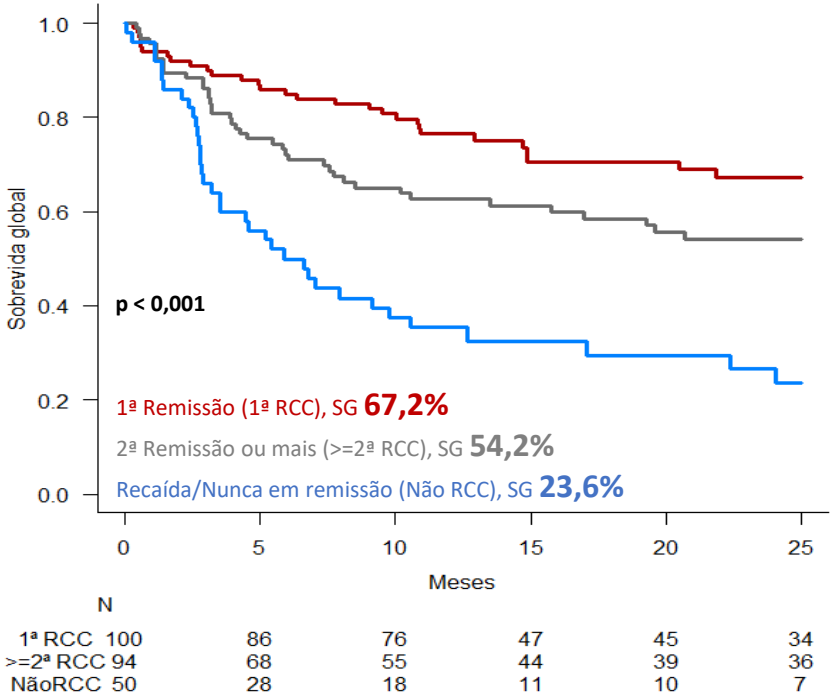
Sobrevida global por **status da doença** após 1º TCTH (n=324)

0-17 anos (n=80)



***NãoRCC: (N=19)*

18 anos ou mais (n=244)



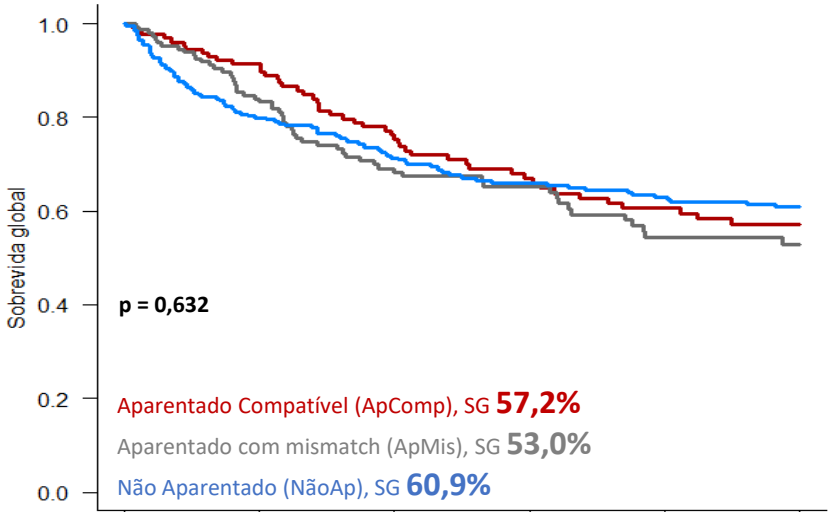
JBMTCT. 2024;5(1).

***Grupos com menos de 20 pacientes não serão apresentados no gráfico*

Leucemia linfoblástica aguda (LLA) – TCTH alogênico

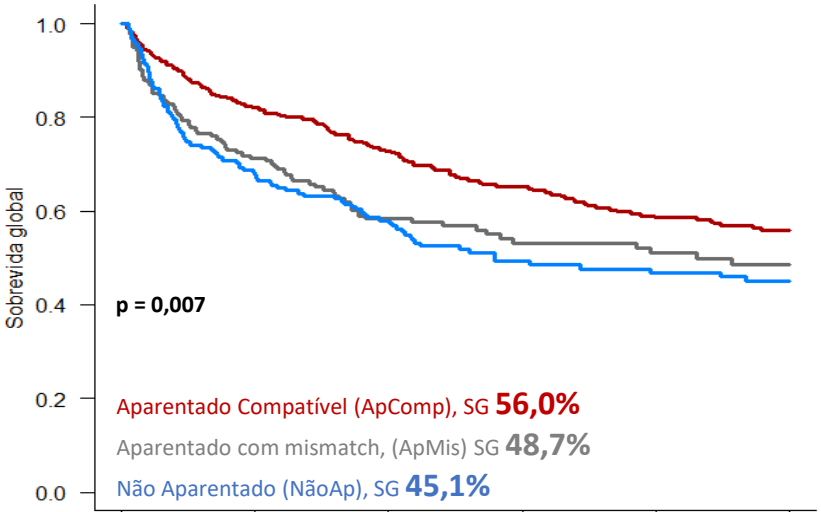
Sobrevida global por **tipo de doador** após 1º TCTH (n=1.213)

0-17 anos (n=525)



N						
ApComp	128	114	88	64	57	44
ApMis	147	117	83	56	45	34
NãoAp	250	195	165	133	125	109

18 anos ou mais (n=688)



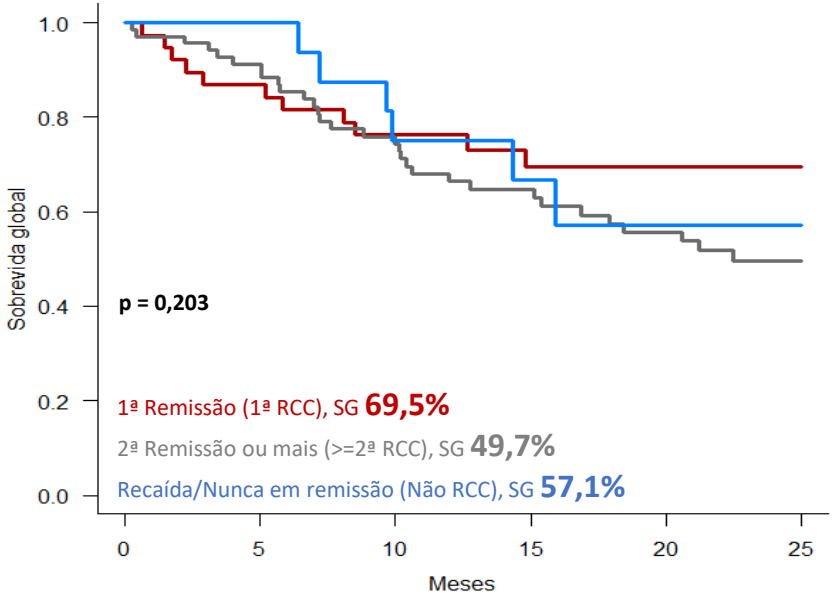
N						
ApComp	327	264	223	156	140	112
ApMis	175	121	93	53	50	31
NãoAp	186	125	97	59	55	47

Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

Leucemia linfoblástica aguda (LLA) – Alogênico **aparentado compatível**

Sobrevida global por **status da doença** após 1º TCTH (n=455)

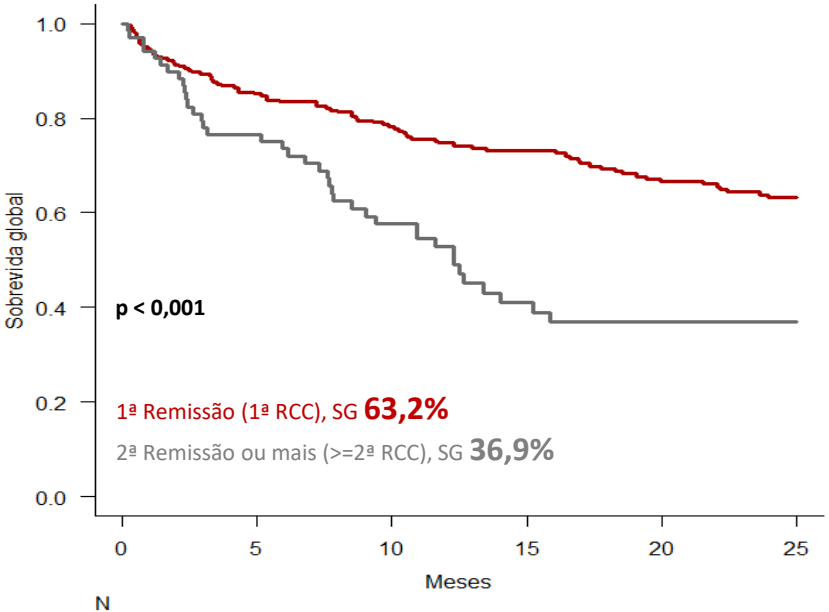
0-17 anos (n=128)



Number at risk

1ª RCC	38	33	29	20	20	17
>=2ª RCC	69	62	47	36	31	22
NãoRCC	21	19	12	8	6	5

18 anos ou mais (n=327)



N

1ª RCC	243	203	180	134	122	101
>=2ª RCC	69	52	36	20	18	11

***NãoRCC: (N=15)*

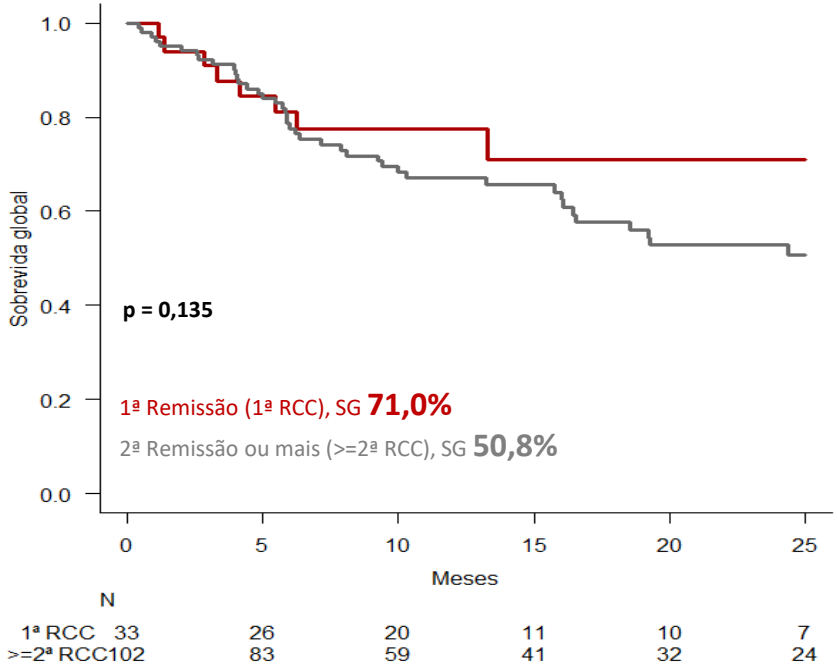
JBMTCT. 2024;5(1).

***Grupos com menos de 20 pacientes não serão apresentados no gráfico*

Leucemia linfoblástica aguda (LLA) – Alogênico **aparentado com mismatch**

Sobrevida global por **status da doença** após 1º TCTH (n=322)

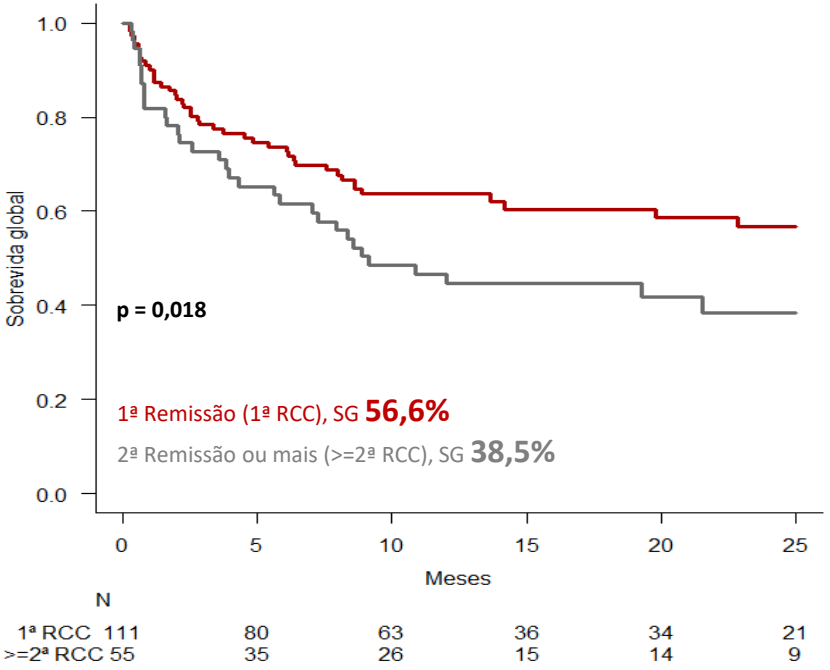
0-17 anos (n=147)



N					
1ª RCC 33	26	20	11	10	7
>=2ª RCC102	83	59	41	32	24

***NãoRCC: (N=12)*

18 anos ou mais (n=175)



N					
1ª RCC 111	80	63	36	34	21
>=2ª RCC 55	35	26	15	14	9

***NãoRCC: (N=9)*

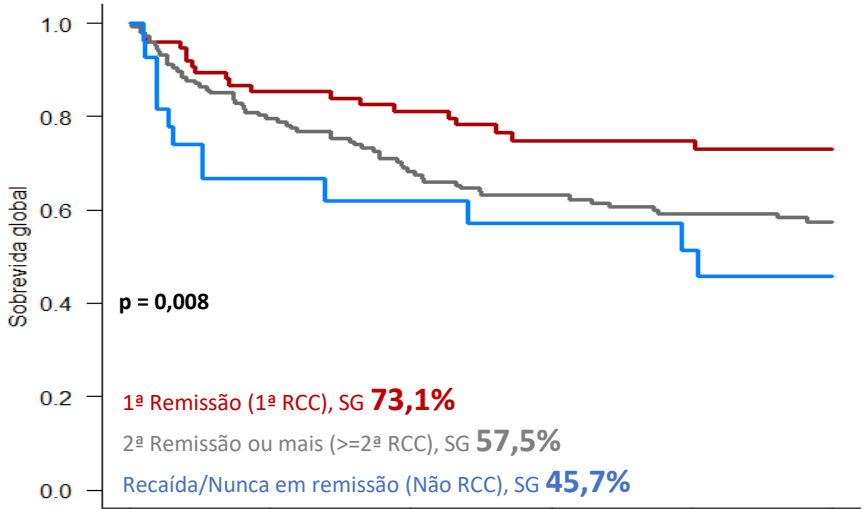
JBMTCT. 2024;5(1).

***Grupos com menos de 20 pacientes não serão apresentados no gráfico*

Leucemia linfoblástica aguda (LLA) – Alogênico **não aparentado**

Sobrevida global por **status da doença** após 1º TCTH (n=436)

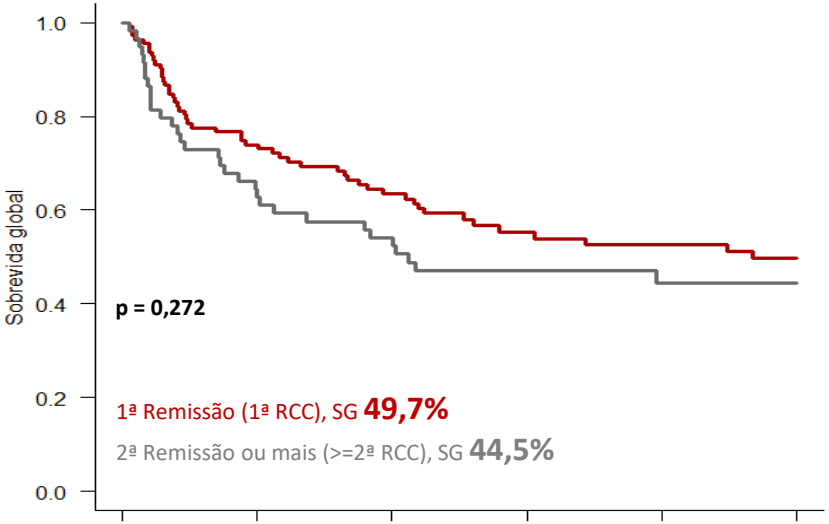
0-17 anos (n=250)



Number at risk

1ª RCC	76	64	57	42	41	35
>=2ª RCC	147	116	95	81	75	67
NãoRCC	27	15	13	10	9	7

18 anos ou mais (n=186)



N

1ª RCC	112	81	62	40	37	30
>=2ª RCC	59	38	31	18	17	16

***NãoRCC: (N=15)*

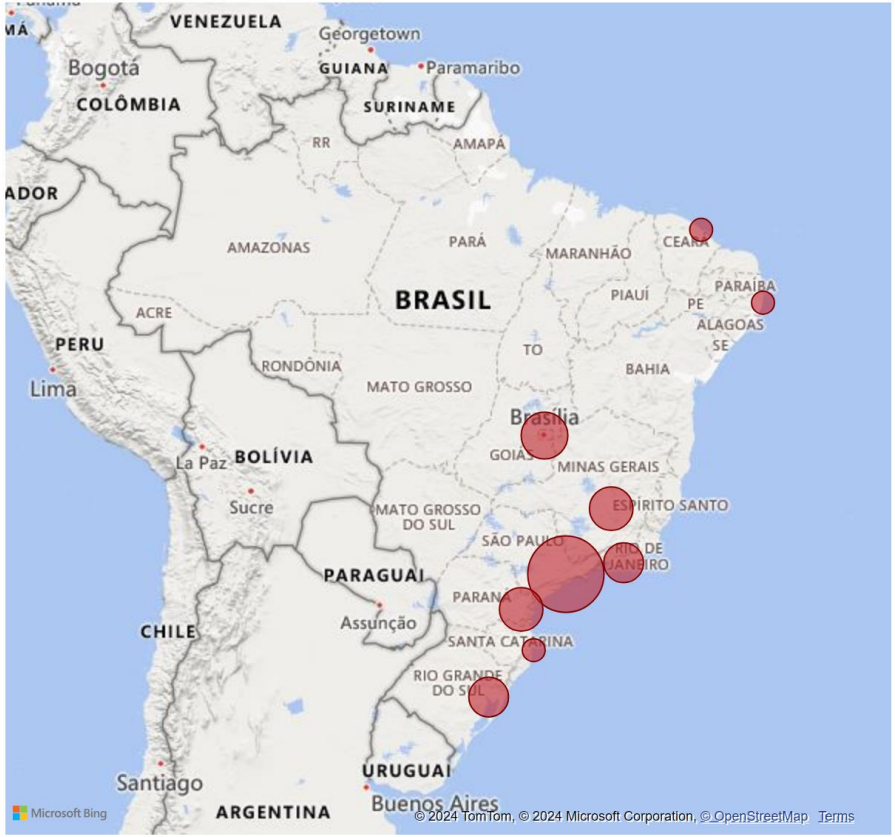
***Grupos com menos de 20 pacientes não serão apresentados no gráfico*

JBMTCT. 2024;5(1).

Localização dos centros participantes (2012-2023)

44

Centros TMO



Estado	Centros TMO
SP	21
DF	5
MG	4
PR	4
RJ	3
RS	3
CE	1
PE	1
RN	1
SC	1
Total	**44**

Simione AJ, et al. *JBMTCT.* 2024;5(1):30-46.

Data from Brazil

Transplants centers in Brazil (N=131)

- 86 Centers registered in the study
- 34 Active HSCT centers in 2022
- 1913 New HSCT registered in CIBMTR

JBMTCT. 2024;5(1).

13 Novos centros autorizados para TCTH em 2023

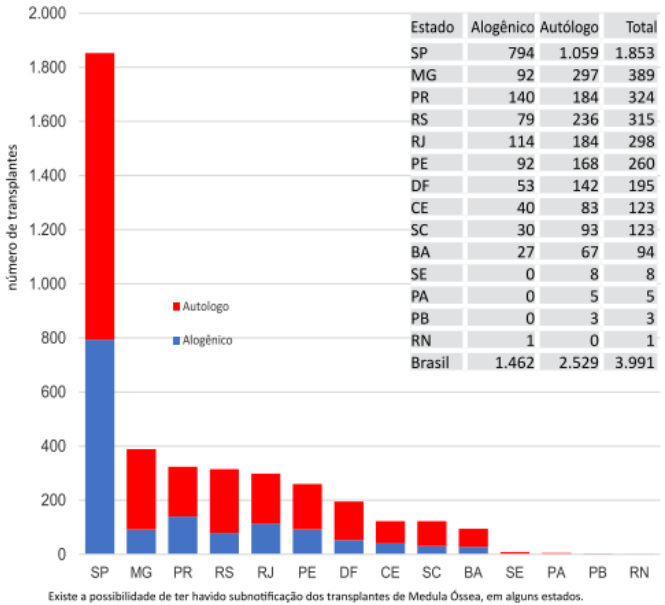
Região	UF	Nome Fantasia	Município	Natureza Jurídica	CNPJ	CNES
CENTRO OESTE	GO	HOSPITAL ESTADUAL DR ALBERTO RASSI HGG	GOIANIA	ADMINISTRAÇÃO PÚBLICA	02.529.964/0007-42	2338734
CENTRO OESTE	DF	HOSPITAL AGUAS CLARAS	BRASILIA	ENTIDADES EMPRESARIAIS	60.884.855/0024-40	0049867
CENTRO OESTE	DF	HOSPITAL ALVORADA DE BRASILIA	BRASILIA	ENTIDADES EMPRESARIAIS	29.435.005/0046-20	6921434
CENTRO OESTE	DF	HOSPITAL SANTA LUZIA	BRASILIA	ENTIDADES EMPRESARIAIS	00.106.435/0001-15	3005402
CENTRO OESTE	DF	HOSPITAL SANTA MARTA TAGUATINGA	BRASILIA	ENTIDADES EMPRESARIAIS	00.610.980/0001-44	2649497
CENTRO OESTE	DF	HOSPITAL UNIVERSITARIO DE BRASILIA	BRASILIA	ADMINISTRAÇÃO PÚBLICA	00.038.174/0006-58	0010510
SUDESTE	SP	SANTA CASA DE MISERICORDIA DE SAO JOSE DOS CAMPOS	SÃO JOSÉ DOS CAMPOS	ENTIDADES SEM FINS LUCRATIVOS	45.186.053/0001-87	2748029
SUDESTE	RJ	SAO CARLOS SAUDE ONCOLOGICA	RIO DE JANEIRO	ENTIDADES EMPRESARIAIS	33.804.212/0001-80	3009947
SUDESTE	RJ	CASA DE SAUDE SAO JOSE	RIO DE JANEIRO	ENTIDADES SEM FINS LUCRATIVOS	60.922.168/0003-48	2271443
SUDESTE	MG	HOSPITAL ALBERT SABIN	JUIZ DE FORA	ENTIDADES EMPRESARIAIS	17.268.871/0001-93	3019063
SUDESTE	MG	HOSPITAL DAS CLIN SAMUEL LIBANIO POUSO ALEGRE	POUSO ALEGRE	ENTIDADES SEM FINS LUCRATIVOS	23.951.916/0004-75	2127989
NORTE	PA	HOSPITAL OPHIR LOYOLA	BELEM	ADMINISTRAÇÃO PÚBLICA	08.109.444/0001-71	2334321
NORDESTE	PI	HOSPITAL SAO MARCOS	TERESINA	ENTIDADES SEM FINS LUCRATIVOS	06.870.026/0001-77	2726998

JBMTCT. 2024;5(1).

Dados ABTO 2022

117 equipes/14 estados

Número de Transplantes de MEDULA ÓSSEA, por estado, durante o ano de 2022

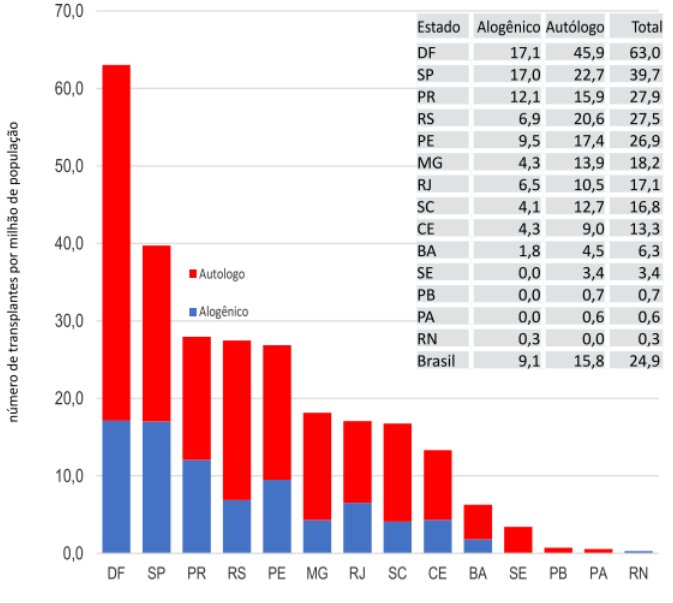


Estado	Alogênico	Autólogo	Total
SP	794	1.059	1.853
MG	92	297	389
PR	140	184	324
RS	79	236	315
RJ	114	184	298
PE	92	168	260
DF	53	142	195
CE	40	83	123
SC	30	93	123
BA	27	67	94
SE	0	8	8
PA	0	5	5
PB	0	3	3
RN	1	0	1
Brasil	1.462	2.529	3.991

Existe a possibilidade de ter havido subnotificação dos transplantes de Medula Óssea, em alguns estados.

JBMTCT. 2024;5(1).

Número por milhão de população de transplantes de MEDULA ÓSSEA, por estado, durante o ano de 2022

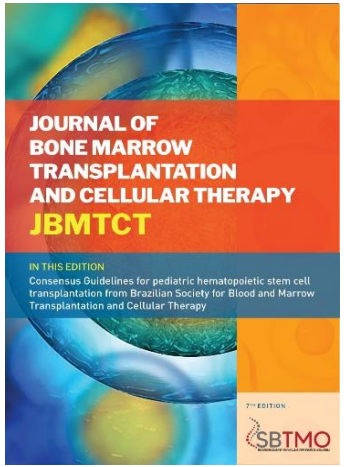


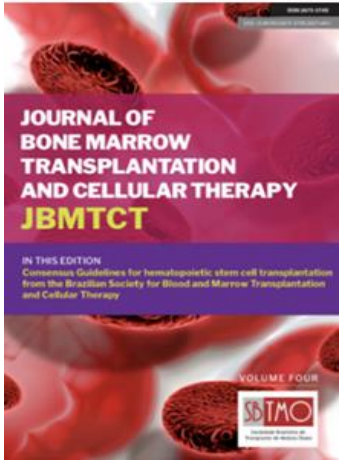
Estado	Alogênico	Autólogo	Total
DF	17,1	45,9	63,0
SP	17,0	22,7	39,7
PR	12,1	15,9	27,9
RS	6,9	20,6	27,5
PE	9,5	17,4	26,9
MG	4,3	13,9	18,2
RJ	6,5	10,5	17,1
SC	4,1	12,7	16,8
CE	4,3	9,0	13,3
BA	1,8	4,5	6,3
SE	0,0	3,4	3,4
PB	0,0	0,7	0,7
PA	0,0	0,6	0,6
RN	0,3	0,0	0,3
Brasil	9,1	15,8	24,9

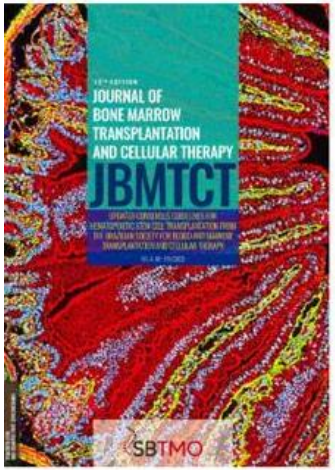
RBT, 2022.

Cenário Atual

- Consenso Brasileiro de TMO
  - Coordenação: Luís Bouzas, Abrahão Hallack e Leonardo Javier
- Consenso Pediátrico de TMO
  - Coordenação: Adriana Seber e Carmem Bonfim







JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY **JBMTCT**

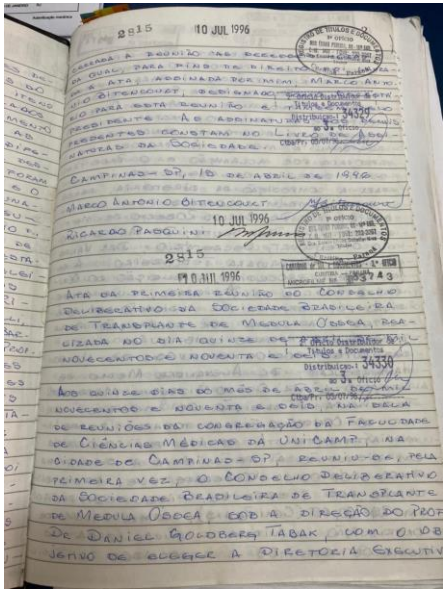
DOI: 10.46765/2675-374X.2023V4N2P200

CURRENT USE AND OUTCOMES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: BRAZILIAN SUMMARY SLIDES - 2023

Anderson João Simione[1], Heliz Regina Alves das Neves[2,29], Cinthya Corrêa da Silva[3], Paula Moreira da Silva Sabaini[4], Bruna Letícia da Silva Santos Geraldo[5], Leonardo Jun Otuyama[7], Marcelo C. Pasquini[6], Vergilio Antonio Rensi Colturato[1], Samir Kanaan Nabhan[2], Vanderson Geraldo Rocha[7], Carmen Silvia Vergueiro[5], Adriana Seber[5,8,9], Alexandre Silvério[10], Maria Claudia Rodrigues Moreira[11], George Maurício Navarro Barros[4], Claudia Caceres Astigarraga[12], Liane Esteves Daudt[13], Maria Cristina Martins de Almeida Macedo[14,15,25], Ricardo Chiattone[9], Yana Augusta Sarkis Novis[16], Juliana Folloni Fernandes[3, 17], Volney Assis Lara Vilela[18], Decio Lerner[19], Rodolfo Daniel de Almeida Soares[20], Phillip Scheinberg[21], Gustavo Machado Teixeira[22], Celso Arrais-Rodrigues[23], Marcos Paulo Colella[24], Roberto Luiz da Silva[25], Vaneuza Araújo Moreira Funke[2,29], Afonso Celso Vigorito[24], Leonardo Javier Arcuri3,[19], Nelson Hamerschlak[3], Jayr Schmidt Filho[26], Vinicius Campos de Molla[27], João Samuel de Holanda Farias[28], Ricardo Pasquini [2,29], Carmem Maria Sales Bonfim[30], Abrahão Elias Hallack Neto[31], Rodolfo Froes Calixto[32], Monique Ammi[33], Luis Fernando Bouzas[34], João Victor Piccolo Feliciano[35], Rafael Dezen Gaiolla[36], Marcelo Capra[37], Angelo Atalla[38], Milton Alexandre Ferreira Aranha[39,40,41], Rony Schaffel[42], Gianne Donato Costa Veloso[43], Antonio Vaz de Macedo[44], Fernando Barroso Duarte[45],

Histórico

- Primeiro transplante no Brasil foi realizado pelos hematologistas Ricardo Pasquini e Eurípedes Ferreira, em outubro de 1979.
- Criação da SBTMO- 15 de abril de 1996



Fundação FAPESP.

Centro de Oncológia e Hematologia BP

Hospital BP Mirante

Hospital BP Mirante

scheinbp@bp.org.br

Educação e Pesquisa

Global Leukemia Academy

BREAK

APTITUDE HEALTH®

Global Leukemia Academy

Current treatment options for relapsed AML in adult and elderly patients

Fabio Santos

APTITUDE HEALTH®

Disclosures

Research support	Nothing to report
Employee	Nothing to report
Consultancy	AbbVie, Bristol Myers Squibb, Novartis, Amgen, Janssen-Cilag, United Medical, Sanofi-Genzyme
Scientific advisory board	Janssen-Cilag, AbbVie, Amgen, Pfizer, Astellas, Servier, Novartis
Speaker	Janssen-Cilag, Bristol Myers Squibb, Novartis, MSD, Amgen, AbbVie, Pfizer, Astellas, Libbs, Servier
Other	Nothing to report

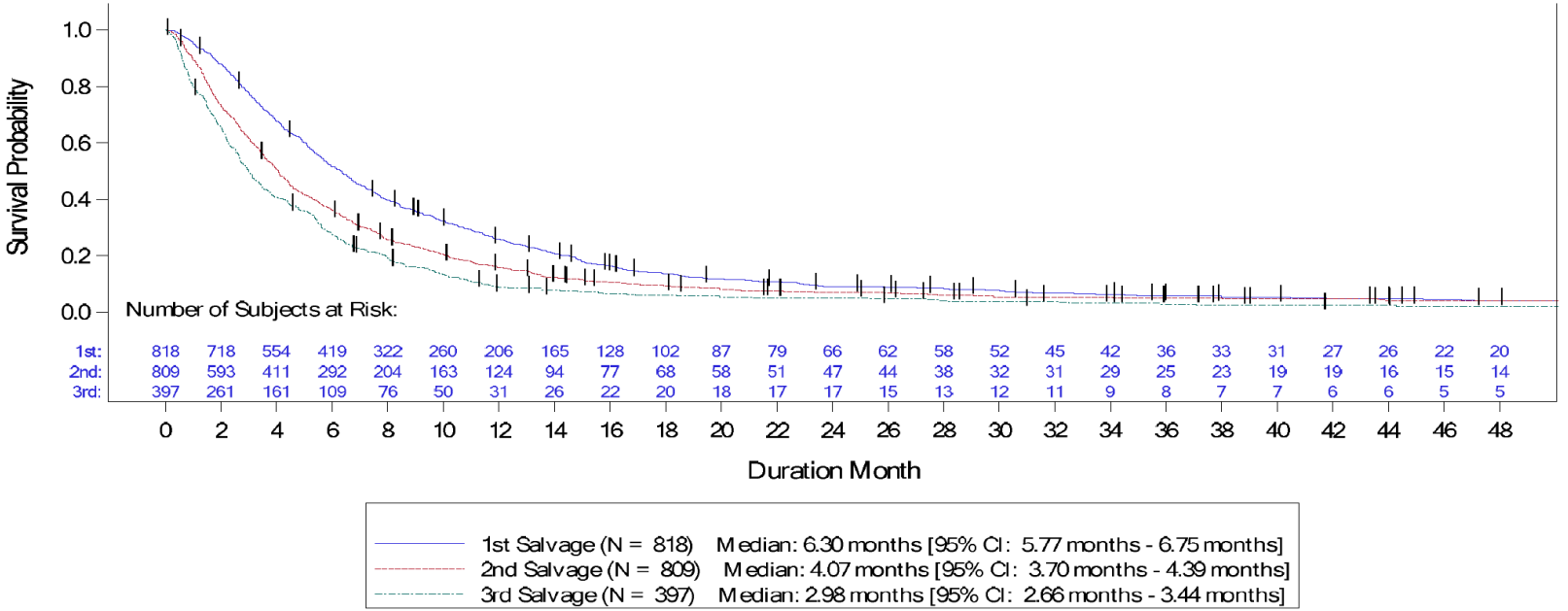
Relapsed/Refractory (R/R) AML

- Relapsed AML → reappearance of leukemic blasts after a patient has a complete remission (CR)
- Refractory AML → patient does not have a CR after at least 2 courses of induction, including at least 1 with intermediate-dose cytarabine
- Cumulative incidence of relapse in AML ranges from 20%–70%, depending on the following risk factors
  - Genomic abnormalities
  - Achievement (or lack of) of negative measurable residual disease (MRD)
  - Therapeutic choices in first-line treatment

Morita K, et al. *J Clin Oncol.* 2018;36:1788-1797; Bazinet A, et al. *Blood Adv*. 2023;7:3284-3296; Döhner H, et al. *Blood*. 2022;140:1345-1377; Ferguson P, et al. *Haematologica*. 2016;101:1351-1358.

Survival Outcomes in R/R AML Are Poor

Figure 1A. Kaplan-Meier Curve of OS



Censor indicated by vertical bar |.

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Ravandi F, et al. *Clin Lymphoma Myeloma Leuk.* 2020;20:e871-e882.

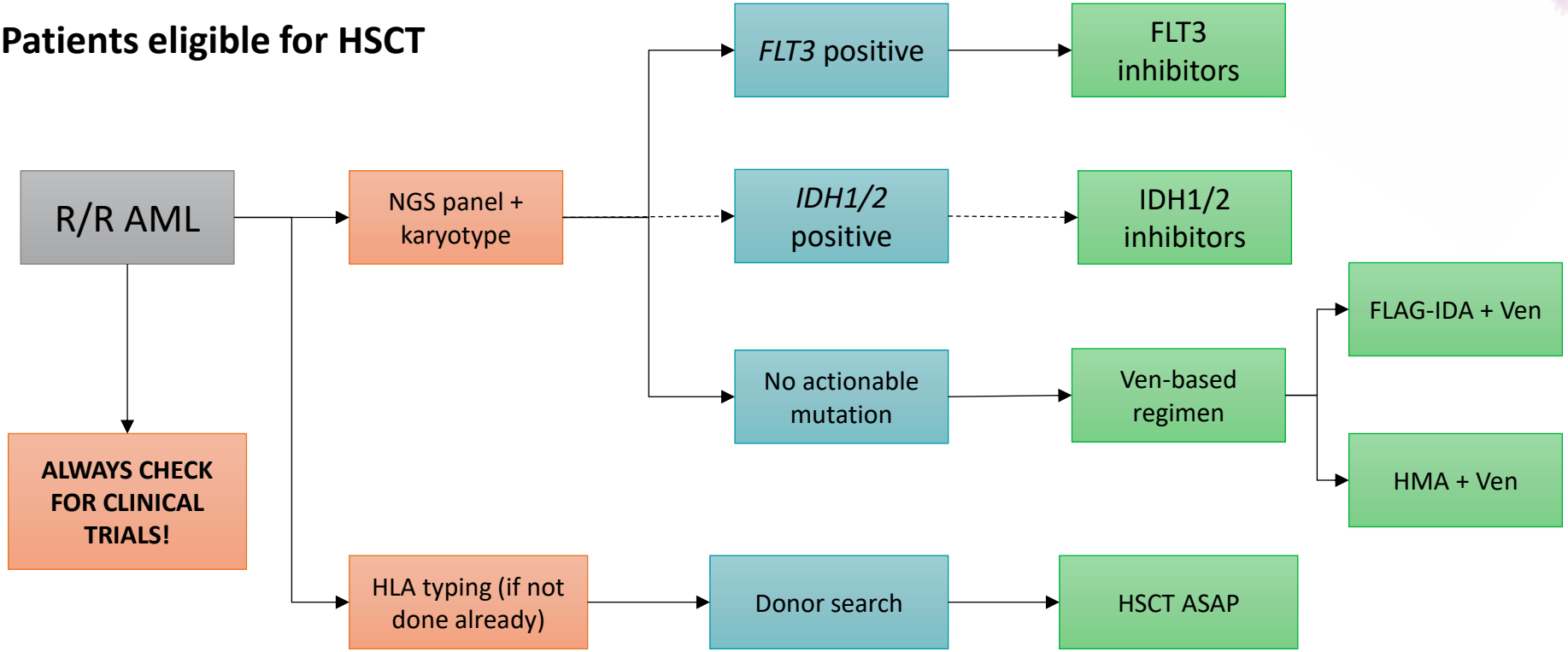
Risk Factors for Poor Outcomes in R/R AML

- Poor risk cytogenetic/molecular abnormalities at diagnosis and/or time of relapse
- Older patients
- Poor performance status
- Duration of prior remission (worse if <6 months)
- Second or later relapse
- Prior hematopoietic stem cell transplantation (HSCT)

Morita K, et al. *J Clin Oncol.* 2018;36:1788-1797; Bazinet A, et al. *Blood Adv*. 2023;7:3284-3296; Döhner H, et al. *Blood*. 2022;140:1345-1377; Ferguson P, et al. *Haematologica*. 2016;101:1351-1358.

How I Treat Patients With R/R AML

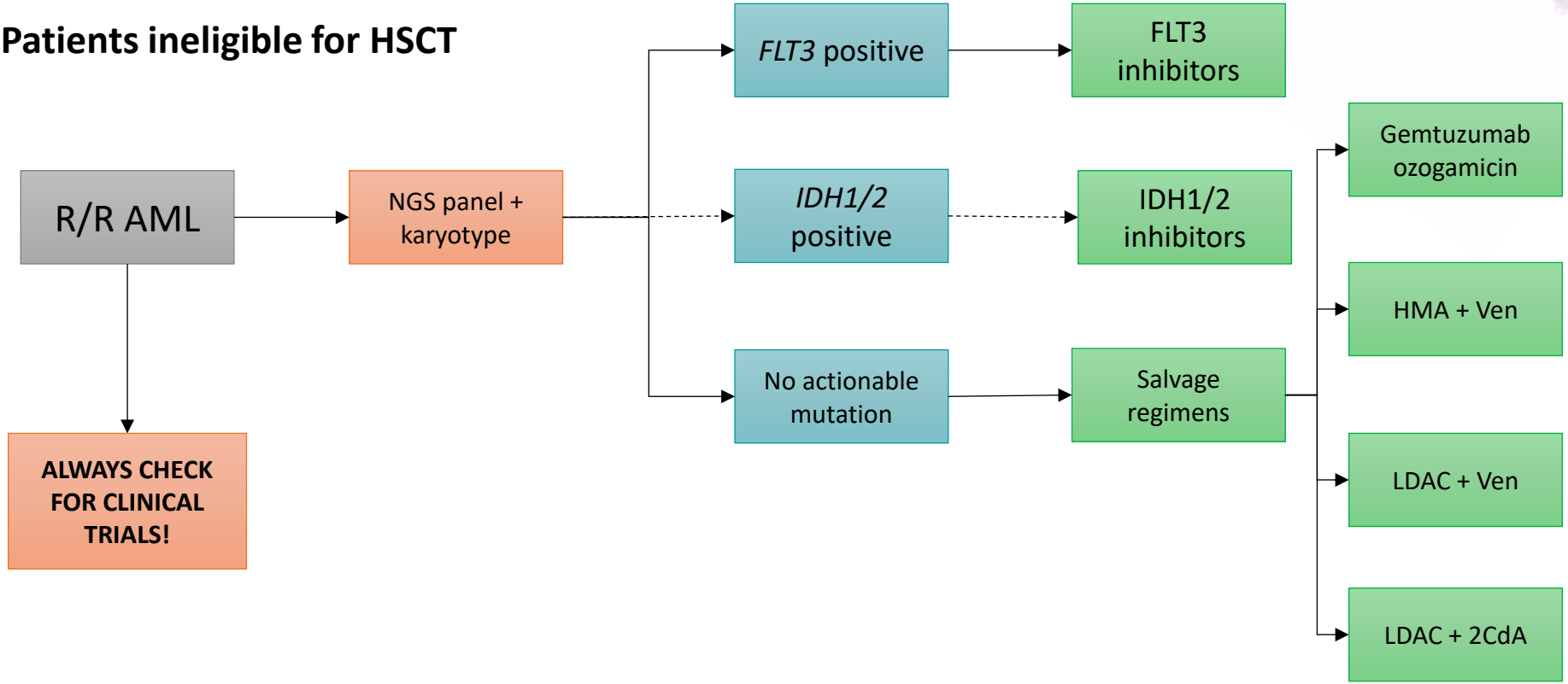
Patients eligible for HSCT



Slide from the author.

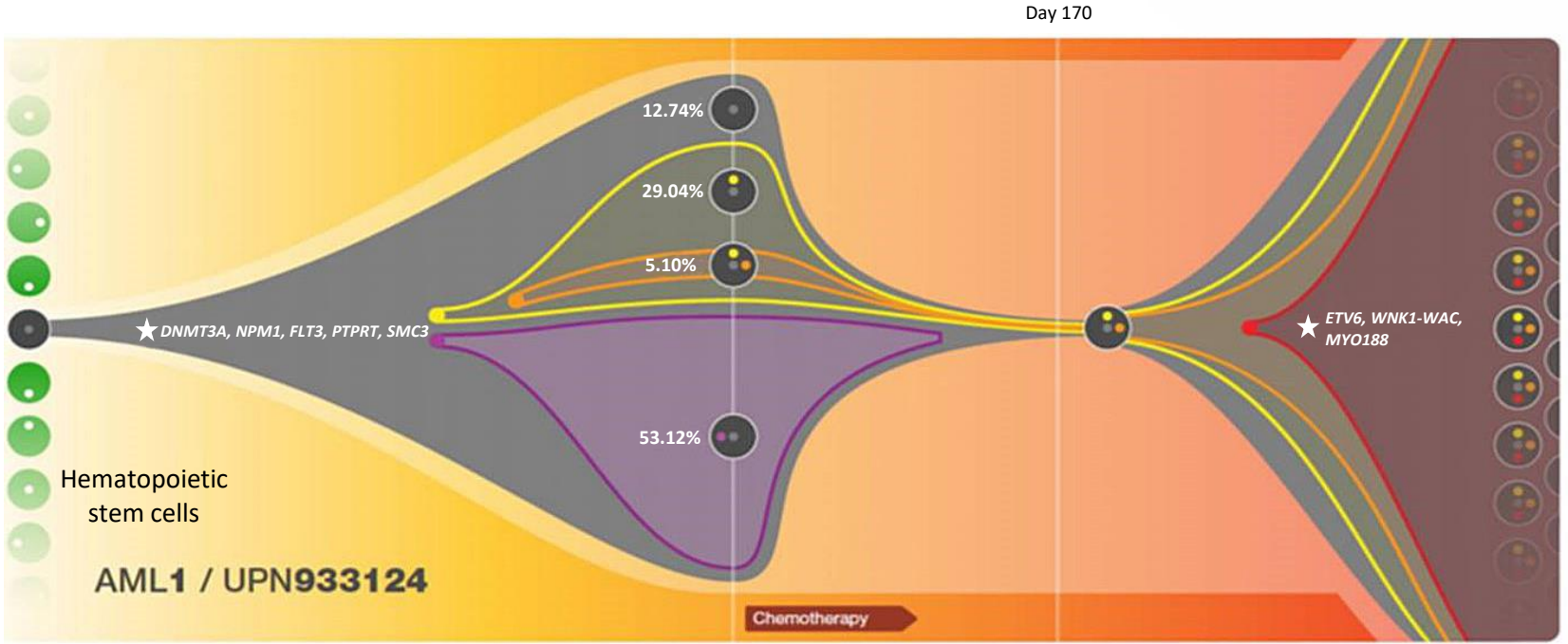
How I Treat Patients With R/R AML

Patients ineligible for HSCT



Slide from the author.

Molecular Evolution of AML Over Time

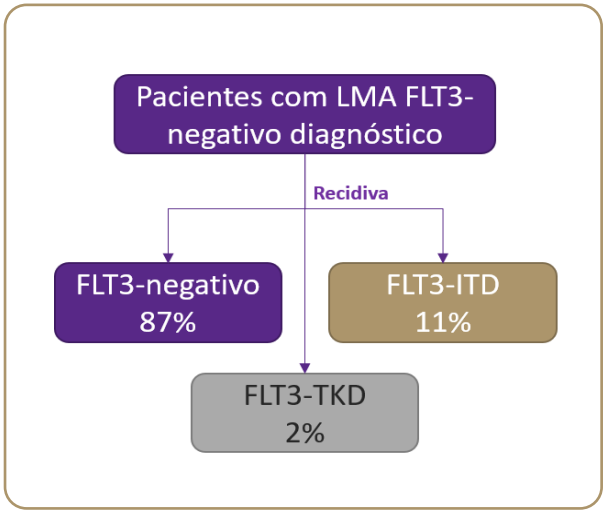


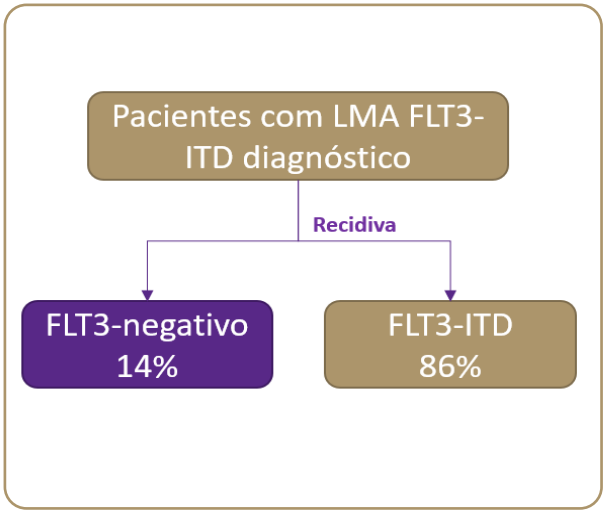
Normal cell
AML cell

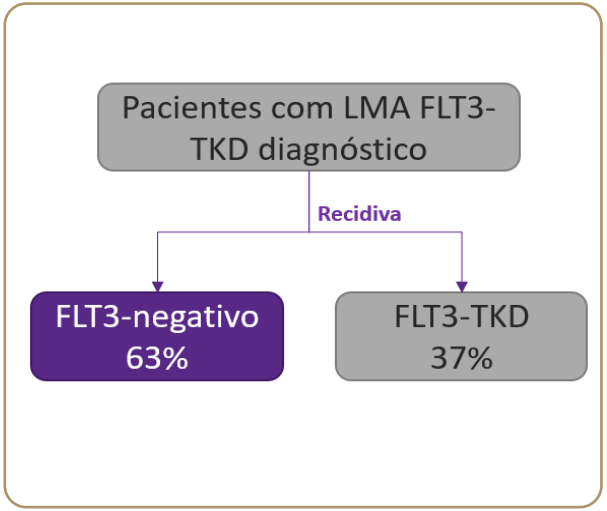
Mutations:
Founding (cluster 1)
Primary specific (cluster 2)
Relapse enriched (cluster 3)
Relapse enriched (cluster 4)
Relapse specific (cluster 5)
Random mutations in HSCs
Pathogenic mutations

Ding L, et al. *Nature*. 2012;481:506-510.

Change in *FLT3* Mutational Status at Relapse







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Data extracted from: Nazha A, et al, *Haematologica.* 2012;97:1242-1245; Janke H, et al. *PLoS ONE.* 2014;9:e89560; McCormick SR, et al. *Arch Pathol Lab Med.* 2010;134:1143-1151.

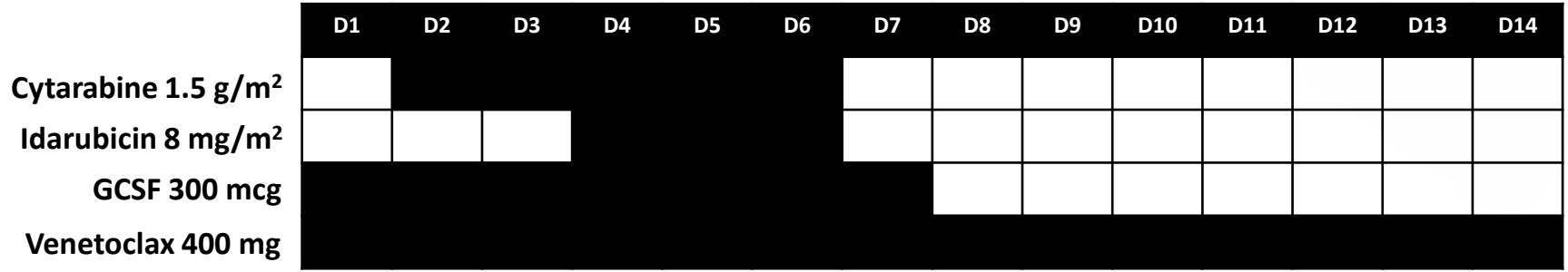
Essentially, at the Present Time for R/R AML We Can Consider

- FLT3 inhibitors for *FLT3*-positive patients
- IDH1/2 inhibitors for *IDH1/2*-positive patients
- Chemotherapy + venetoclax for any patient
- Allogeneic HSCT for eligible patients
- Enroll in clinical trials whenever possible!!

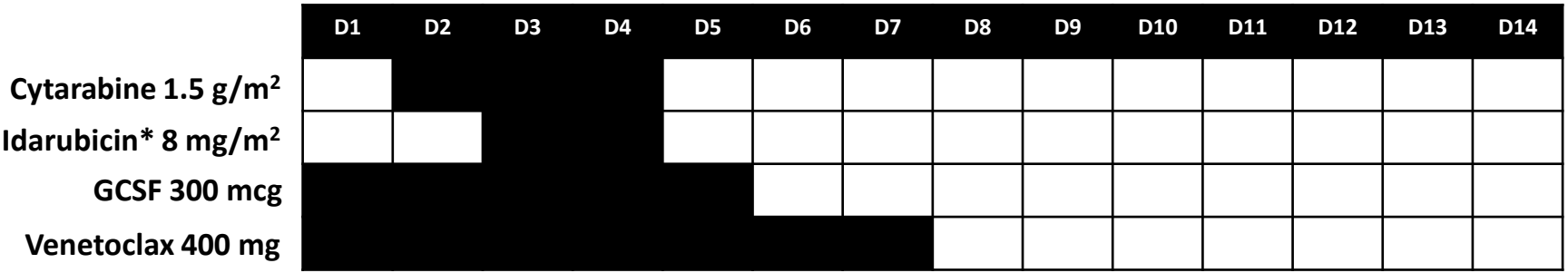
Chemotherapy + Venetoclax

FLAG-Ida + Venetoclax

INDUCTION (cycle 1)



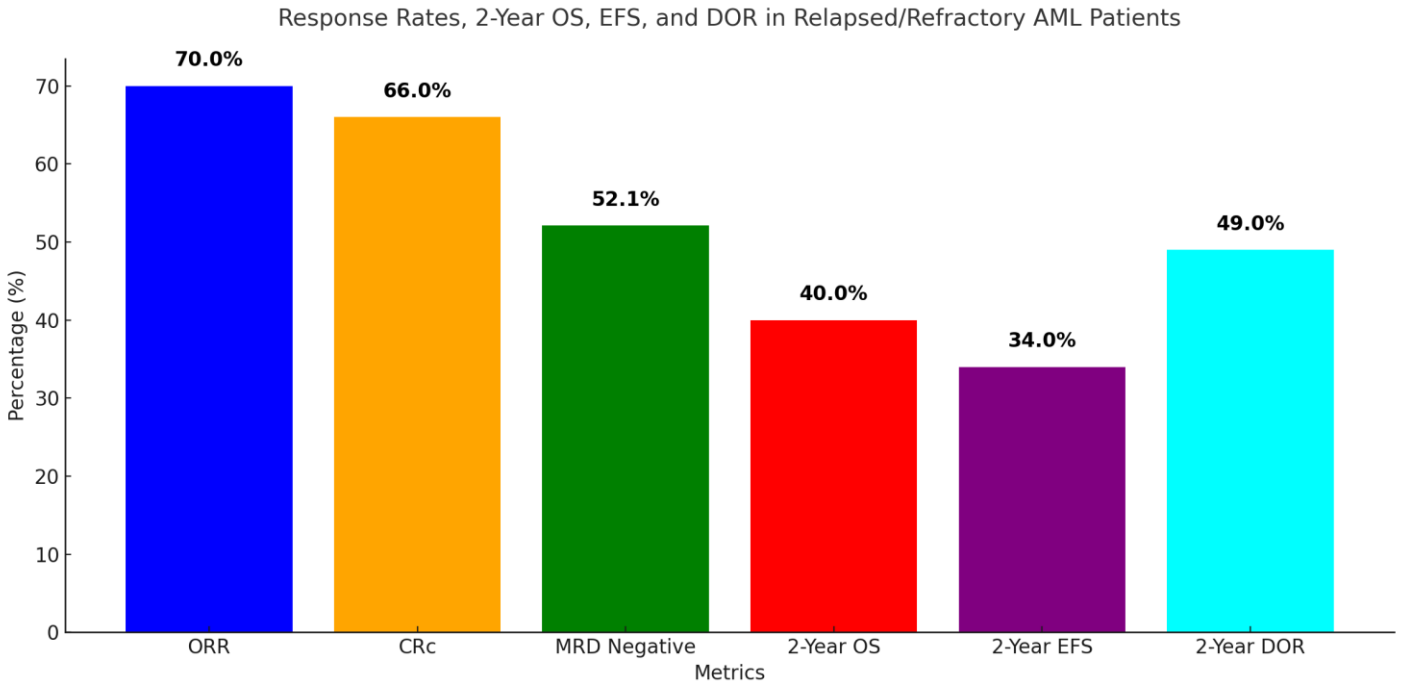
CONSOLIDATION (cycles 2–6)



*Idarubicin used in consolidation for a maximum of 2 cycles.

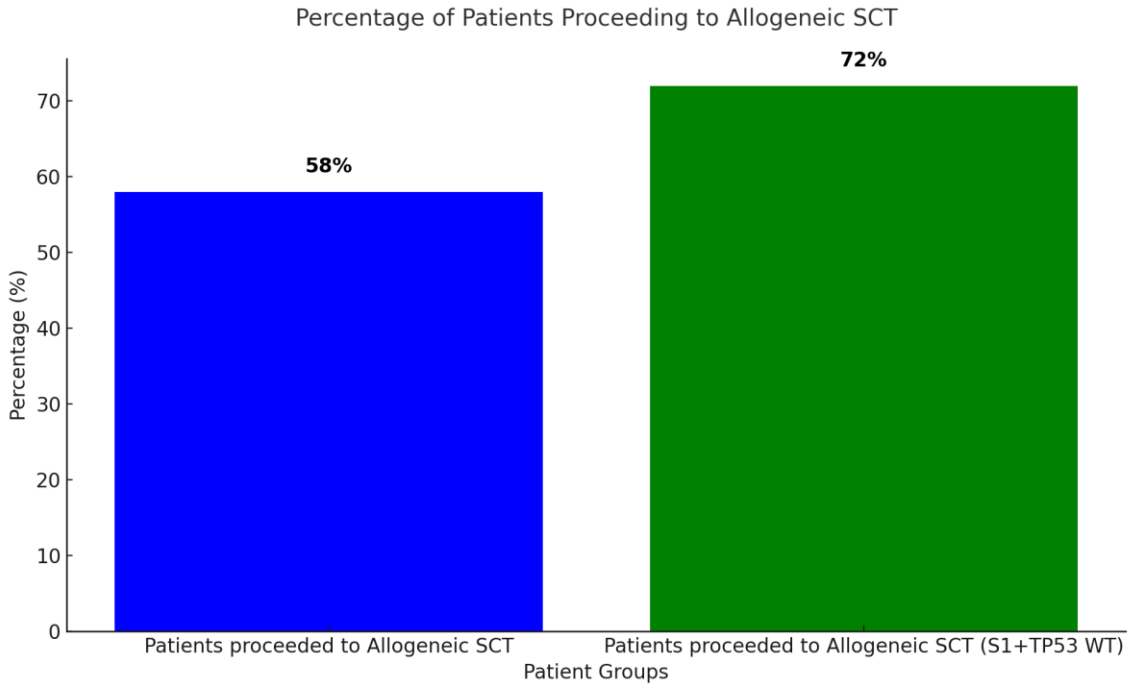
DiNardo CD, et al. *J Clin Oncol.* 2021;39:2768-2778.

FLAG-Ida + Venetoclax



Data extracted from Jen W-Y et al, "Flag-Ida + Venetoclax (VEN) in Newly Diagnosed (ND) or Relapsed / Refractory (RR) AML", presented at the 2024 European Hematology Association Annual Meeting

FLAG-Ida + Venetoclax



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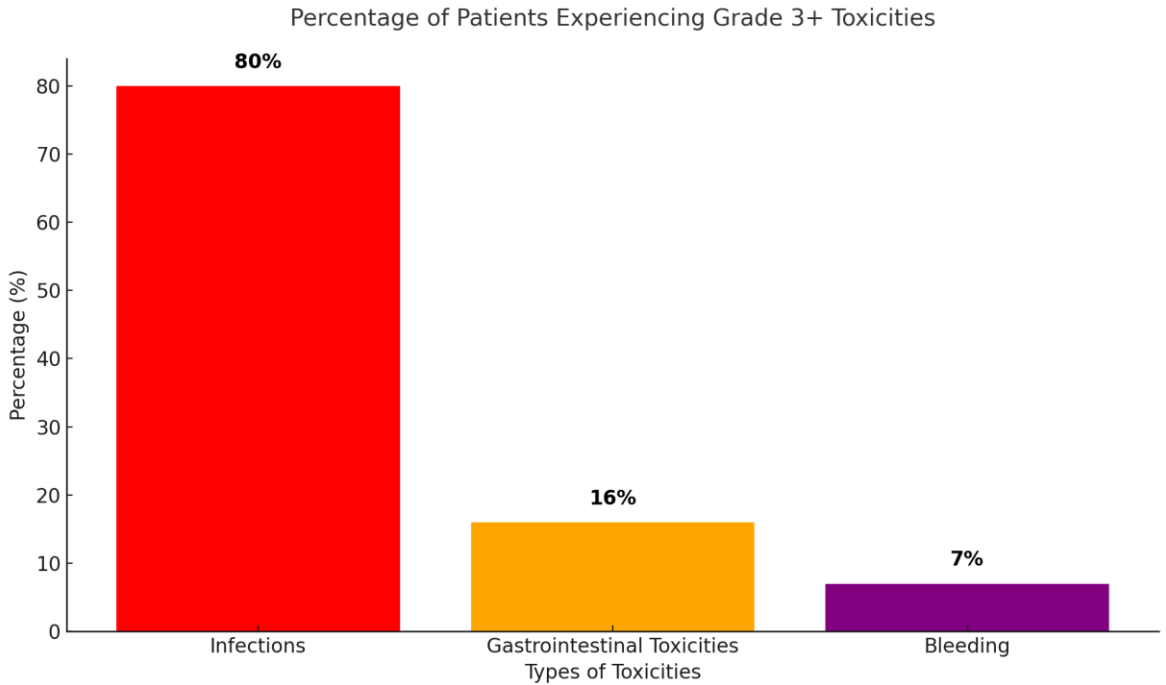
FLAG-Ida + Venetoclax



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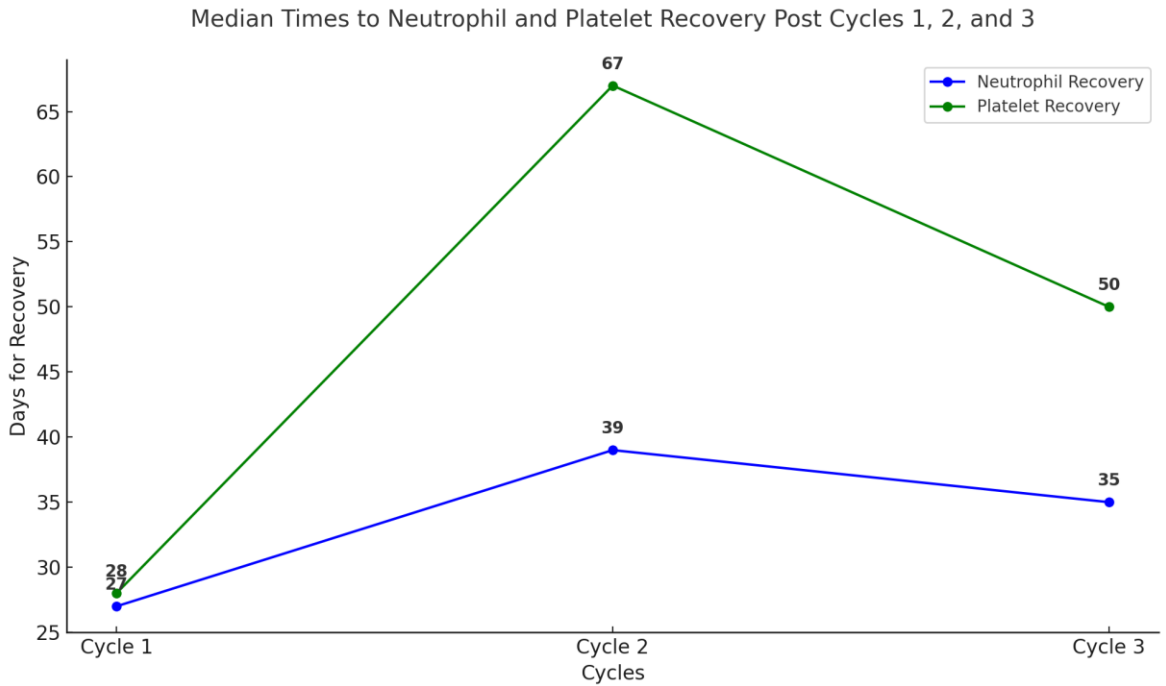
FLAG-Ida + Venetoclax



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LDAC + Venetoclax: For <15% Blasts/MRD-Positive Cases

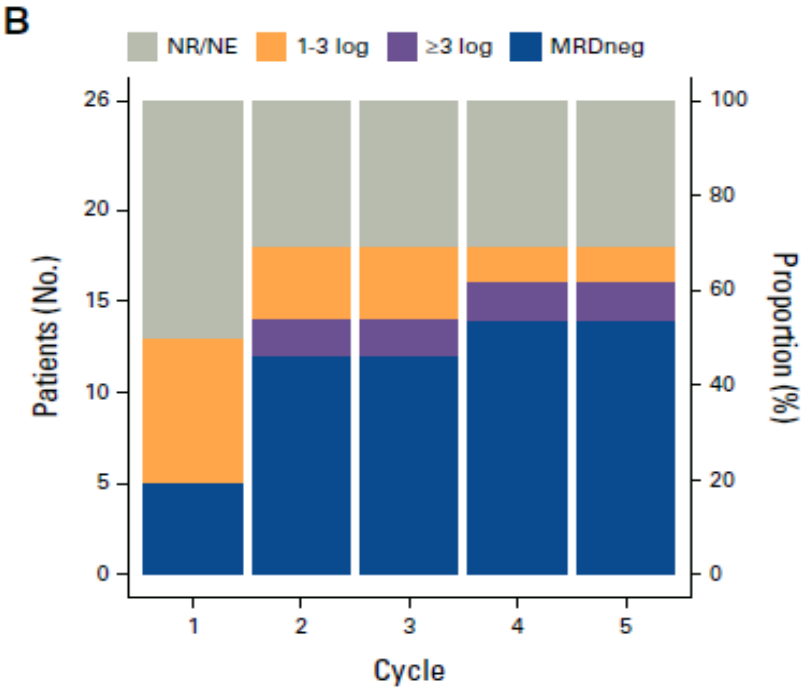
Targeting Molecular Measurable Residual Disease and Low-Blast Relapse in AML With Venetoclax and Low-Dose Cytarabine: A Prospective Phase II Study (VALDAC)

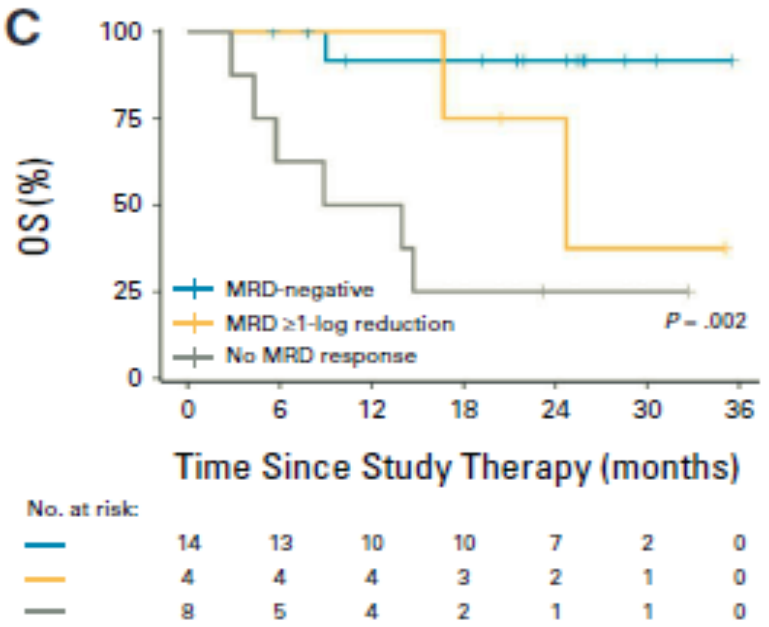
Ing Soo Tiong, MBChB, MPhil, FRACP, FRCPA[1,2]; Devendra K. Hiwase, MD, PhD, FRACP, FRCPA[3,4,5]; Emad Abro, MBBS, BSc(Hons), FRACP, FRCPA[6]; Ashish Bajel, MBBS, FRACP, FRCPA[2,7]; Emma Palfreyman, MBBS, FRACP, FRCPA[8]; Ashanka Beligaswatte, BA, MBBS, MD, FRACP, FRCPA[4,9]; John Reynolds, PhD[1]; Natasha Anstee, PhD[7,10]; Tamia Nguyen, BSc, MLabMed[2,7]; Sun Loo, MBBS, FRACP, FRCPA[2,7,10,11]; Chong Chyn Chua, MBBS, PhD, FRACP, FRCPA[1,7,10,11]; Michael Ashby, MBBS, FRACP, FRCPA[1]; Kaitlyn M. Wiltshire, MBBS[1]; Shaun Fleming, MBBS, PhD, FRACP, FRCPA[1]; Chun Y. Fong, MBBS, PhD, FRACP, FRCPA[12]; Tse-Chieh Teh, MBBS, PhD, FRACP, FRCPA[1,13]; Piers Blombery, MBBS, PhD, FRACP, FRCPA[2,14]; Richard Dillon, MA, PhD, MRCP, FRCPath[15,16]; Adam Ivey, BSc, MSc, PhD[1]; and Andrew H. Wei, MBBS, PhD, FRACP, FRCPA[2,7,10]

DOI https://doi.org/10.1200/JCO.23.01599

Tiong IS, et al. *J Clin Oncol*. 2024;42(18):2161-2173.

LDAC + Venetoclax: For <15% Blasts/MRD-Positive Cases





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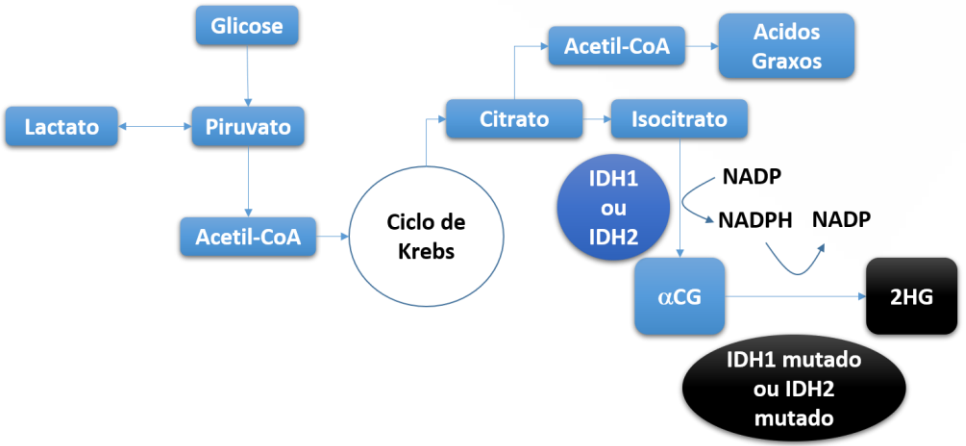
Tiong IS, et al. *J Clin Oncol*. 2024;42(18):2161-2173.

IDH1 and IDH2 Inhibitors

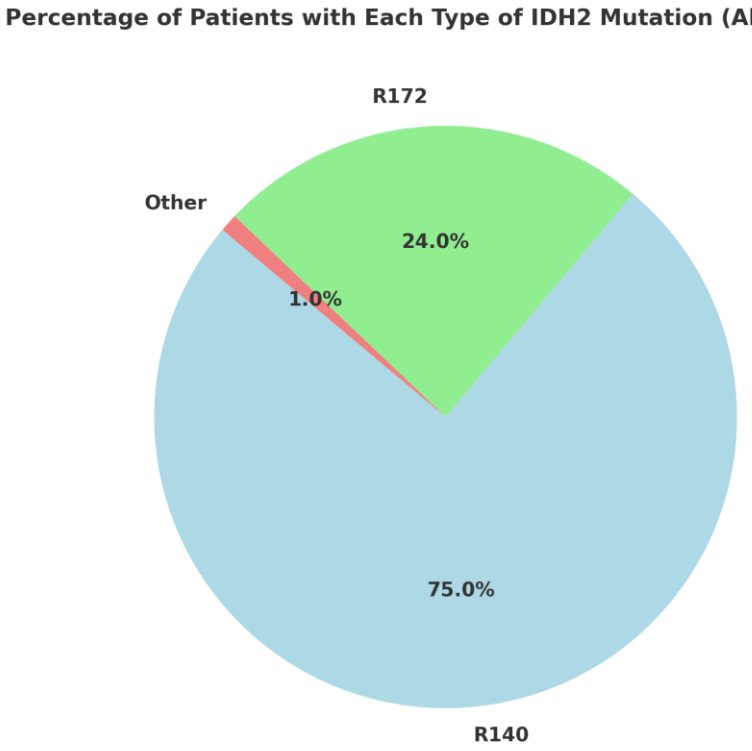
IDH1 and *IDH2* Mutations in AML

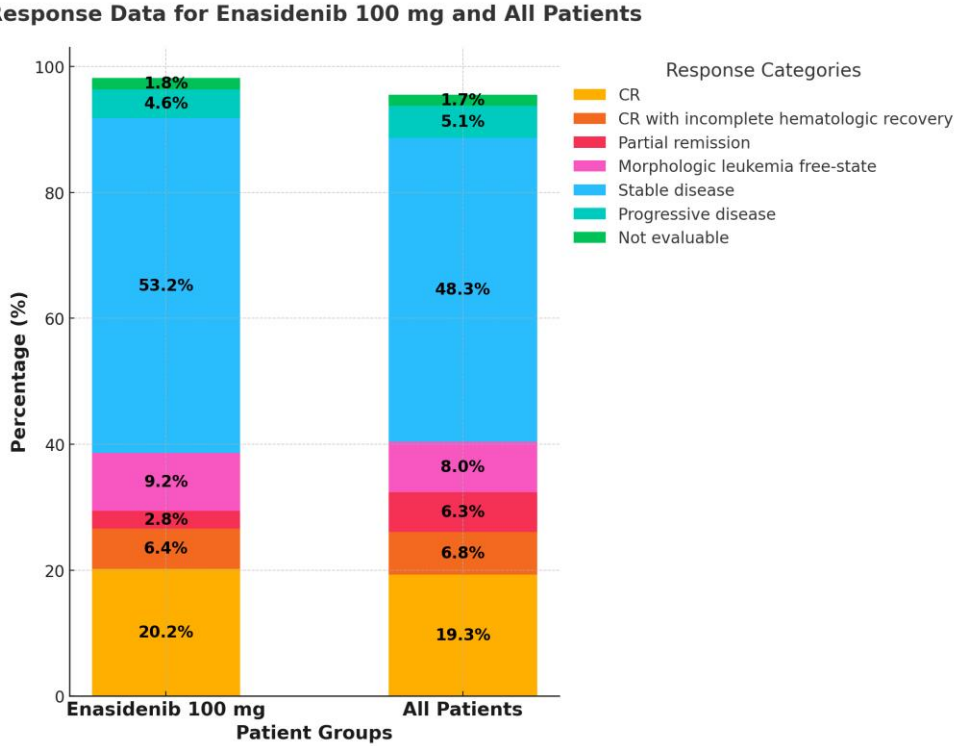
- *IDH1* is present in cytoplasm and *IDH2* in mitochondria
- *IDH1* (7.5%) and *IDH2* (15%) mutations that are found in AML lead to the production of 2-hydroxyglutarate (2-HG) instead of alpha-ketoglutarate
- 2-HG inhibits activity of the TET family of enzymes, leading to increased DNA methylation



Prensner JR, Chinnaiyan AM. *Nat Med.* 2011;17:291-293; Figueroa ME, et al. *Cancer Cell.* 2010;18:553-567; Cairns RA, et al. *Nat Rev Cancer.* 2011;11:85-95.

Enasidenib in R/R *IDH2*-Positive AML





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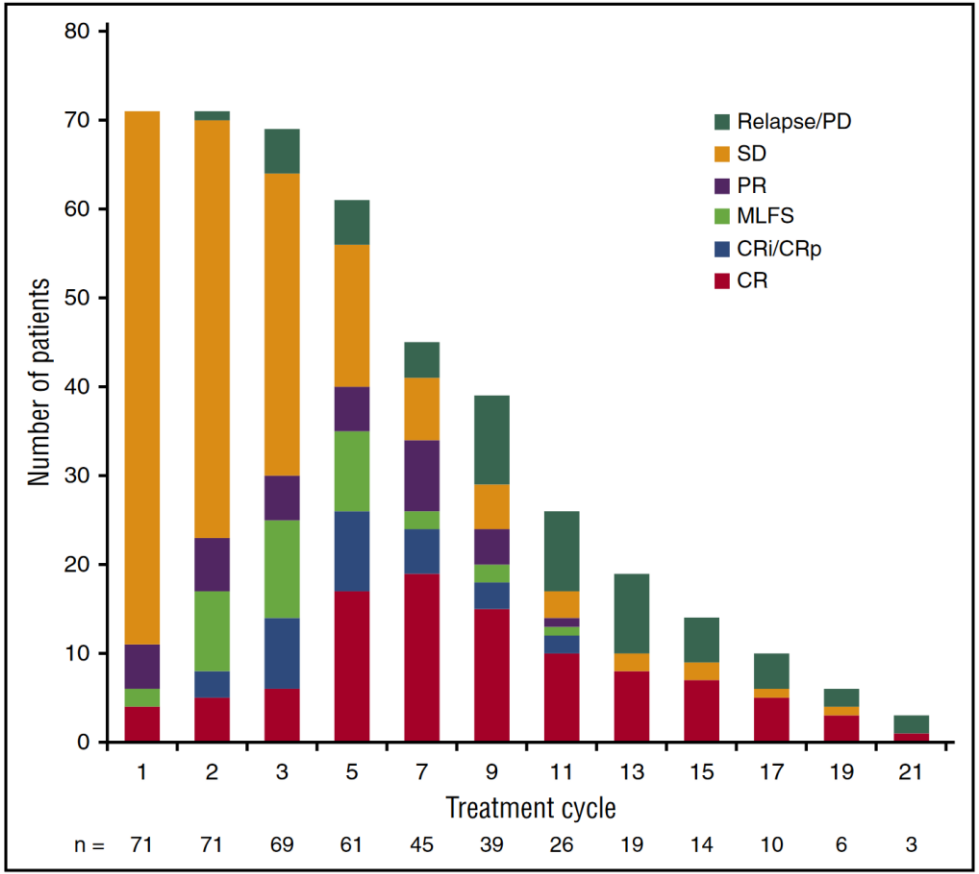
Stein EM, et al. *Blood*. 2017;130:722-731.

Enasidenib in R/R *IDH2*-Positive AML



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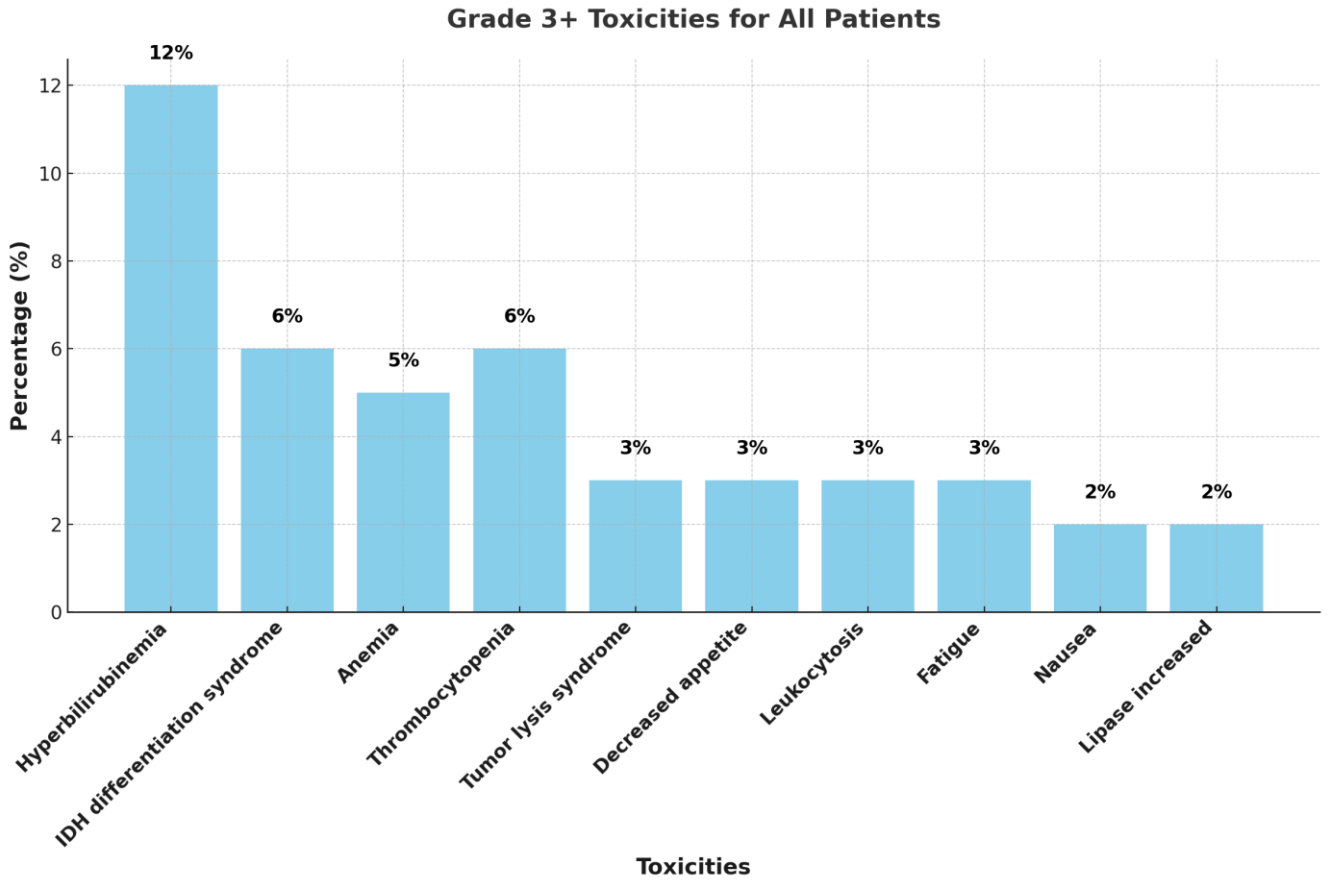
Stein EM, et al. *Blood*. 2017;130:722-731.

Enasidenib in R/R *IDH2*-Positive AML



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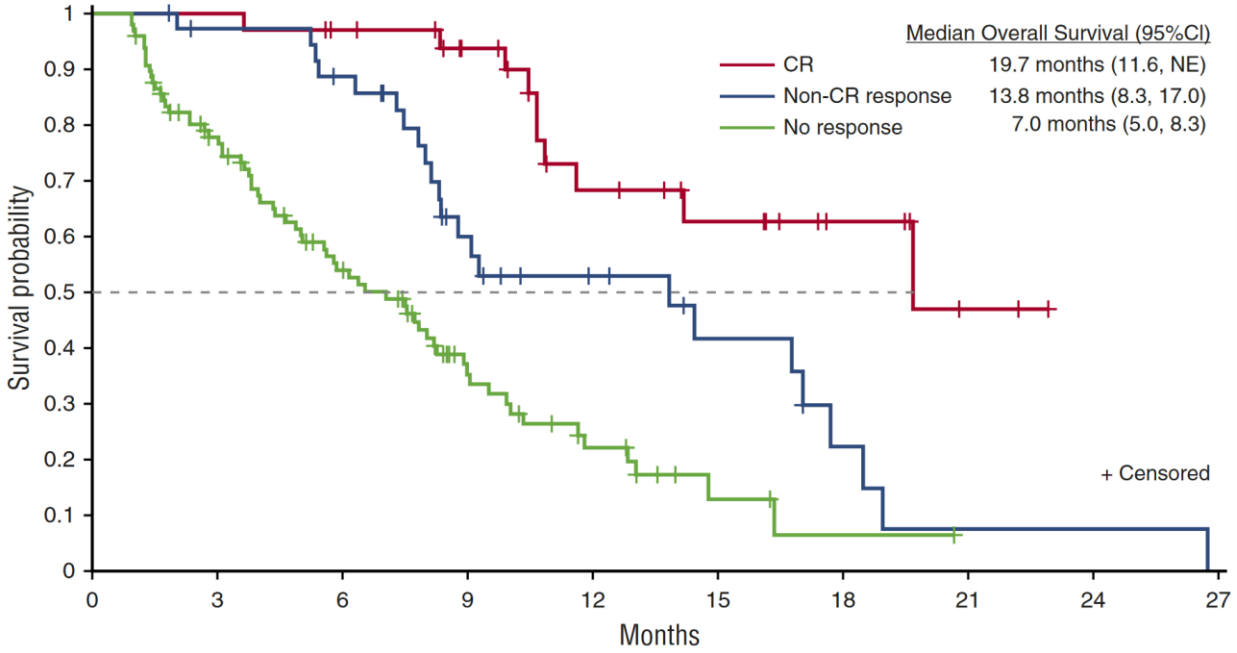
Stein EM, et al. *Blood*. 2017;130:722-731.

Enasidenib in R/R *IDH2*-Positive AML

B



Patients at risk:

CR	34	34	31	25	15	11	6	2	0	
Non-CR response	37	34	30	17	11	7	3	1	1	0
No response	97	68	43	20	10	3	1	0		

CR, complete remission

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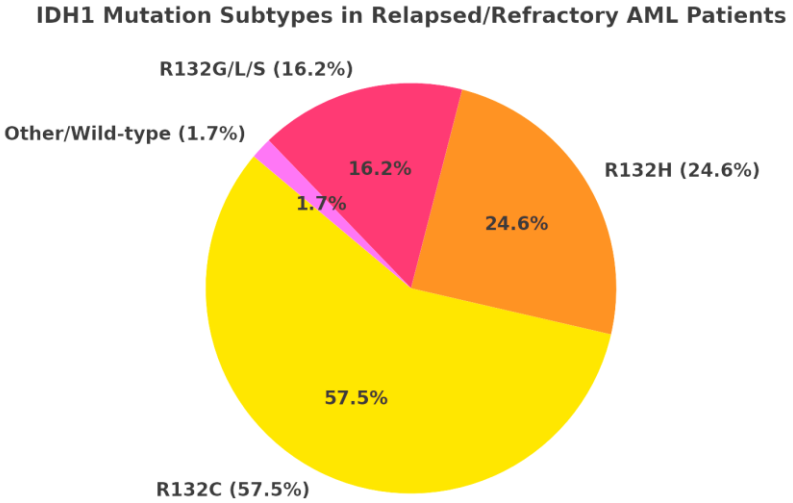
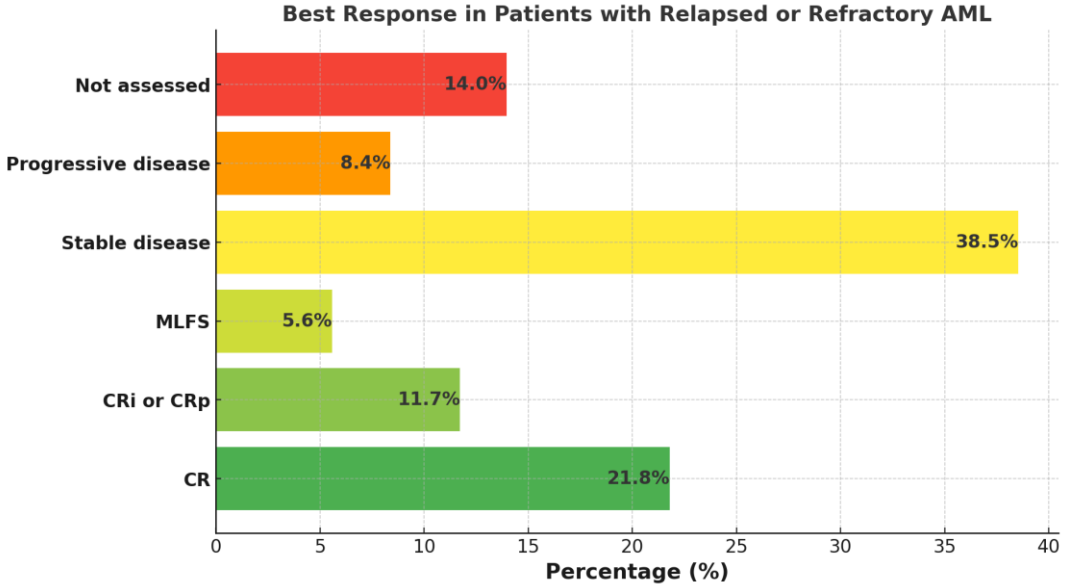
Stein EM, et al. *Blood*. 2017;130:722-731.

Ivosidenib in R/R *IDH2*-Positive AML





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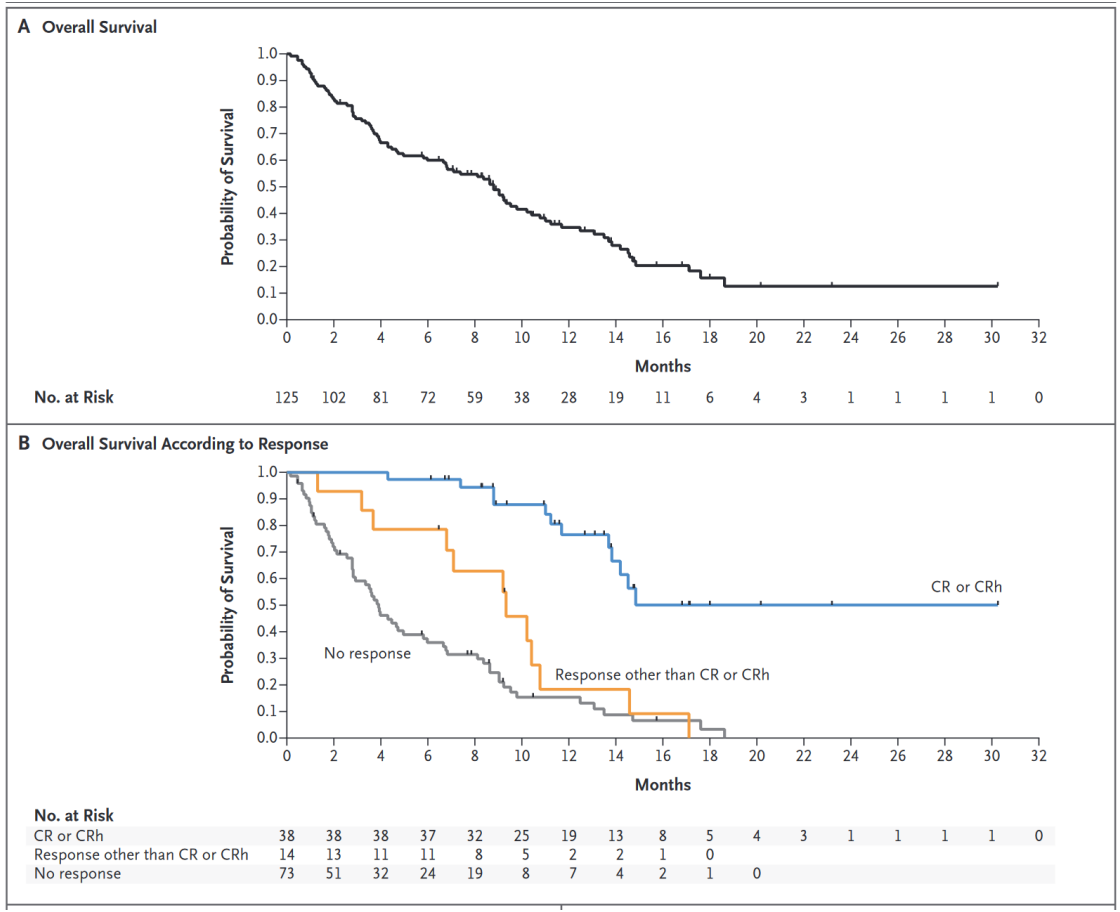
DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398.

Ivosidenib in R/R *IDH2*-Positive AML



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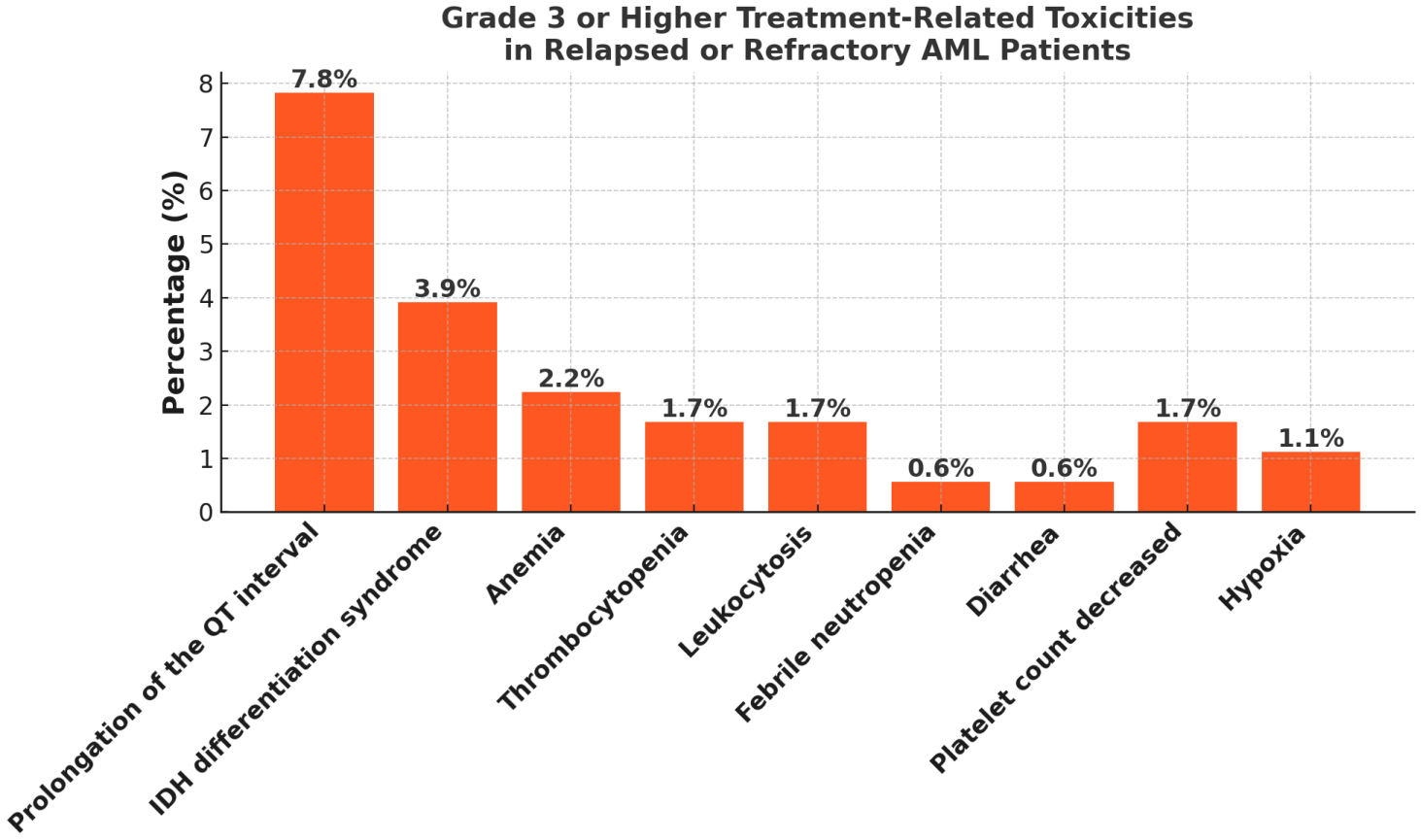

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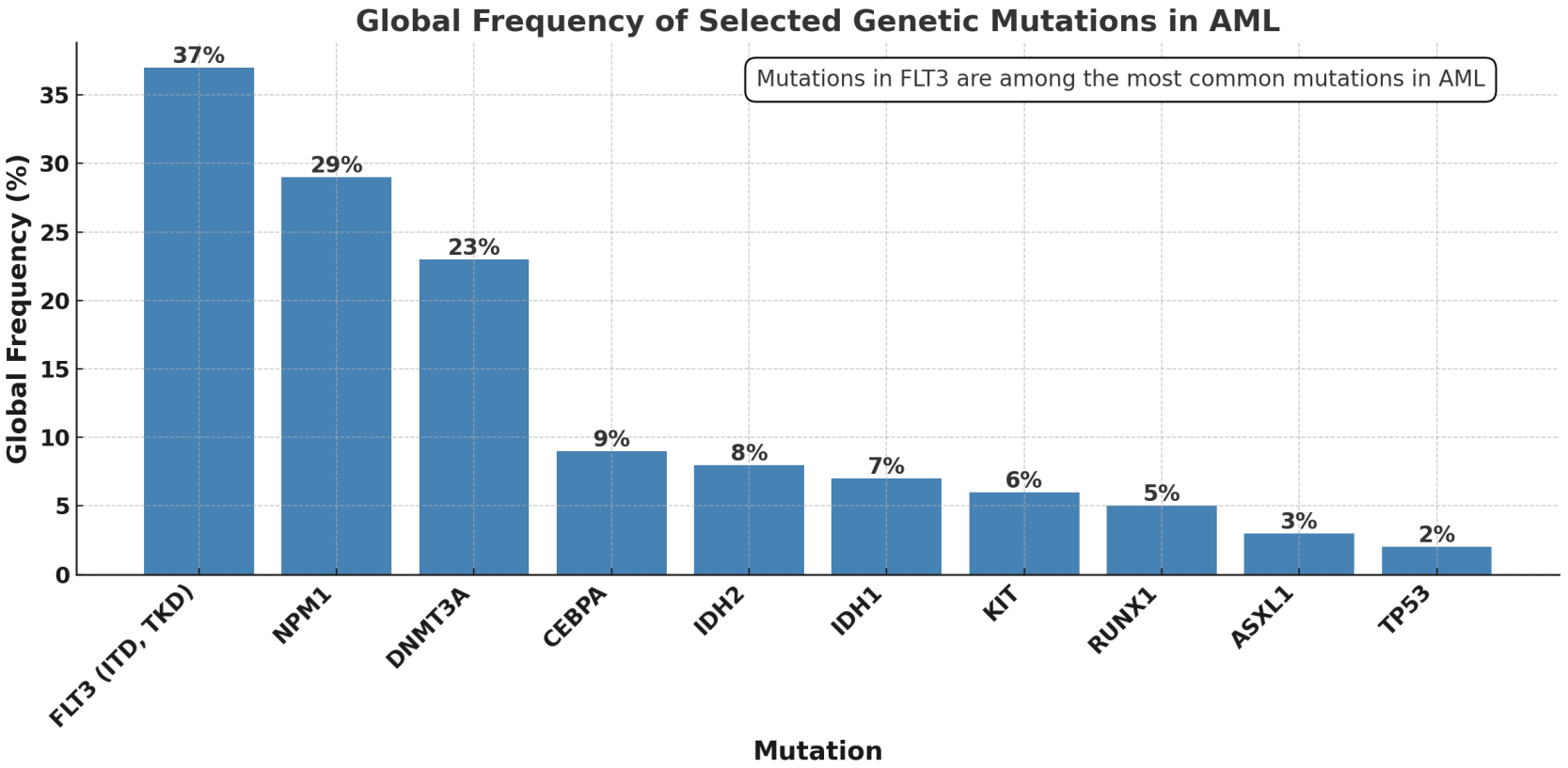
DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398.

FLT3 Inhibitors

FLT3 Mutations in AML



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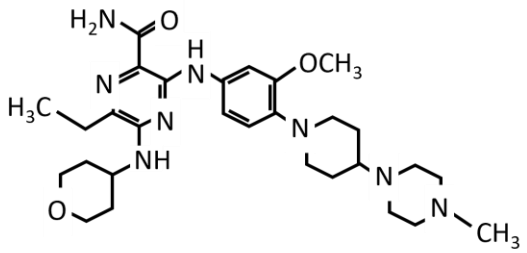
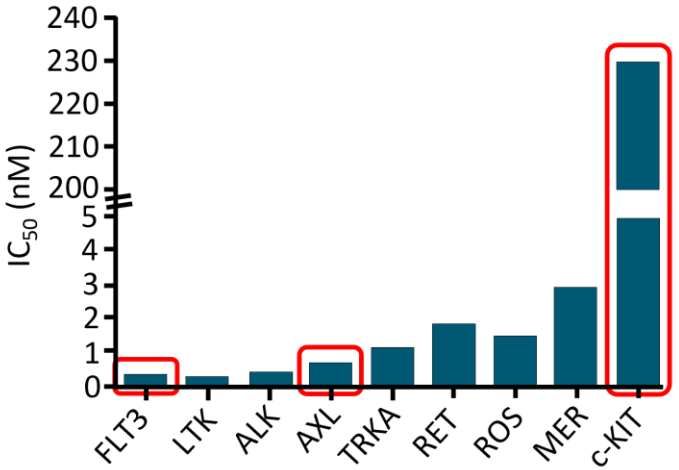
Patel JP, et al. *N Engl J Med.* 2012;366:1079-1089.

Gilteritinib



Atividade de Gilteritinib contra Quinases selecionadas



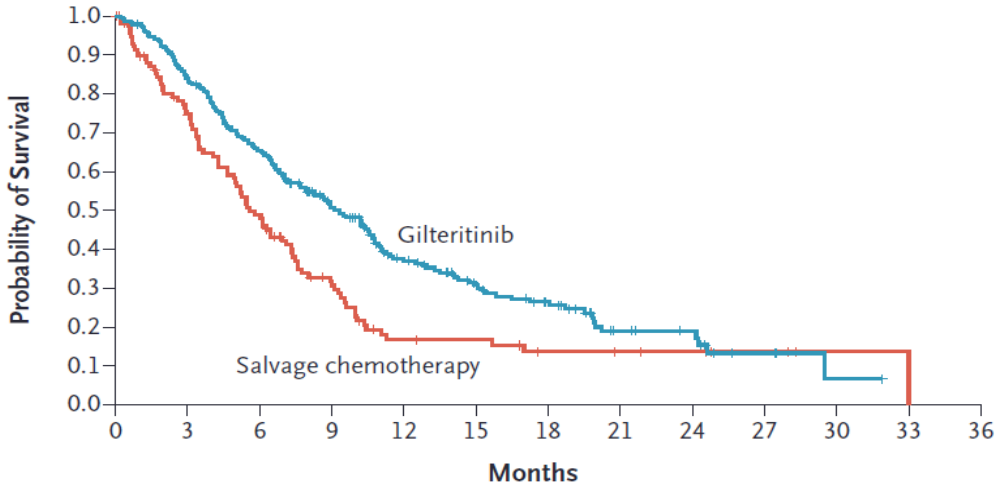
- Active against TKD mutations that are refractory to sorafenib and other type II inhibitors (eg, quizartinib)

FLT3 Receptor Type	Gilteritinib IC_{50} (nM)
WT	5
Molm14 (ITD)	1.8
TF/ITD	1.4
Ba/F3 ITD	0.7
Ba/F3 D835Y	0.5
Ba/F3 D835H	1.9
Ba/F3 D835V	0.7
Ba/F3/ITD F691L	17.6

Lee LY, et al. *Blood*. 2017;129:257-260.

ADMIRAL Trial: Gilteritinib vs Chemo in *FLT3*-Mutated R/R AML

A Overall Survival



No. at Risk													
Gilteritinib	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

	Median Overall Survival (95% CI)
	mo
Gilteritinib	9.3 (7.7–10.7)
Salvage Chemotherapy	5.6 (4.7–7.3)

Hazard ratio for death, 0.64 (95% CI, 0.49–0.83)
P<0.001

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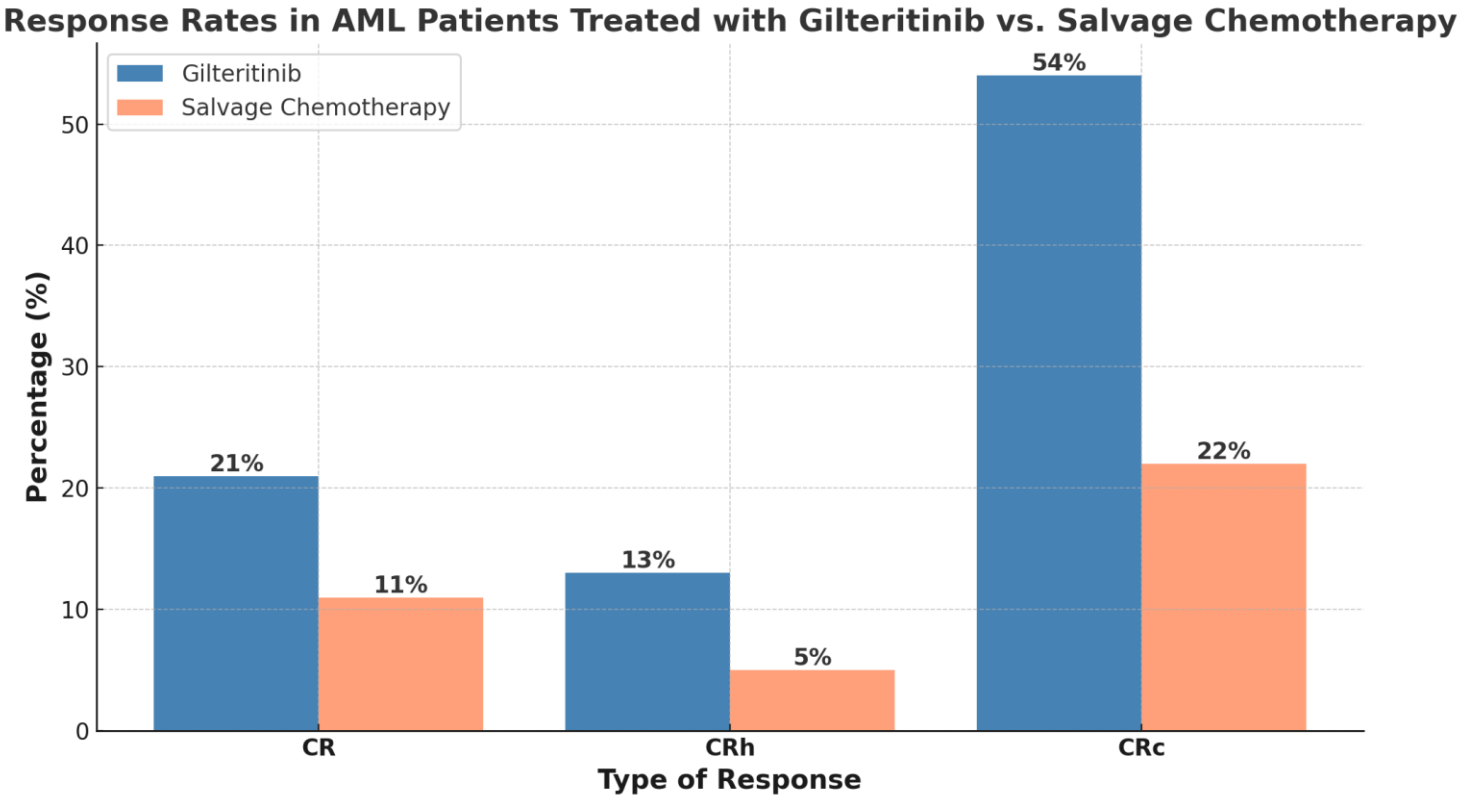
Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

ADMIRAL Trial: Gilteritinib vs Chemo in *FLT3*-Mutated R/R AML



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

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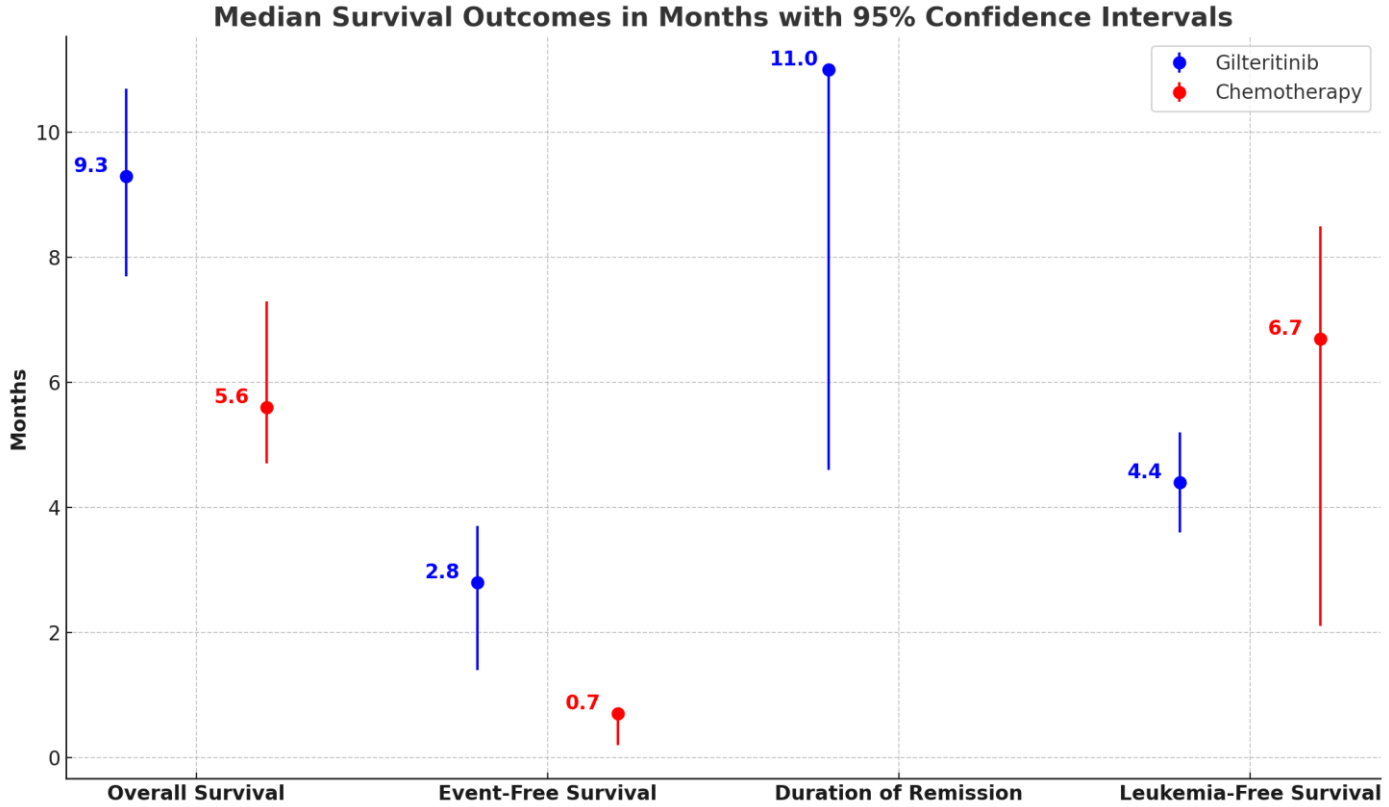

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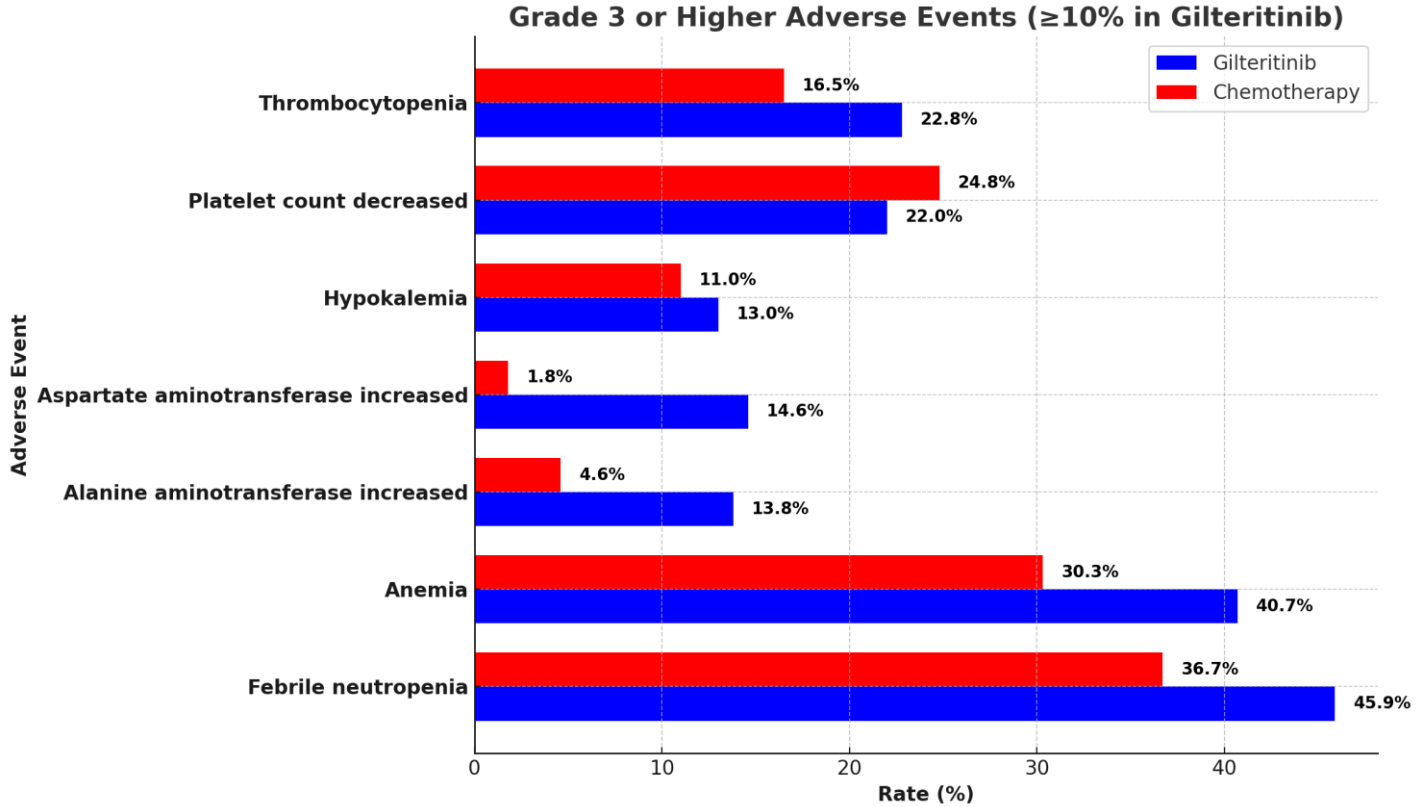
Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

ADMIRAL Trial: Gilteritinib vs Chemo in *FLT3*-Mutated R/R AML



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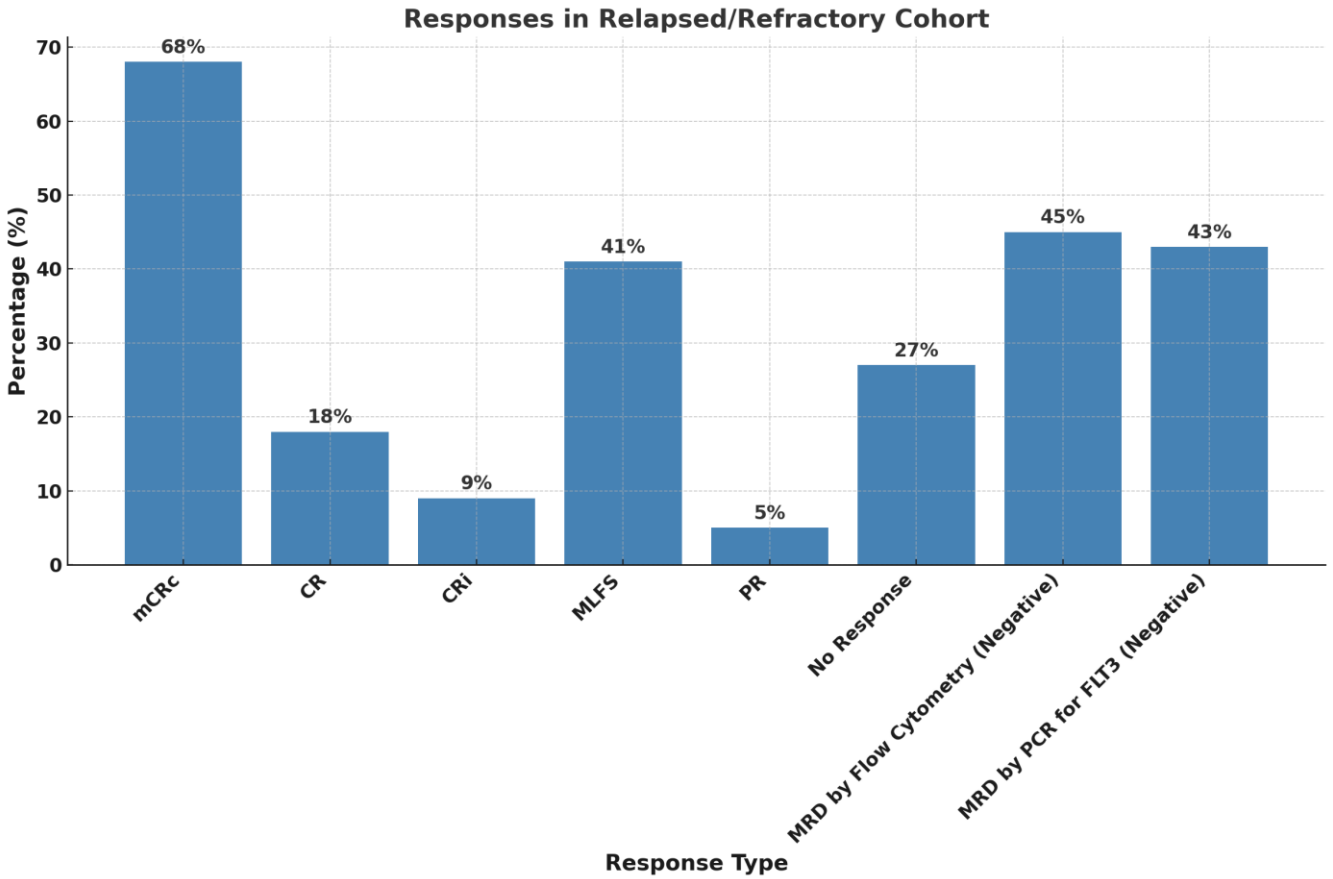
Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

Aza + Ven + Gilt for *FLT3*-Mutated AML



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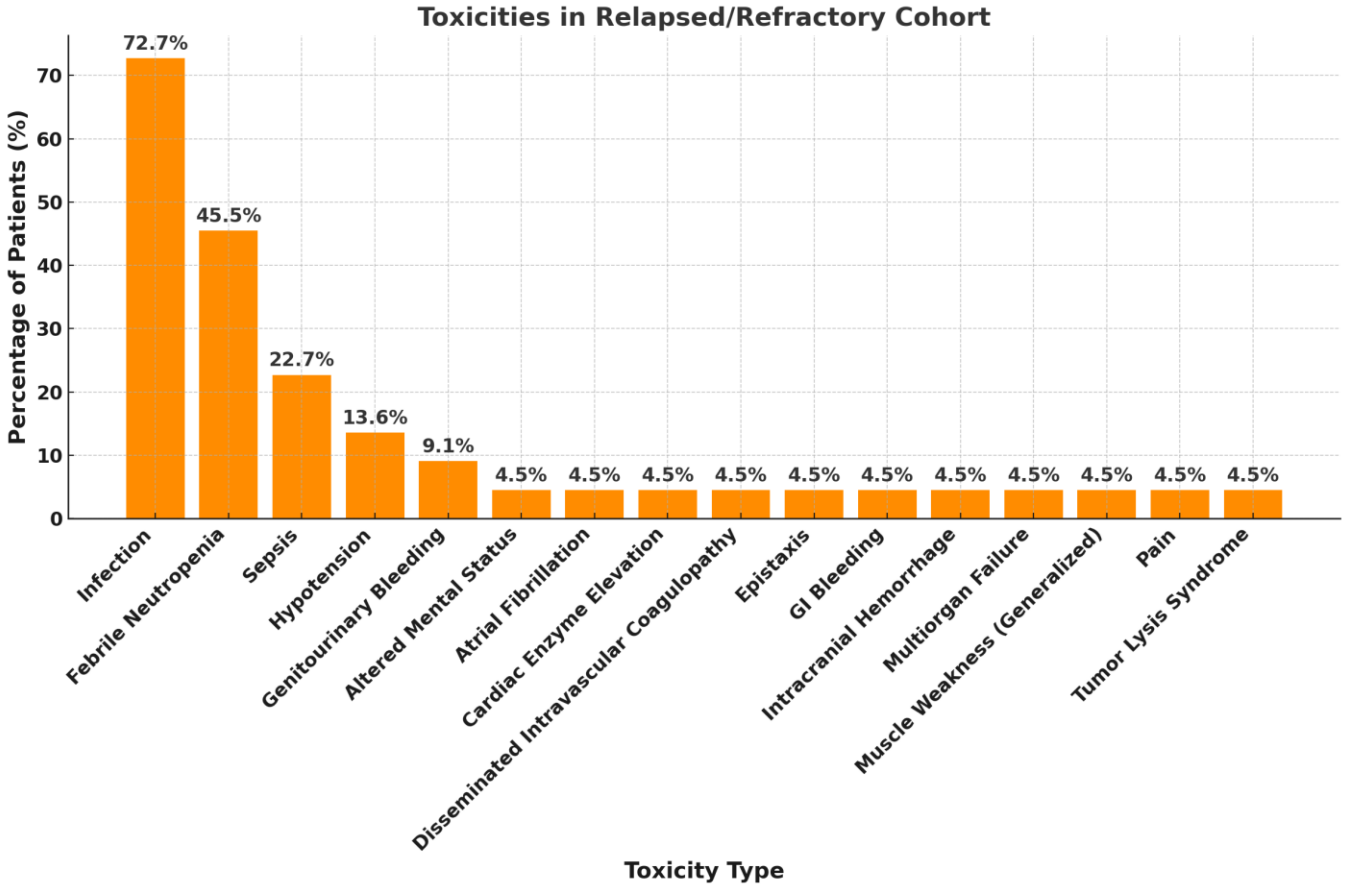
Short NJ, et al. *J Clin Oncol.* 2024;42:1499-1508.

Aza + Ven + Gilt for *FLT3*-Mutated AML



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Short NJ, et al. *J Clin Oncol.* 2024;42:1499-1508.

Allogeneic HSCT

ASAP Trial: Immediate HSCT vs Induction Chemotherapy for R/R AML

Background

- Evaluates standard salvage chemotherapy vs immediate allogeneic HSCT
- Focus: Patients with relapsed or poor responsive AML

Methods

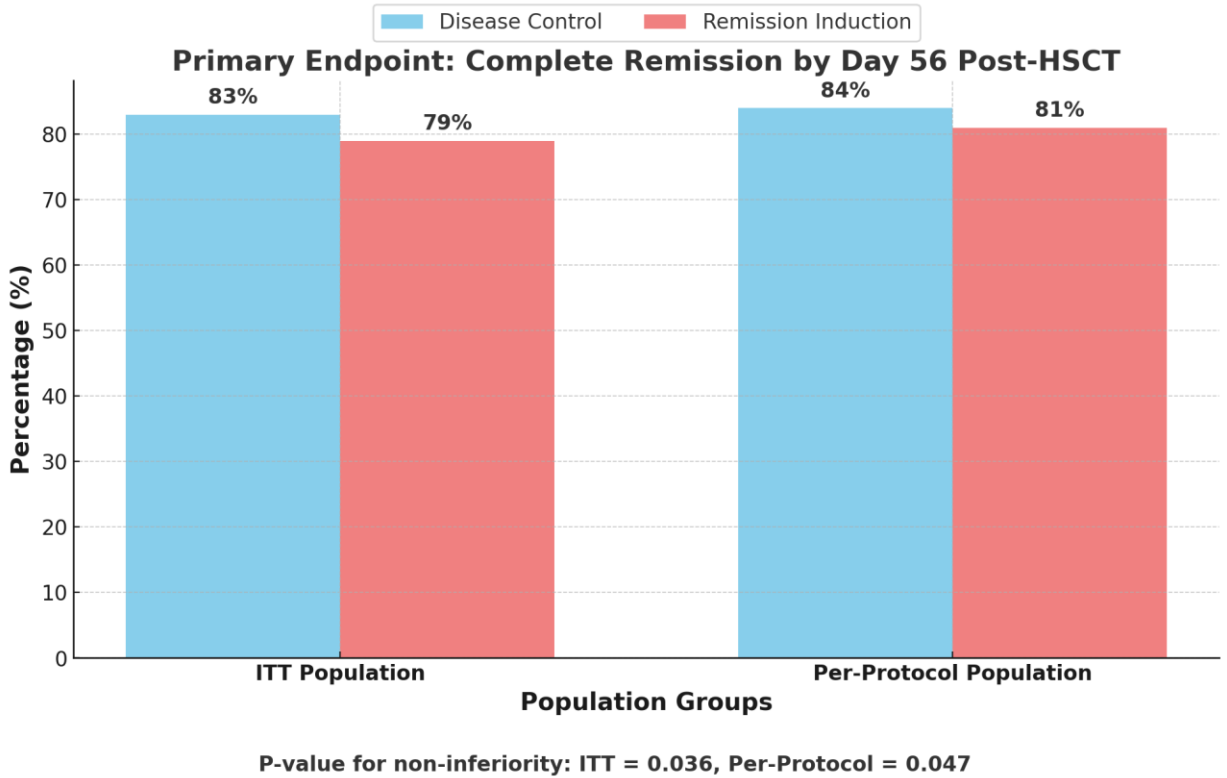
- Phase III, randomized, open-label, non-inferiority trial
- Participants: 281 patients with AML, aged 18–75, with poor response or first relapse
- Groups: Salvage chemotherapy + HSCT vs immediate HSCT after intensive conditioning

Endpoints

- **Primary Endpoint:** Complete remission by day 56 post-HSCT
- **Secondary Endpoints**
  - Overall survival, nonhematologic adverse events, time spent in hospital

Stelljes M, et al. *Lancet Haematol.* 2024;11:e324-e335.

ASAP Trial: Immediate HSCT vs Induction Chemotherapy for R/R AML



P-value for non-inferiority: ITT = 0.036, Per-Protocol = 0.047

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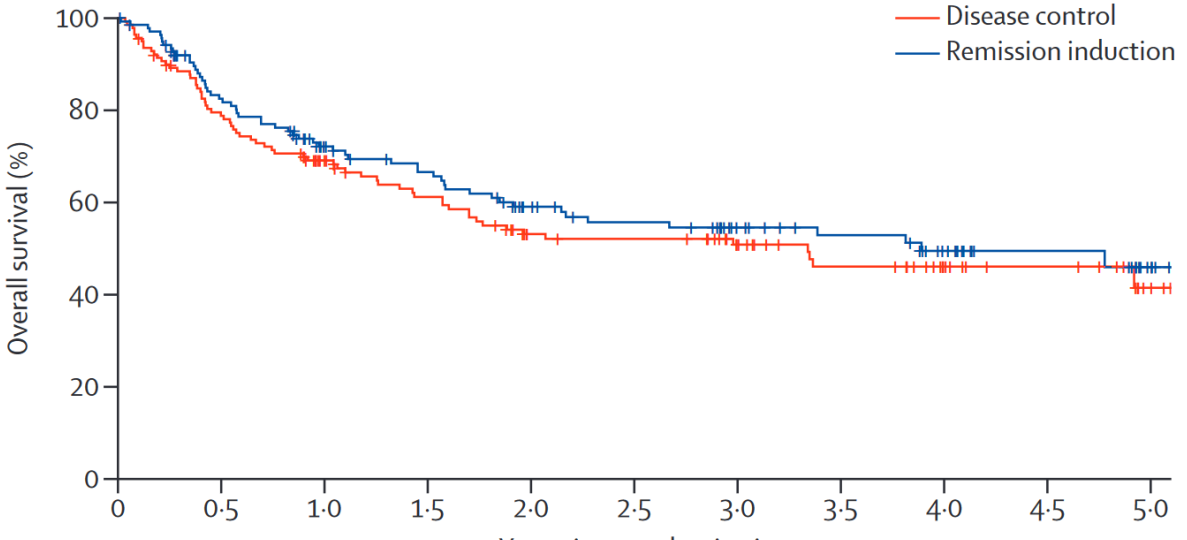
Stelljes M, et al. *Lancet Haematol.* 2024;11:e324-e335.

ASAP Trial: Immediate HSCT vs Induction Chemotherapy for R/R AML



Number at risk (number censored)											
Disease control	140	106	83	69	51	49	41	29	21	14	5
	(0)	(5)	(15)	(20)	(29)	(30)	(37)	(46)	(54)	(61)	(69)
Remission induction	141	105	82	71	56	49	39	32	24	14	6
	(1)	(13)	(23)	(28)	(35)	(39)	(48)	(54)	(60)	(70)	(77)

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Stelljes M, et al. *Lancet Haematol.* 2024;11:e324-e335.

ASAP Trial: Immediate HSCT vs Induction Chemotherapy for R/R AML

Limitations

At baseline → 60% of patients already had a donor identified in the disease control group

- Median time to HSCT was only 4.4 weeks in the disease control (vs 7.4 weeks in the remission induction group) → a rapid referral to transplant is key for the success of this strategy
- Salvage chemotherapy was HAM (Ara-C + mitoxantrone) → there were no novel agents utilized (eg, venetoclax, FLT3 inhibitors, IDH1/2 inhibitors)
- Despite these limitations, the results underscore the limits of salvage therapy in R/R AML and underscore the need for referring patients for allogeneic HSCT ASAP (as the trial name suggests)

Stelljes M, et al. *Lancet Haematol.* 2024;11:e324-e335.

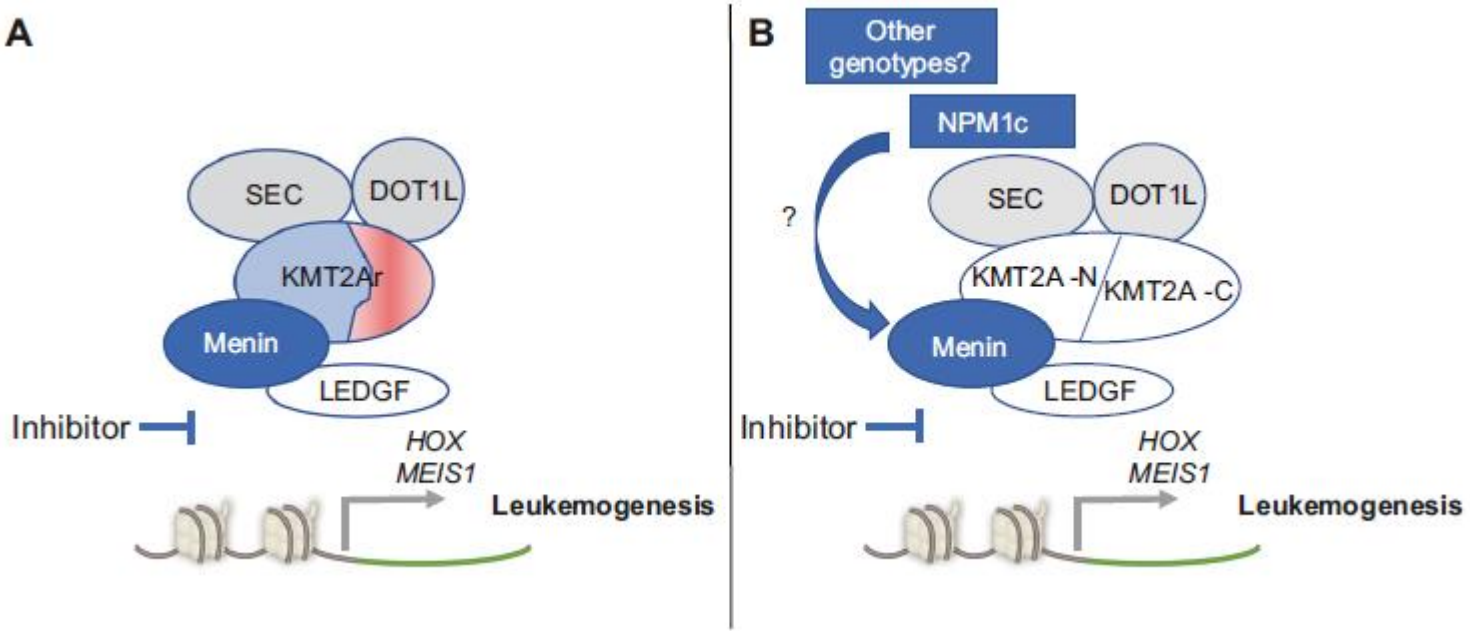
Novel Drugs and Strategies

Novel Drugs and Strategies

Novel drugs

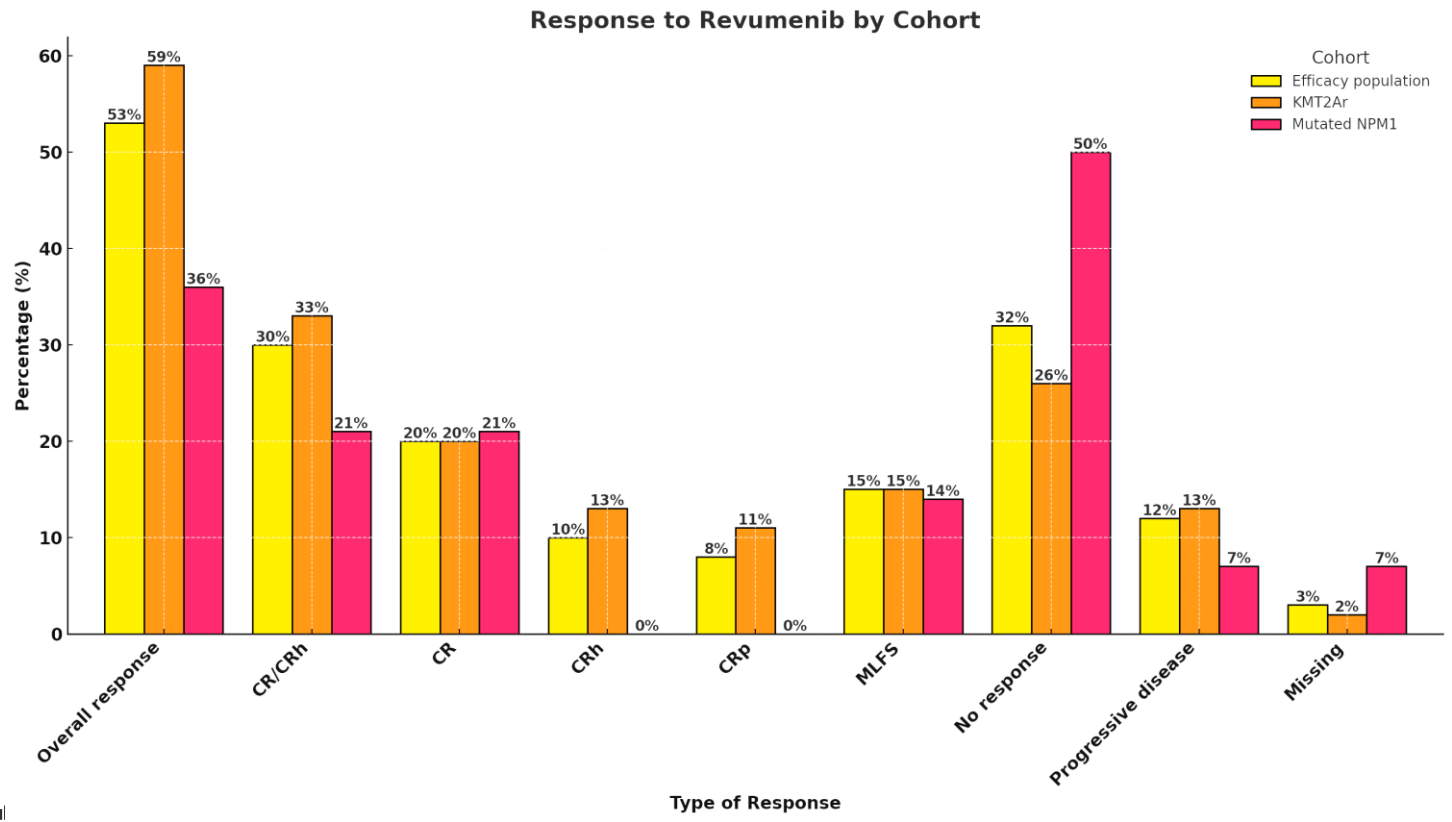
- Menin inhibitors → revumenib, JNJ-75276617, BMF-219, ziftomenib
- Selinexor → exportin-1 inhibitor
- Tuspetinib → myeloid kinase inhibitor
- SAR443579 → engages NK cells and CD123 (found in AML stem cells)
- Olutasidenib → novel IDH1 inhibitor

Menin Inhibitors: Mechanism of Action



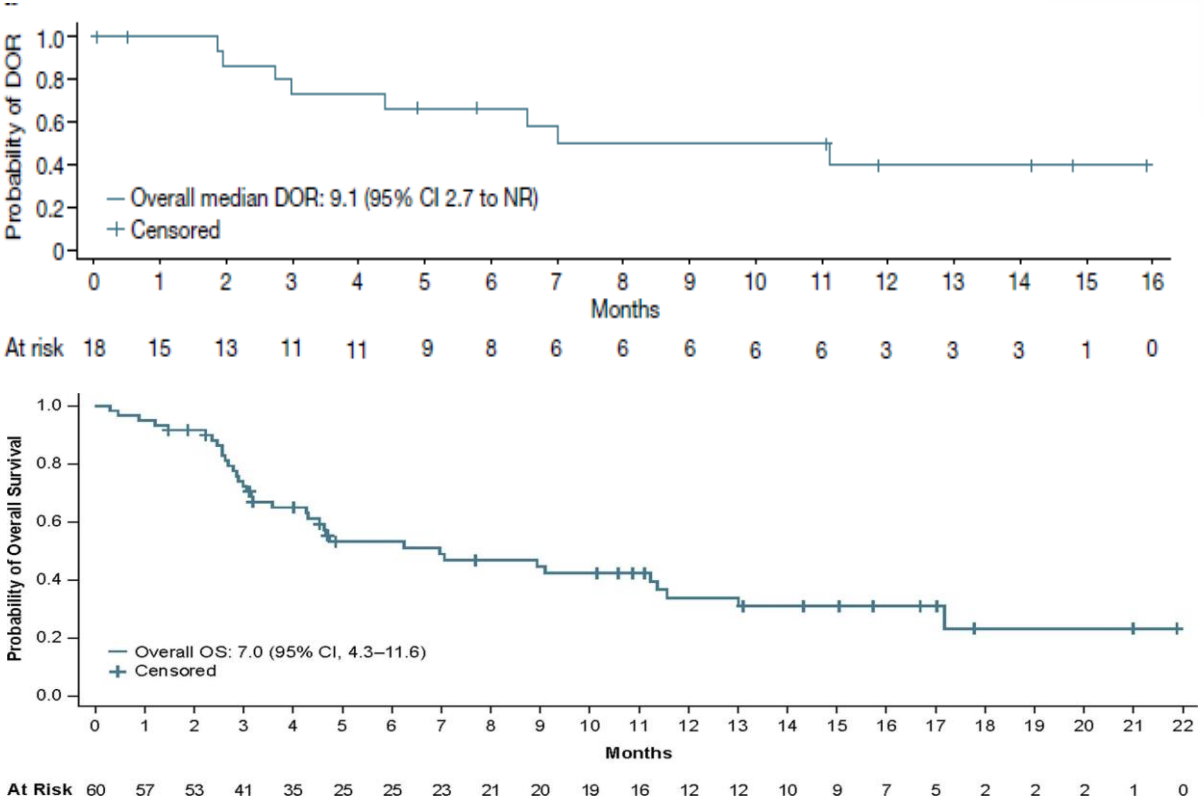
Issa GC, et al. *Leukemia*. 2021;35:2482-2495.

Revumenib Phase I Trial in *KMT2A*-Rearranged or *NPM1*-Mutated R/R AML



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

Revumenib Phase I Trial in *KMT2A*-Rearranged or *NPM1*-Mutated R/R AML



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

Conclusions

- **Treatment for R/R AML has improved**
  - Several agents are developed and in development
  - Importance of identifying molecular targets
- **Allogeneic HSCT remains a cornerstone of therapy of R/R AML**
  - Patients should be referred to HSCT as soon as possible
  - Ideally identify HLA donors prior to relapse
- **Molecular status of AML can change over time**
  - Repeat NGS analysis at time of relapse
  - May facilitate use of novel drugs based on markers
- **Refer patients to clinical trials whenever possible**
  - Clinical trials are key to improvement of outcomes in patients with R/R AML
  - Referring patients to trials helps development of novel drugs and therapeutic options

Thank you!

Email: santos.fabio2@einstein.br
Twitter: @fabiopss

Global Leukemia Academy

AML case-based panel discussion

Fabio Santos

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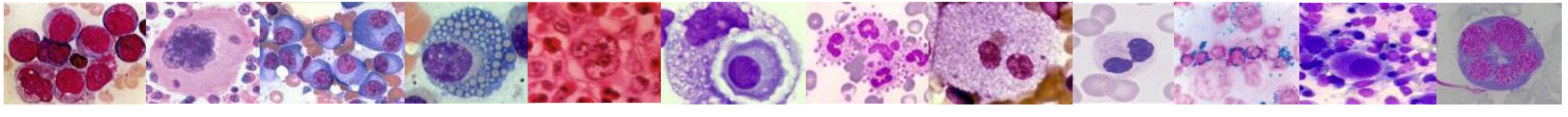
Clinical Case

Luana Nóbrega da Costa, MD
Beneficência Portuguesa Hospital, São Paulo, Brazil



Disclosures

- Nothing to declare

Man, 80 years old

Medical history

- Dyslipidemia, hypothyroidism, 3 MI with stents, biologic aortic valve replacement, ex-smoker

History of present illness

- Jan/21: ED with history of fatigue and fever → laboratory with pancytopenia
  - Hb 10.8 / MCV 98 / Leuko 1040 / Neutro 187 / Plat 93 mil / No blasts
- Initial investigation ruled out common causes
- Bone marrow aspirate and biopsy were performed

Man, 80 years old

Bone marrow

- Aspirate: granulocyte dysplasia, **16% of blasts**
- Flow cytometry: **10% of CD34+ cells** that were CD13, CD15, CD33, CD38, CD71, CD117, HLA-DR e cyMPO. Ogata score 3
- Karyotype: 46,XY,del(5)(q13q31),t(7;10)(q22;q24),?t(9;21)(q22;q22)[17]/46,XY[3]
- FISH: *EGR1* deletion (-5q) and *RUNX1* deletion in approximately 20%
- NGS panel: ***TP53* P152L** e V157F, *DMNT3A* N838fs
- Biopsy: hypercellular marrow with **20% of myeloblast (CD34+ and CD117+)**

Hematologic diagnosis

- ICC 2022: AML with *TP53* mutation
  - Adverse risk by ELN 2022

Man, 80 years old

Treatment

1. Azacitidine + venetoclax
   - After first cycle: CMR and MRD positive (1.5%)
   - After fifth cycle
     - Admitted to the hospital with neutropenic fever
     - CBC: Hb 11.5 / Leuko 790 / Plat 45 mil / Blasts 16%
     - Aspirate with 60% blasts / Kt e FISH remained the same

2. Cladribine 5 mg/m^2 D1–D4 + cytarabine 20 mg 2×/d D1–D10
   - After first cycle: some hematologic response, but rapidly evolution with pancytopenia and 45% blasts

3. Gemtuzumab ozogamicin
   - No response after 1 cycle, progression, infection
   - Best supportive care

Summary

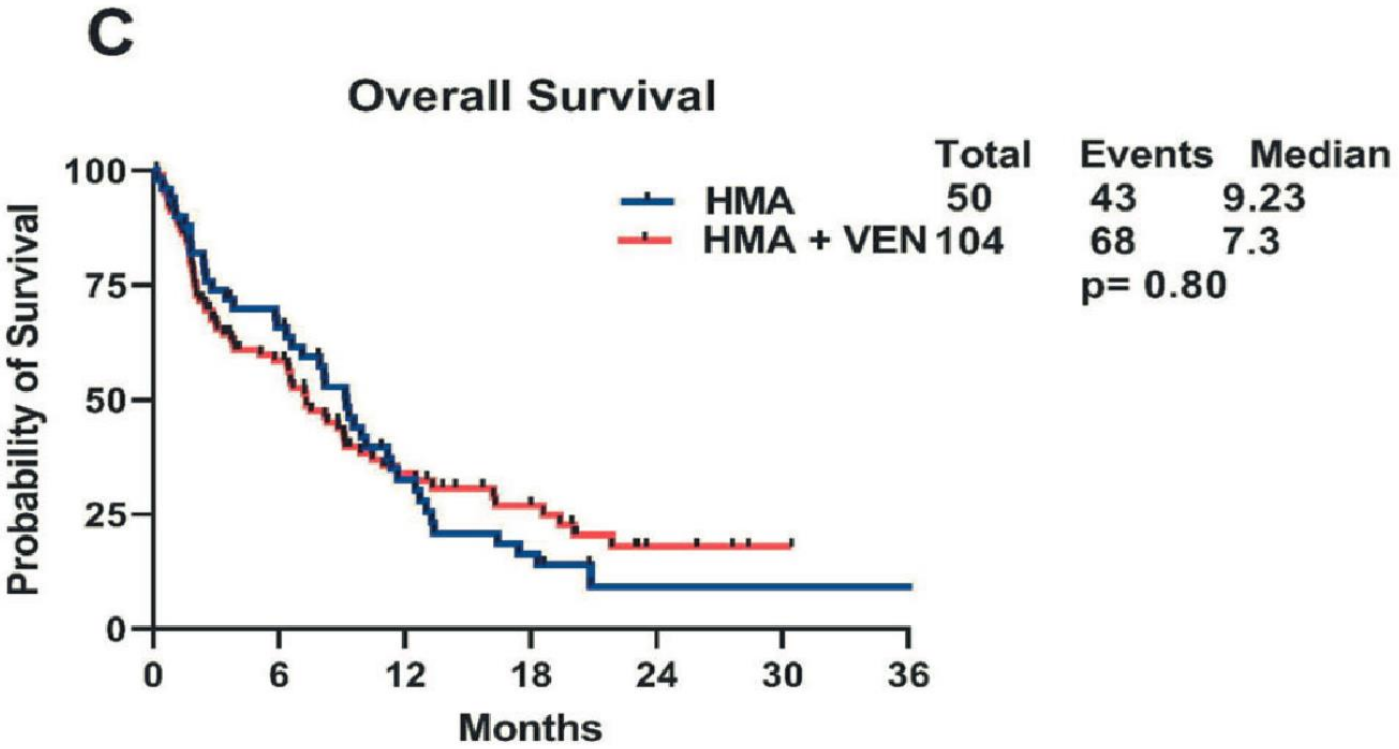
Old/unfit

Several comorbidities

AML with *TP53* mutation/complex karyotype

Initial response to azacitidine + venetoclax, but progression with relapsed/refractory disease and death

Venetoclax and *TP53* – COMMAND



Questions for the audience

How would you treat an elderly patient with newly diagnosed AML with *TP53*?

- Azacitidine + venetoclax OR azacitidine alone?

How would you treat those patients when they experience relapse?

Would you have treated this patient differently?

Thank you for your attention!

ALBERT EINSTEIN

AML Case

Carolina Perrone, MD
Hospital Israelita Albert Einstein – São Paulo, Brazil

Case Report

ALBERT EINSTEIN

- A 42-year-old man with no significant past medical history presented to the emergency department with complaints of progressive fatigue, fever, and gingival thickening

- Initial Workup (04/2023)
  - *Hb: 10.7g/dL | Leukocytes: 53.780 | Neut: 538 | Lymph: 8067 | Monocytes: 1076 | Platelets: 74.000*
  - ***81% of cells are moderately to largely sized with a high nucleus-to-cytoplasm ratio***

Case Report

ALBERT EINSTEIN

- **Bone Marrow Aspirate:** 89% of cells are myeloid and monoblastic blasts
- Immunophenotyping
  - ***14.4% myeloid population***
  - ***61.4% monocytic lineage population***
- **FISH:** *KMT2A* gene rearrangement (chromosome 11q23)
- **Karyotype**: 46XXt(6;11)(q27;q23)[28]/50idem+8+13+19+21[2]
- **Myeloid panel:** *FLT3* TKD variant N841T (36%) and *FLT3* ITD

Case Report

ALBERT EINSTEIN

He was diagnosed with

- Acute myeloid leukemia (AML) with defining genetic abnormalities (WHO, 2022)
  - *Adverse risk (ELN, 2022)*
- AML-defining recurrent genetic abnormalities (ICC, 2022)

Treatment Induction

- Protocol 3+7 (daunorubicin and cytarabine) + midostaurin
- C1D1 on 04/2023

Case Report

ALBERT EINSTEIN

On post-induction bone marrow evaluation, the disease was found to be **refractory**.

He had 83% blast cells in the bone marrow, and it was decided to initiate salvage treatment.

Post-Induction Evaluation

- **Bone marrow aspirate:** 83% blastic cells
- **Immunophenotyping:** compatible with AML with a monocytic component (77% of immature cells)
- **Karyotype:** 46XXt(6;11)(q27;q23)[18]/46XX[2]
- **FISH:** *KMT2A* rearrangement in 81% of nuclei
- **Myeloid panel:** compared with the previous test released on 05/03/2023, there is a decrease in the allelic frequency of the N841T variant in *FLT3* (13%) and the absence of the ITD variant in the same gene

Case Report

ALBERT EINSTEIN

Rescue Treatment

- Venetoclax 400 mg/day + gilteritinib 120 mg/day
  - *C1: 05/2023*
  - *C2: 06/2023*

Post-Rescue Evaluation

- Bone marrow aspirate: morphologic remission
- Immunophenotyping: minimal residual disease (MRD) positive (0.5%)
- Karyotype: 46, XX [20]
- FISH: *KMT2A* gene rearrangement in 11% of analyzed nuclei
- Myeloid panel: absence of both *FLT3* variants (ITD and TKD [N841T])
- *FLT3* ITD and TKD mutation PCR: negative

Case Report

Bone Marrow Transplantation

ALBERT EINSTEIN

- Haploidentical related donor (brother) 5 × 10 rejection direction 5 × 10 GvHD direction
  - *HLA-DPB1 non-permissive*
  - *B leader: mismatch*
  - *PRA: positive | Presence of anti–HLA-A*33:01 DSA at low titer and negative crossmatch on 29/05/2023*
- Pre-HSCT disease status: second morphologic remission with positive MRD
- Conditioning: Bu4Flu AUC 5000 + post-transplant cyclophosphamide (PTCy) (myeloablative)
- Stem cell source: bone marrow
- Product: TNC 5.85×10^8 // CD34 3.14×10^6 // CD3 2.16×10^7
- ABO blood group: recipient (R) A+/ donor (D) 0+ (anti A<64) - minor incompatibility
- Cytomegalovirus status: R positive/D positive
- Toxoplasmosis status: R negative/D negative
- GvHD prophylaxis: tacrolimus (FK) + mycophenolate mofetil + PTCy

Case Report

ALBERT EINSTEIN

D+30 (08/2023)

- **Bone marrow examination:** morphologic remission
- **Immunophenotyping:** positive MRD
- **Karyotype**: 46, XX | **FISH** negative
- **STR chimerism:** >98%
- ***FLT3*** **PCR:** negative

Maintenance therapy with gilteritinib 80 mg/day

Case Report

ALBERT EINSTEIN

D+64 (09/06/2023)

- **Bone marrow examination:** morphologic remission
- **Immunophenotyping:** negative MRD
- **Karyotype**: 46, XX | FISH negative
- **STR chimerism:** 100%
- ***FLT3*** **PCR:** negative

D+100 evaluation: still on remission

Case Report

ALBERT EINSTEIN

Relapse on 01/2024 (D+196)

- Bone marrow examination: 33.2% blast cells
- Immunophenotyping: 10.4% blast cells
- Karyotype: 46,XX,t(6;11)(q27;q23)
- STR chimerism: 72% (negative HLA LOSS)
- Myeloid panel: *FLT3* negative

Rescue treatment: decitabine (10d) + venetoclax

Bone marrow evaluation after rescue treatment

- Bone marrow examination: 67% blast cells
- Karyotype: 46,XX,t(6;11)(q27;q23)[19]/46,XX[1]
- FISH: *KMT2A* gene rearrangement (chromosome 11q23) detected in 99% of analyzed nuclei
- STR chimerism: 13%
- *FLT3* negative

Case Report

ALBERT EINSTEIN

- In light of the **refractoriness** to the proposed salvage treatment and the **unavailability of menin inhibitors in Brazil**, it was suggested to the patient that he go to the USA to receive experimental therapy

- In May 2024, **2 months after starting treatment** with a menin inhibitor, the patient presented in **morphologic remission** and is scheduled to undergo a second allogeneic bone marrow transplant

QUESTIONS

Question 1

- What other rescue treatments could be considered for refractory AML if menin inhibitors are unavailable?

Question 2

- Would you take this patient for a second bone marrow transplant?

Question 3

- If you take this patient for a second bone marrow transplant, would you continue maintenance with menin inhibitors?

THANKS!

carolina.marques@einstein.br

Global Leukemia Academy

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

Naval Daver and all faculty

APTITUDE HEALTH®

Panel Discussion

- Will CAR Ts and bispecifics change the treatment landscape?
- What is the evolving role of HSCT—will it still be necessary?
- What does the future in Latin America look like in terms of
  - Adoption of new therapies?
  - Evolving standards of care?

Global Leukemia Academy

ARS questions

Naval Daver

APTITUDE HEALTH®

Question 3 [REPEATED]

Which of the following is NOT true for ALL?

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

B. Kinase inhibitors can be combined with other therapy modalities in Ph-positive ALL

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

D. There are no effective consolidation treatments for patients who remain MRD positive after induction therapy

Question 4 [REPEATED]

The prognosis of patients with R/R AML 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

Global Leukemia Academy

Session close

Naval Daver

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