Allogeneic Transplat in MDS and AML: When to indicate and When to avoid

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Beneficência Portuguesa de SP

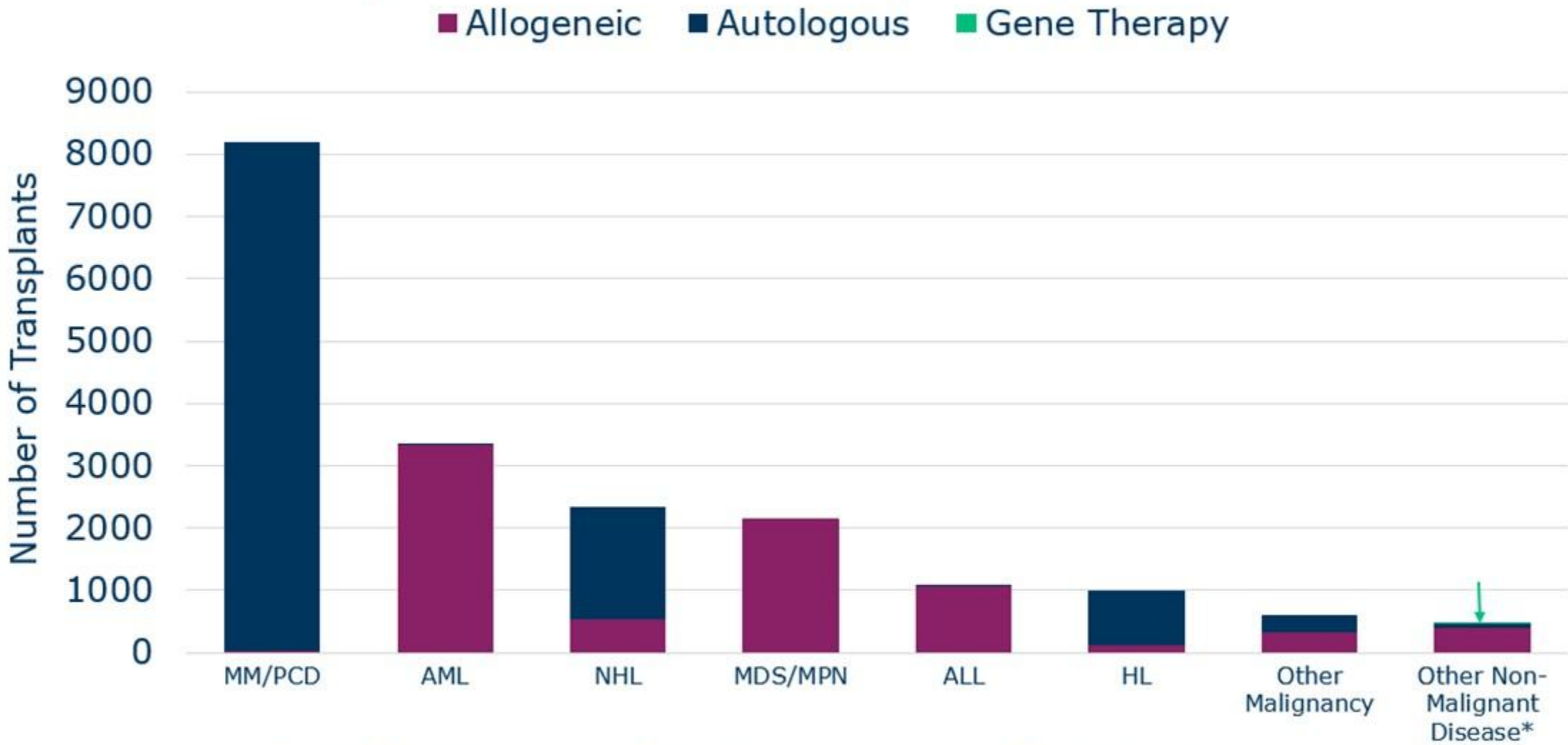
UNIFESP

Autologous and Allogeneic HCT in Adults with relapsed Acute Promyelocytic Leukemia: Results of a Systematic Review and Meta-Analysis

- Pooled PFS : 63% for autologous HCT x 43% for allogeneic HCT.
- Pooled OS: 82% for autologous HCT x 58% for allogeneic HCT.
- There is a higher pooled NRM rate with an allogeneic HCT (29% versus 5%).
- Pooled relapse rates: 24% for autologous HCT x 23% for allogeneic HCT.

Mothy R et al. Transpl Cell Therapy, 2024

Number of HCTs by Indications in the US, 2023, Adult



*Includes 22 limited gene therapy events

Abbreviations:
ALL, acute lymphoblastic leukemia;
AML, acute myeloid leukemia;
CLL, chronic lymphocytic leukemia;
HL, Hodgkin lymphoma;
MDS, myelodysplastic syndromes;
MM, multiple myeloma;
MPN, myeloproliferative neoplasms;
NHL, non-Hodgkin lymphoma;
PCD, plasma cell disorders.

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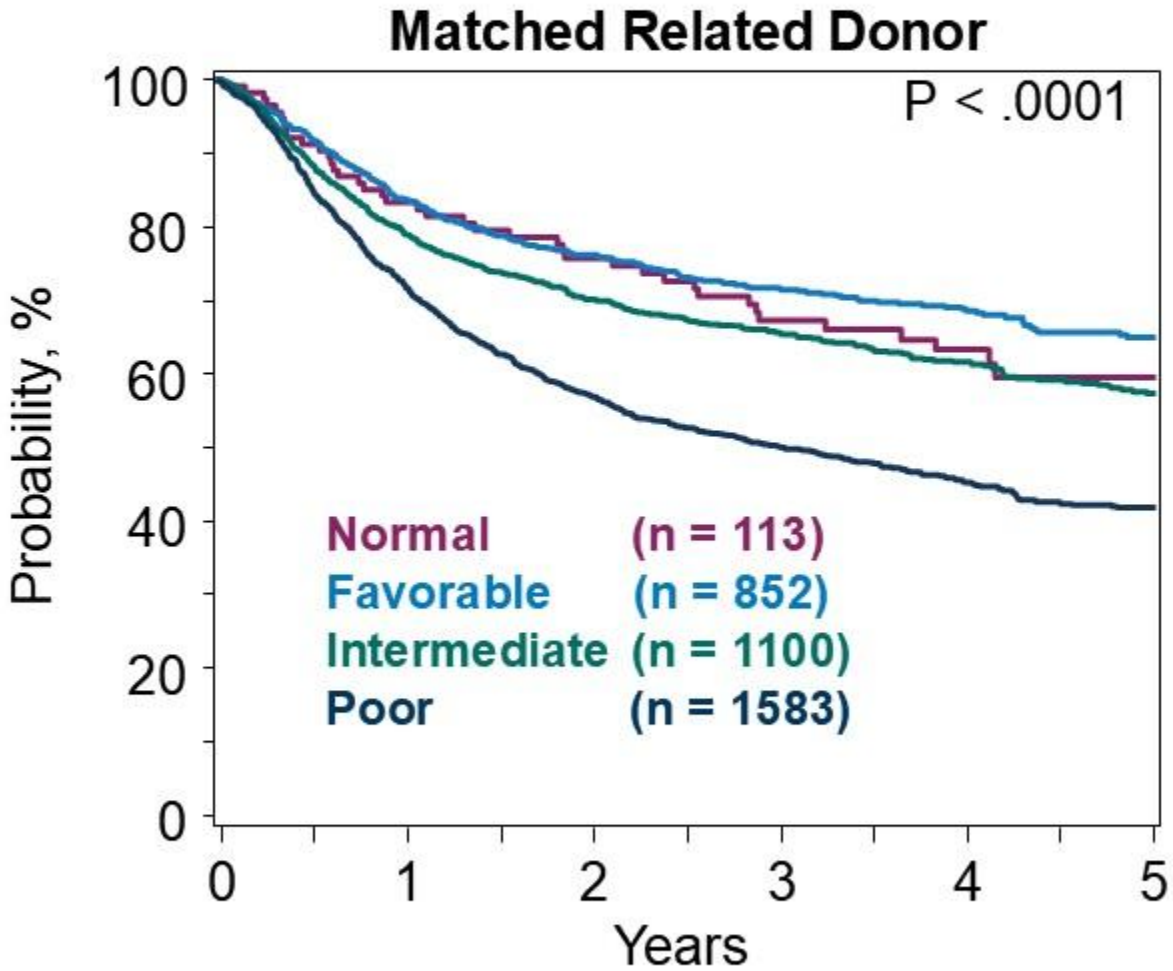
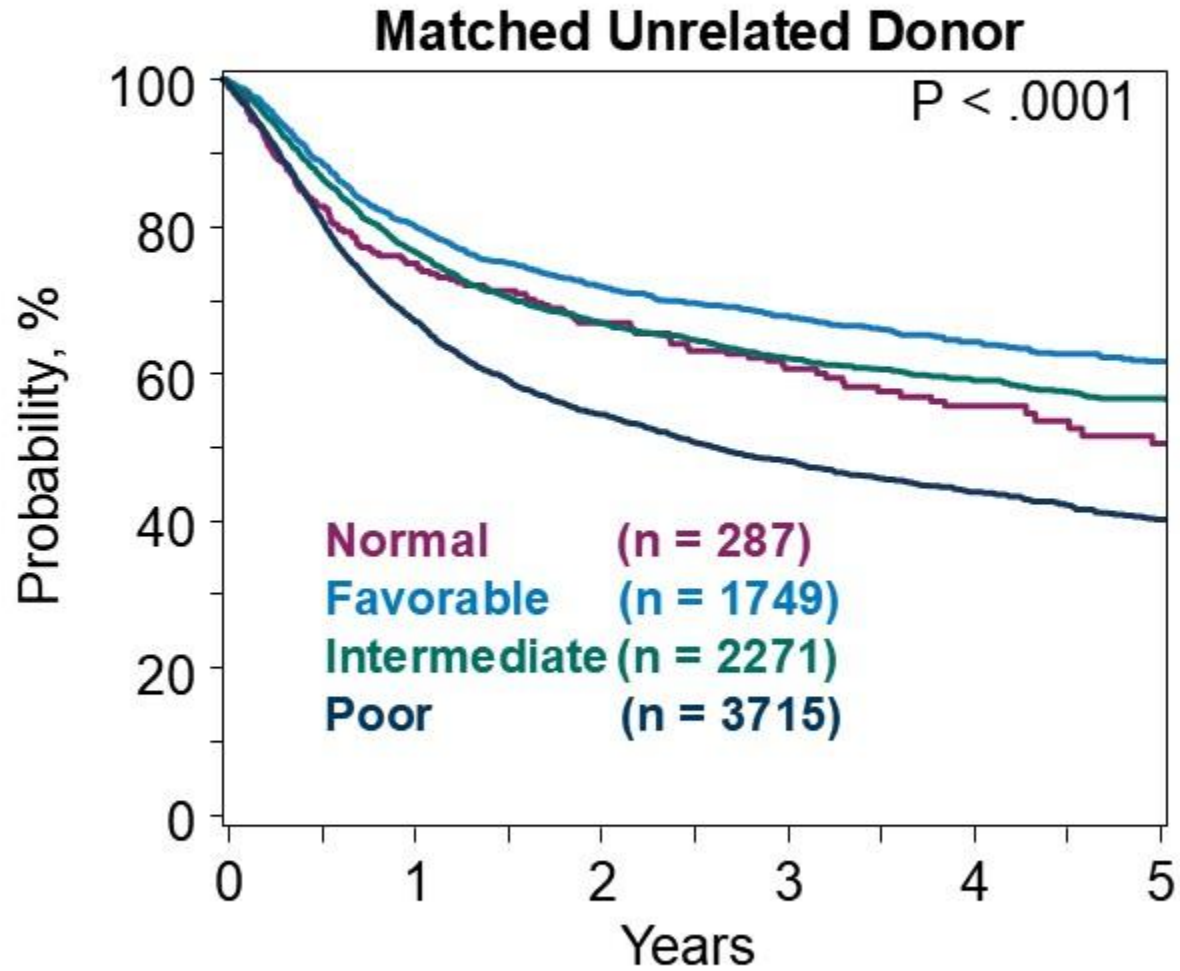
Survival after Allogeneic HCTs for Acute Myeloid Leukemia, Using Matched Donors in the US, 2017-2022, Adults, by ELN Cytogenic Risk Score





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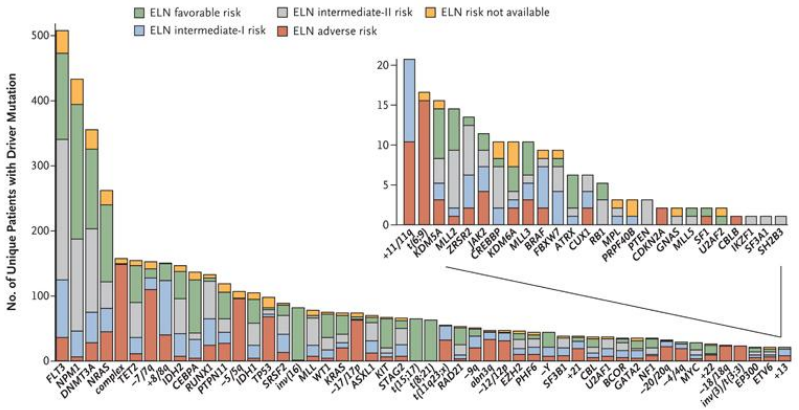
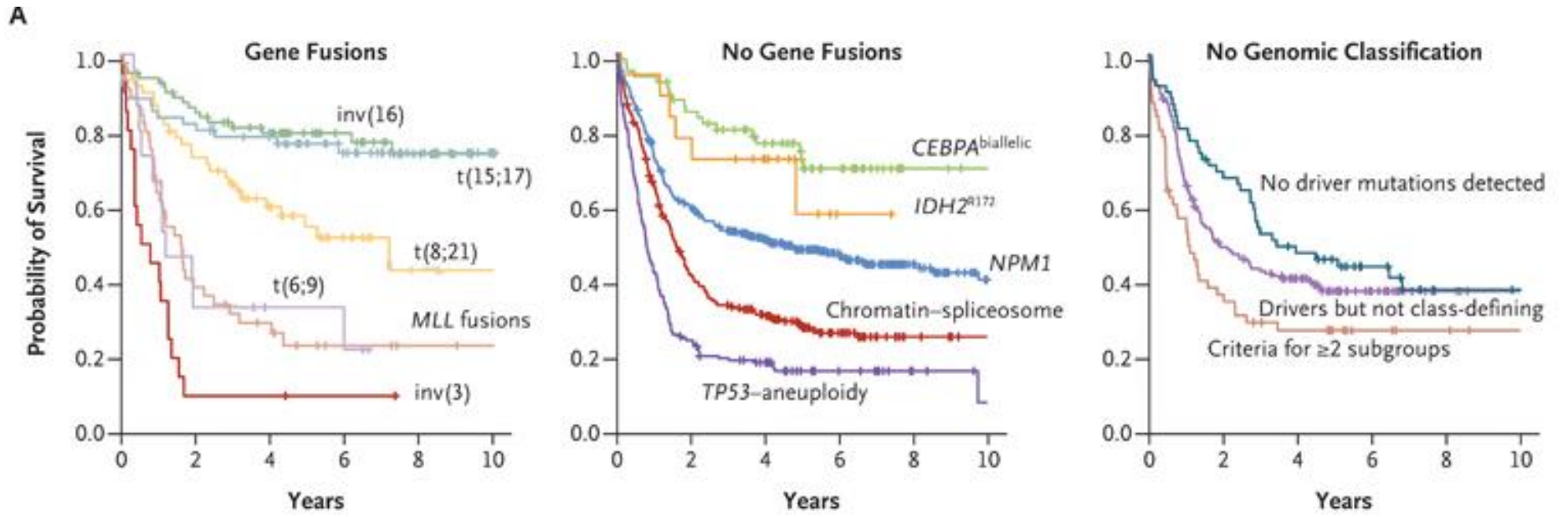
Abbreviations: ELN, European LeukemiaNet; HCT, hematopoietic cell transplantation.

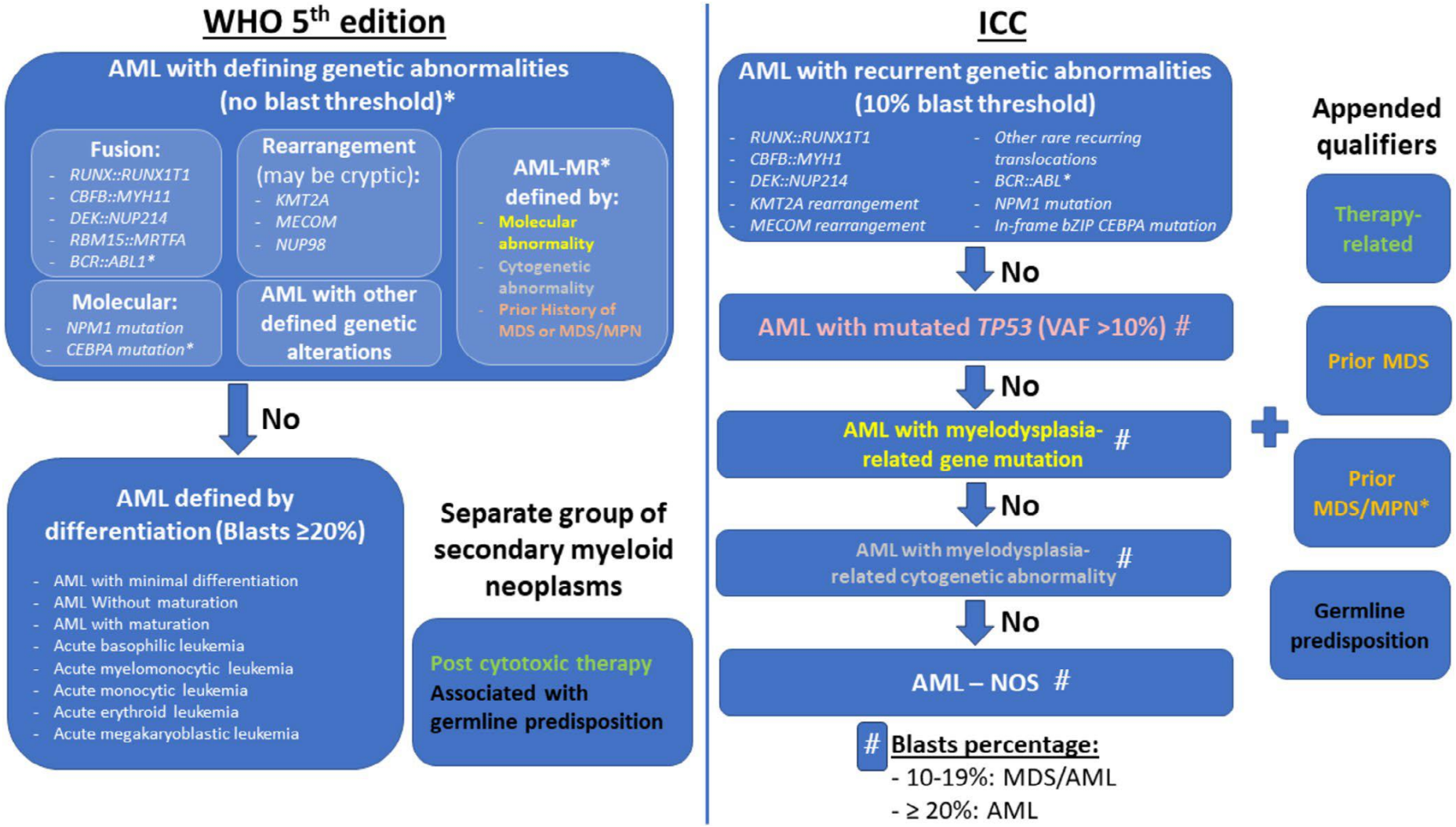
Genomic Classification and Prognosis in Acute Myeloid Leukemia





Papaemmanueil, E. N Engl J Med. 2016 Jun 9; 374(23): 2209–2221

Comparison between WHO 5th versus ICC AML definitions



Symoni S et al. American Journal of Hematology, 2025; 100:860–891

AML ELN – Risk stratification by genetics

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[a]
	inv (16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[a]
	Mutated *NPM1* without *FLT3*-ITD[b]
	bZIP in-frame mutated *CEBPA*[c]
Intermediate	*FLT3*-ITD (irrespective of allelic ratio or *NPM1* mutation)
	t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[d]
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/*DEK::NUP214*
	t(v;11q23.3)/*KMT2A* rearranged (excluding *KMT2A-PTD*)
	t(9;22)(q34.1;q11.2)/*BCR::ABL1*
	(8;16)(p11;p13)/*KAT6A::CREBBP*
	inv (3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
	t(3q26.2;v)/*MECOM(EVI1)*-rearranged
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype (change in definition)[e]; Monosomal Karyotype[f]
	Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[g]
	Mutated *TP53* (variant allele frequency ≥ 10%)

"Allogeneic HCT should be considered when the relapse probability without the procedure is predicted to be 35% to 40%."

IDAC

Allogeneic HCT
Autologous HCT/IDAC

Allogeneic HCT

Dohner, H et al. Blood. 2017 Jan 26; 129(4): 424–447.

Caso Clínico – masculino, 48a

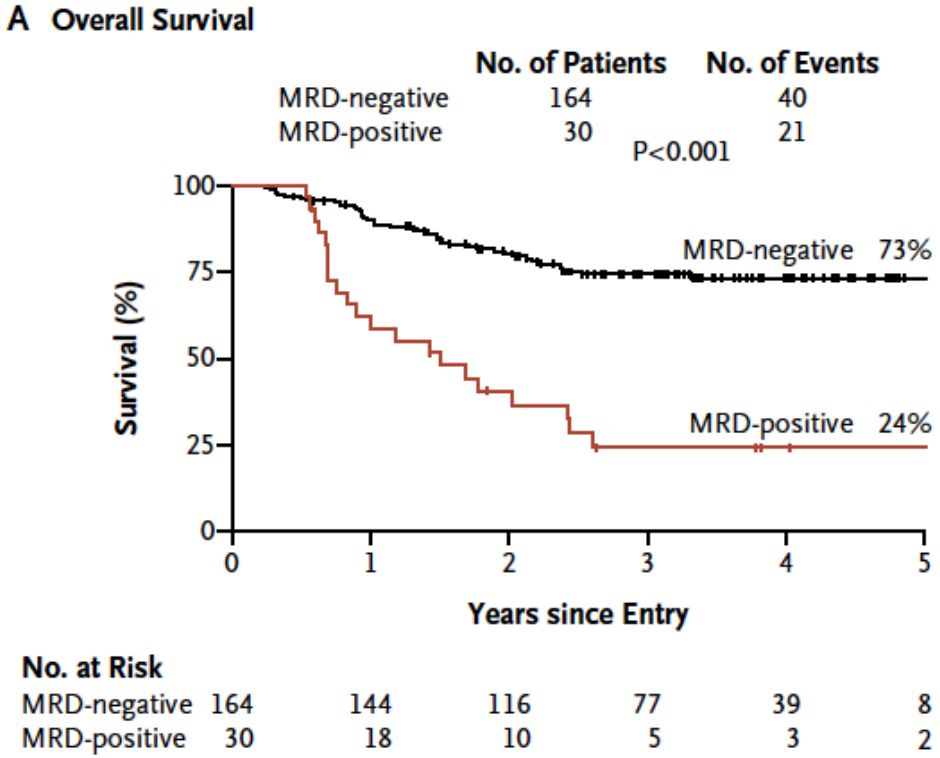
LMA monocítica – Risco Favorável
46 XY
DNMT3A (40,7%) / NPM1 (23,88%)

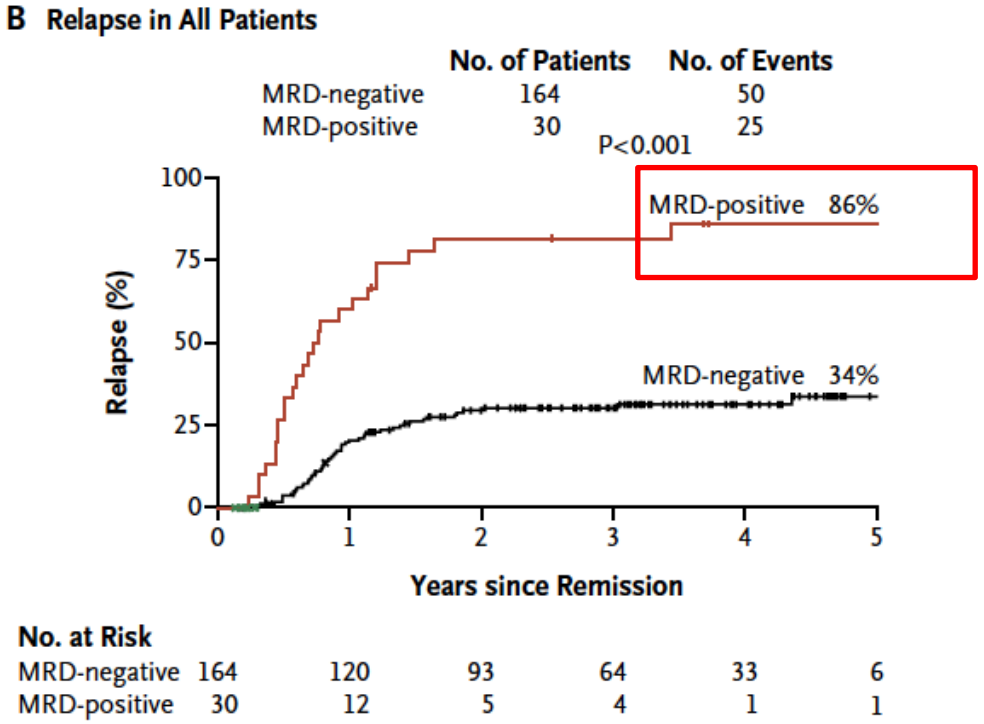
Tto Quimioterapico:
- Indução: 3+7 (Di:15/02/2019)+MADIT: DRM- (citometria)
- Consolidação com hi-DAC: 1º ciclo: 28/03: NPM1 positivo
- Consolidação com hi-DAC: 2º ciclo: 08/05
- Consolidaçao com hi-DAC: 3º ciclo: 18/06
- Consolidaçao com hi-DAC: 4º ciclo: 06/08: NPM1 positivo

Minimal Residual Disease in Standard-Risk AML (NPM1+)

- N= 346
- Intensive treatment (AML17 trial)
- RT-qPCR - *median sensitivity 1 x 10^{-5}*

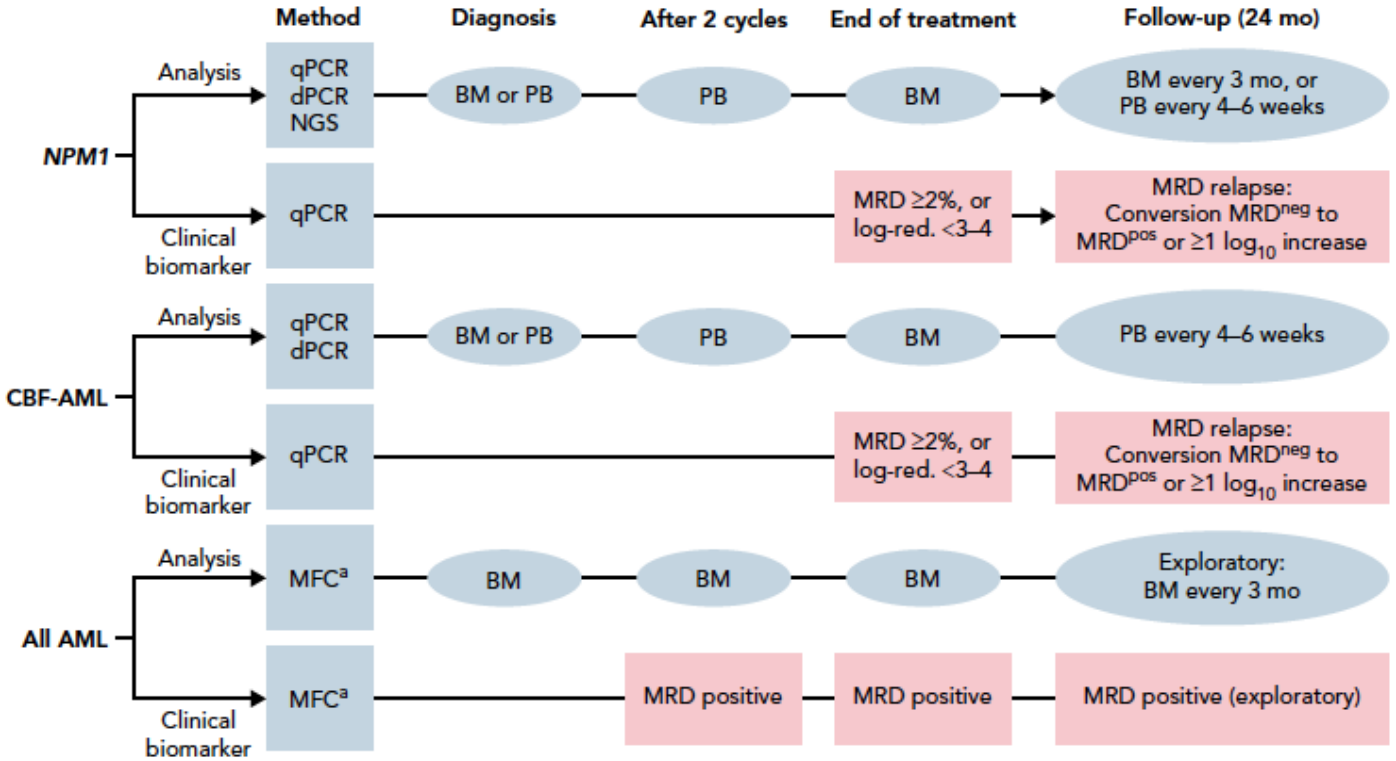
NPM1-mutated transcripts in blood was present in 15% of the patients after the second chemotherapy cycle





UK ALMWG Ivay A et al. N Engl J Med 2016;374:422-33.

MRD assessment algorithm for different subtypes of AML



!

MRD⁺ by MFC after
2 cycles of intensive chemotherapy
Consolidation chemotherapy
Prior/after to stem cell transplantation

***NPM1*/CBF failed to reach a 3- to 4-log reduction**
After completion of consolidation chemotherapy

MRD relapse (either molecular or MFC)
single positive MRD test does not guarantee relapse

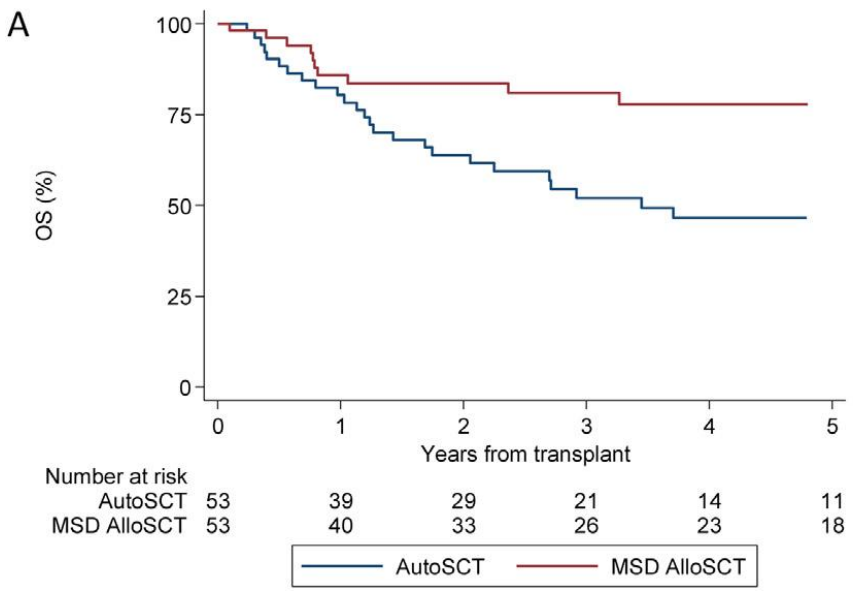
Dohner, H et al. Blood. 2017 Jan 26; 129(4): 424–447.

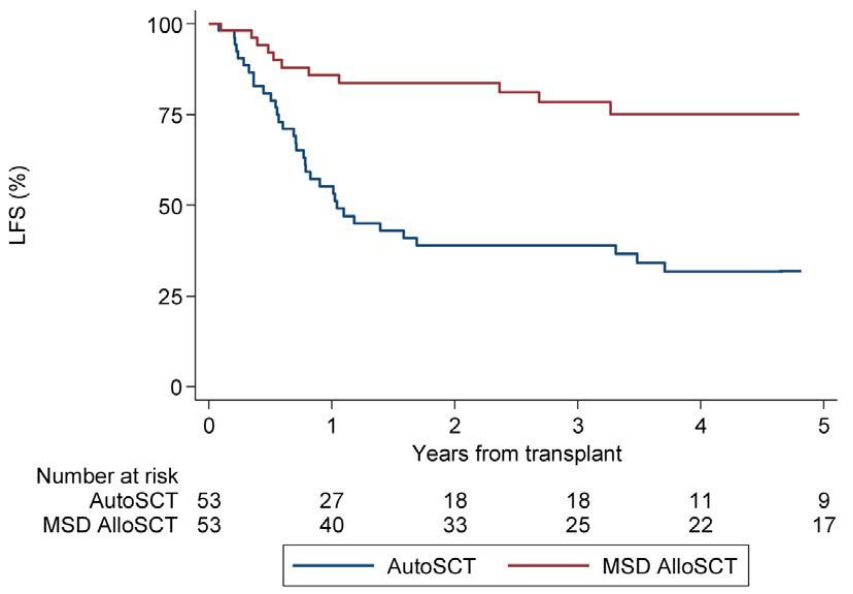
Intermediate	*FLT3*-ITD (irrespective of allelic ratio or *NPM1* mutation)
	t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[d]
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Allogeneic HCT

Autologous HCT/IDAC??

Auto x Allo: A PETHEMA Study





E. Rodríguez-Arbolí et al. / Transplantation and Cellular Therapy 27 (2021) 311.e1 311.e10

FLT3 Inhibitors as Post-Transplant Maintenance in FLT3-ITD AML

Study (Year)	Drug	Outcomes
SORMAIN (Lancet Oncol 2020)	Sorafenib	- 2-yr RFS: 53% (sorafenib) vs. 36% (placebo) (HR 0.39, *p*=0.013)
		- OS benefit: Trend (not significant)
RATIFY post-hoc (Blood 2019)	Midostaurin	**- 4-yr OS: 63% (midostaurin + HSCT) vs. 41% (chemo alone)**
QUANTUM-First (ASH 2022)	Quizartinib	- 3-yr OS: 72% (quizartinib) vs. 58% (placebo) (HR 0.66, *p*=0.032)
		- Reduced relapse risk by 45%
Gilteritinib (BMT CTN 1706, ongoing)	Gilteritinib	- Primary endpoint: RFS
		- Early data: 1-yr RFS ~80% (vs. 55% historical)
MEMIC (Leukemia 2023)	Midostaurin	- 2-yr RFS: 78% (midostaurin) vs. 52% (no maintenance)

Caso Clínico – masculino, 75a, hígido sem comorbidades

LMA – Alto Risco
25% blastos
46 XY +10, +8
RUNX1 23%

Tratamento:
Azacitidina + Venetoclax - 4 ciclos

Resposta:
RC, DRM-

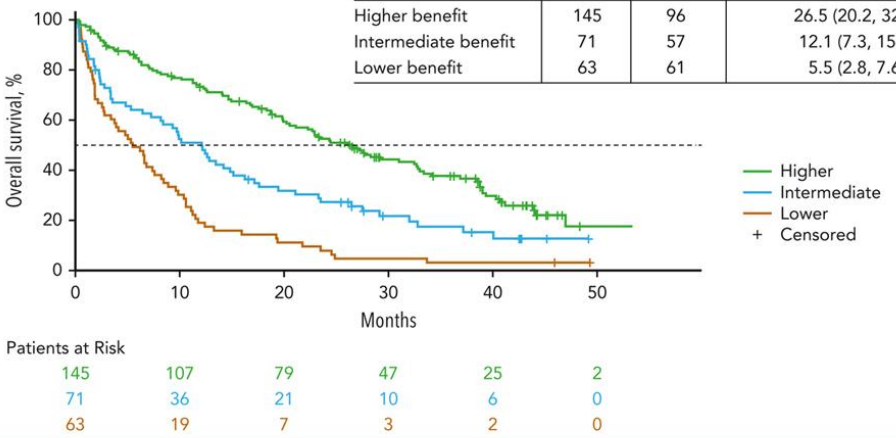
Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations

Outcomes with Venetoclax-Azacitidine by Genetic Risk in Newly Diagnosed Acute Myeloid Leukemia (AML)

Context of Research: In this post hoc pooled analysis, ELN 2017 and 2022 classification systems and a 4-gene signature developed by a bioinformatic algorithm were assessed as potential prognostic frameworks for risk stratification of outcomes with venetoclax-azacitidine in newly diagnosed AML

Four-gene prognostic risk classifier:

Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher benefit	145	96	26.5 (20.2, 32.7)
Intermediate benefit	71	57	12.1 (7.3, 15.2)
Lower benefit	63	61	5.5 (2.8, 7.6)



Conclusion: Although ELN 2017 and 2022 classification systems failed to discriminate outcomes, the application of a bioinformatic algorithm identified a 4-gene prognostic risk classifier (*FLT3*-ITD, *KRAS*, *NRAS*, and *TP53*) that successfully differentiated outcomes among patients with newly diagnosed AML treated with venetoclax-azacitidine.

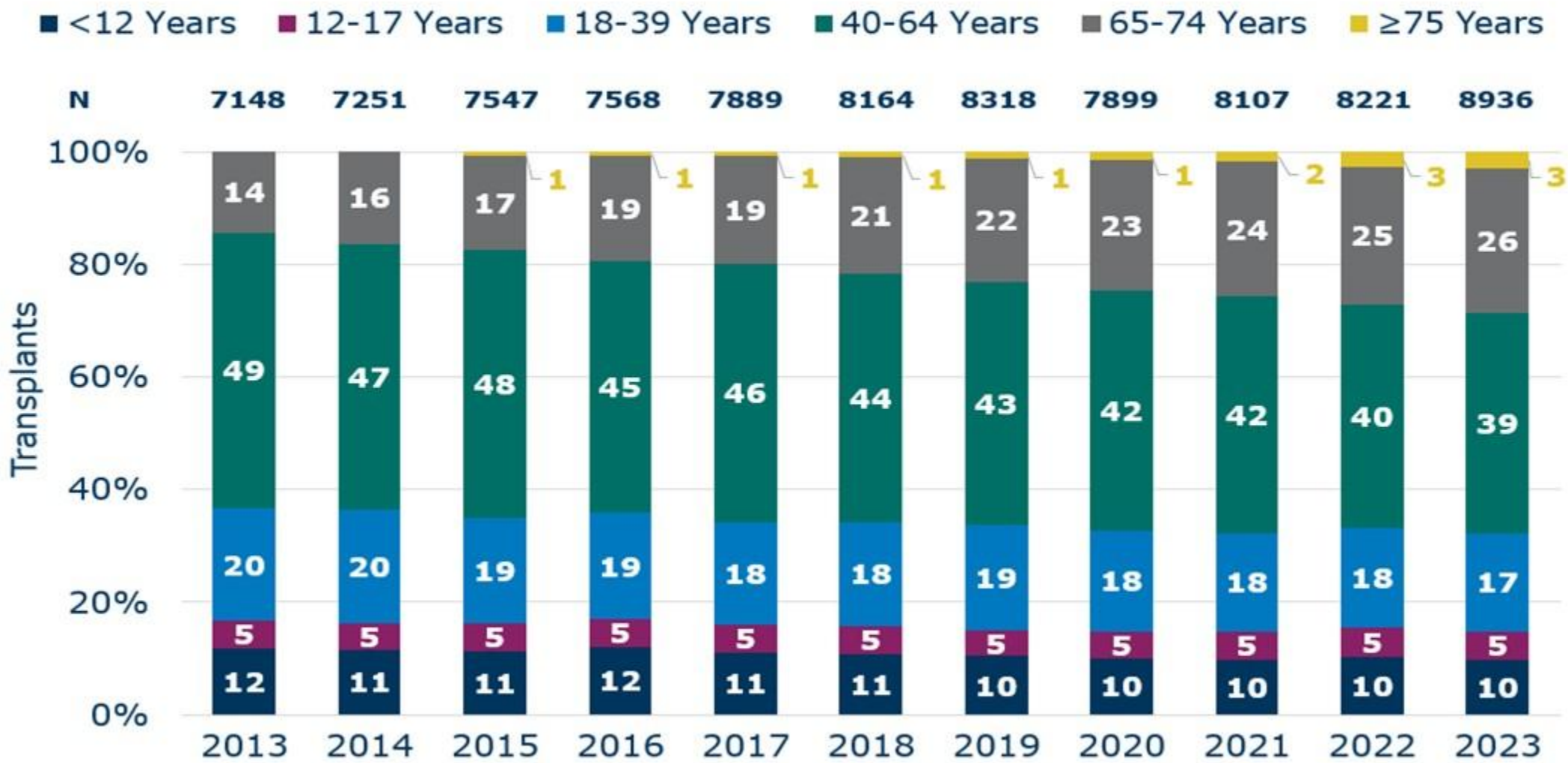
*Döhner et al. DOI: 10.1182/**blood**.2024024944*

blood Visual Abstract

Genetic marker	Median OS, mo
Favorable-risk group	
Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39
Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37
Mutated *IDH1** (*TP53*^{wt})	29
Mutated *DDX41*	>24
AML with MR gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23
Intermediate-risk group	
AML with MR gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13
Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12
Adverse-risk group	
Mutated *TP53*	5-8

Dohner, H et al. *Blood* (2024) 144 (21): 2169–2173.

Recipient Age of Allogeneic HCTs in the US



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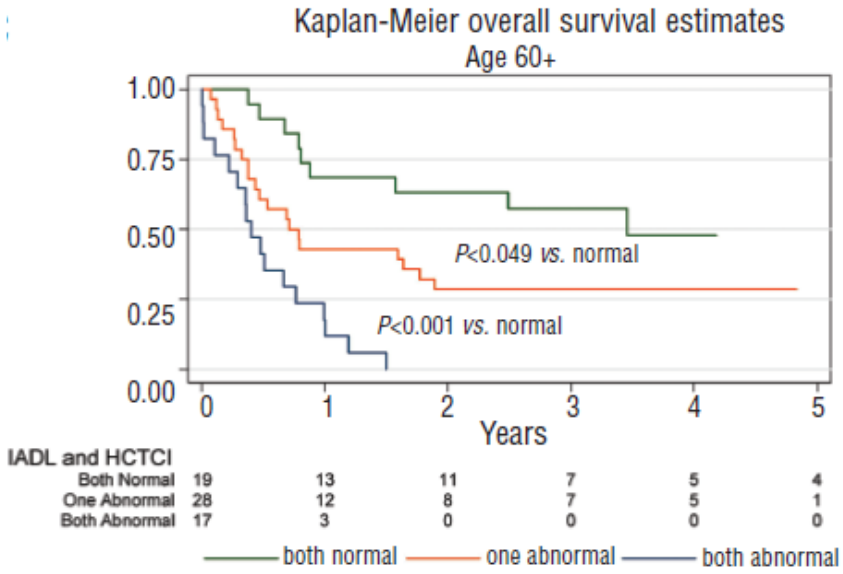
Tools – HCT-CI & GA

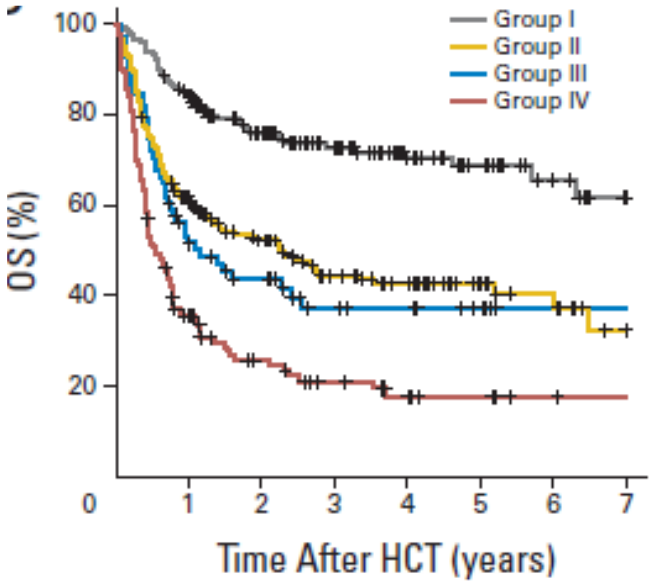
ECOG/PS – Still very reliable!

Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients



Muffly LS et al. Haematologica 2014

Comorbidity and Disease Status–Based Risk Stratification of Outcomes Among Patients With Acute Myeloid Leukemia or Myelodysplasia Receiving Allogeneic Hematopoietic Cell Transplantation



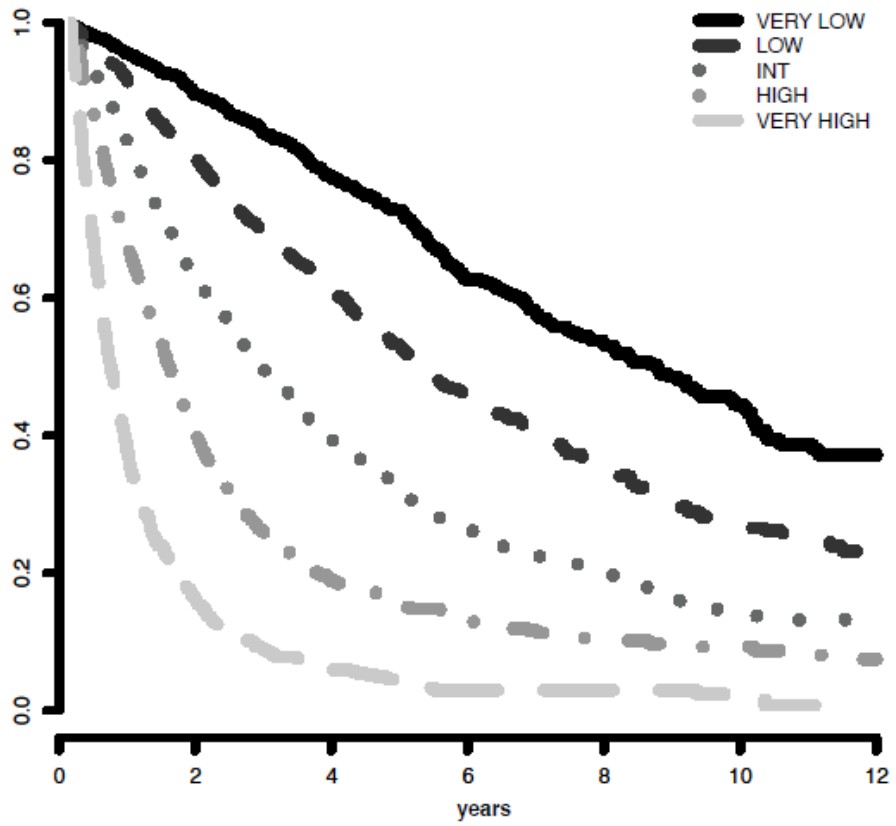
Sorror MS et al. J Clin Oncol 2007

Caso Clínico – feminina, 60a, hígida sem comorbidades

SMD – Muito alto risco
6% blastos
TP53 IHQ

Laudo
Resultado:
46,XX,der(5)t(5;12)(q13;q13),-12,del(13)(q14q22),+mar[4]/45~46,idem,der(9;14)(p10;q10),der(11)t(1;11)(q21;q14),-del(13)(q14q22),der(14;22)(q10;q10),add(16)(q12-13),-18,+1~2mar[cp8]/46,XX[8]

Revised-IPSS



Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

Muito bom
Del(11q)
-Y

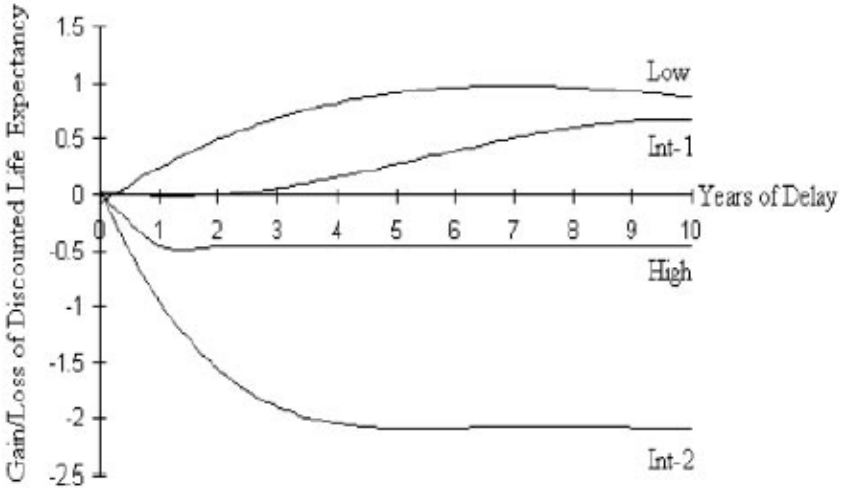
Bom
Normal
Der(1;7)
Del(5q)± 1 alteração
Del(20q)
Del(12p)

Ruim
-7/7q- + 1 alteração
3q21/3q26
3 alterações

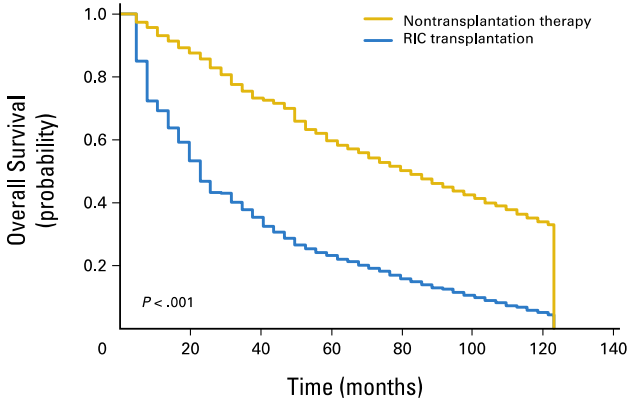
Muito Ruim
> 3 alterações

Greenber PL et al. Blood, 2012; 120(12): 2454-2465

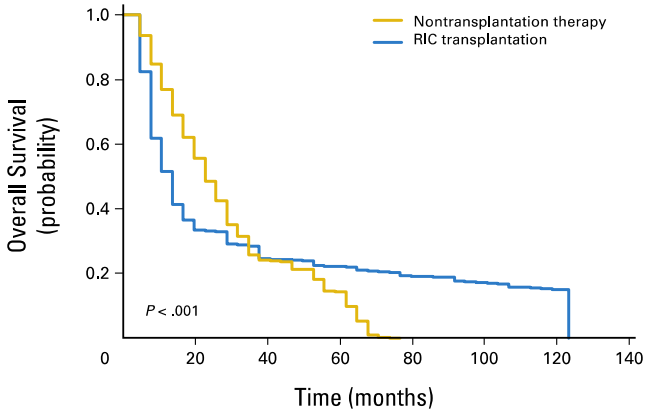
Marcov decision Model - MDS



low/intermediate-1



Intermediate-2/high

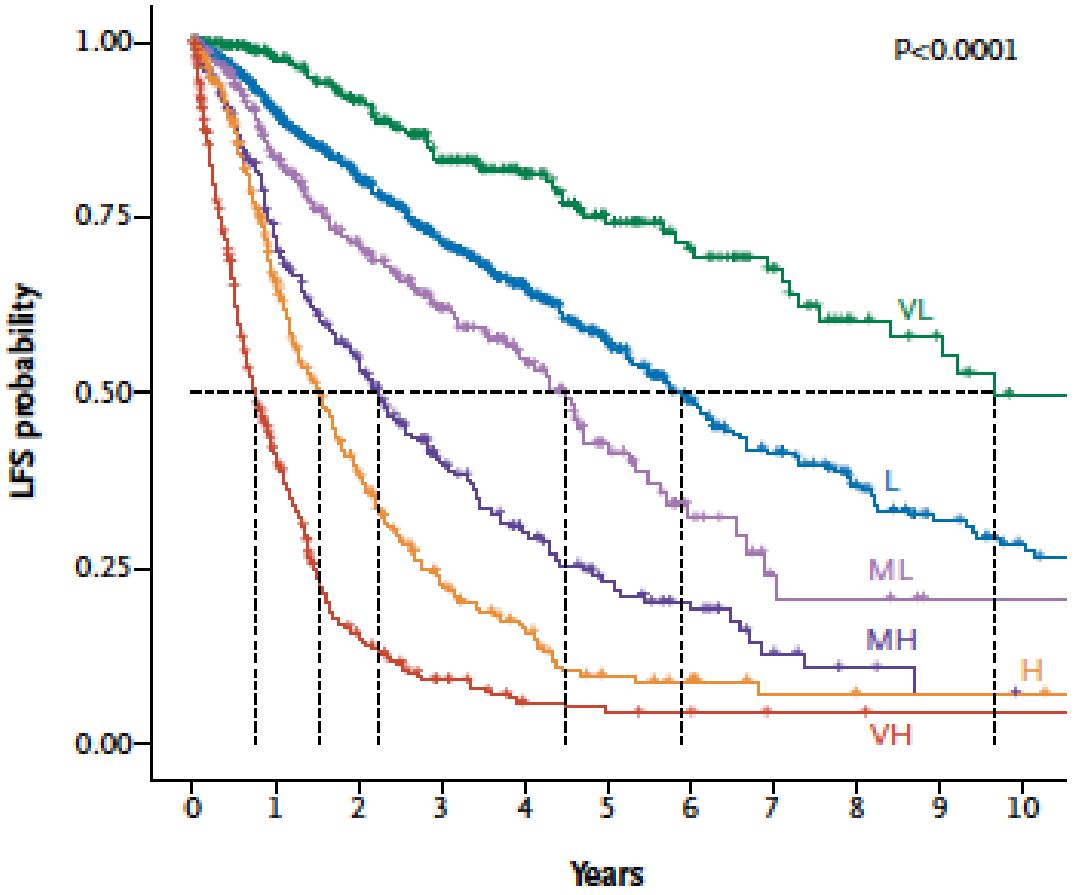


Koreth J et al. J Clin Oncol; 2013, 31: 2662-2671 CIBMTR - Cutler CS. et al. Blood; 2004, 104: 579-585

Molecular International Prognostic Scoring System for Myelodysplastic Syndromes

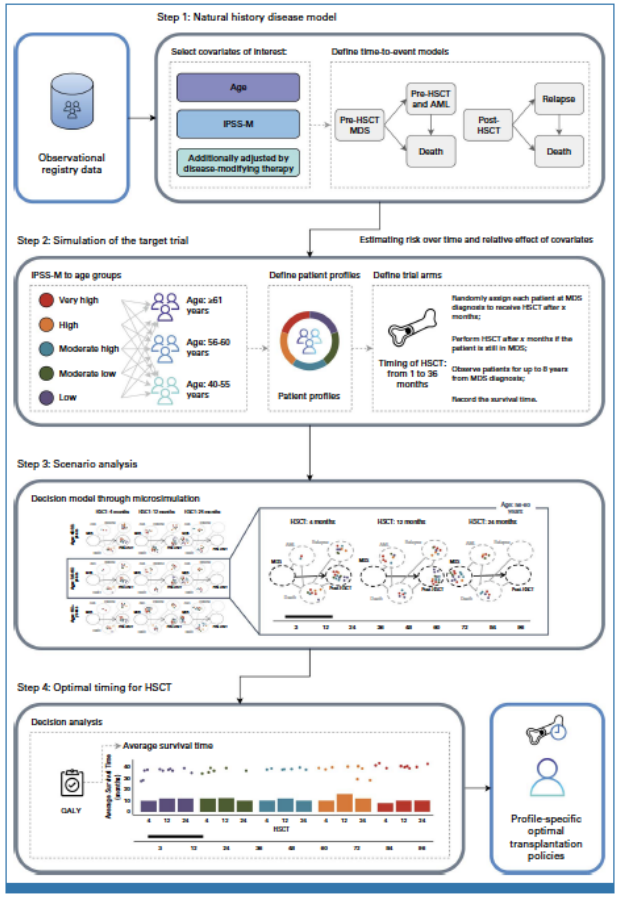
Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

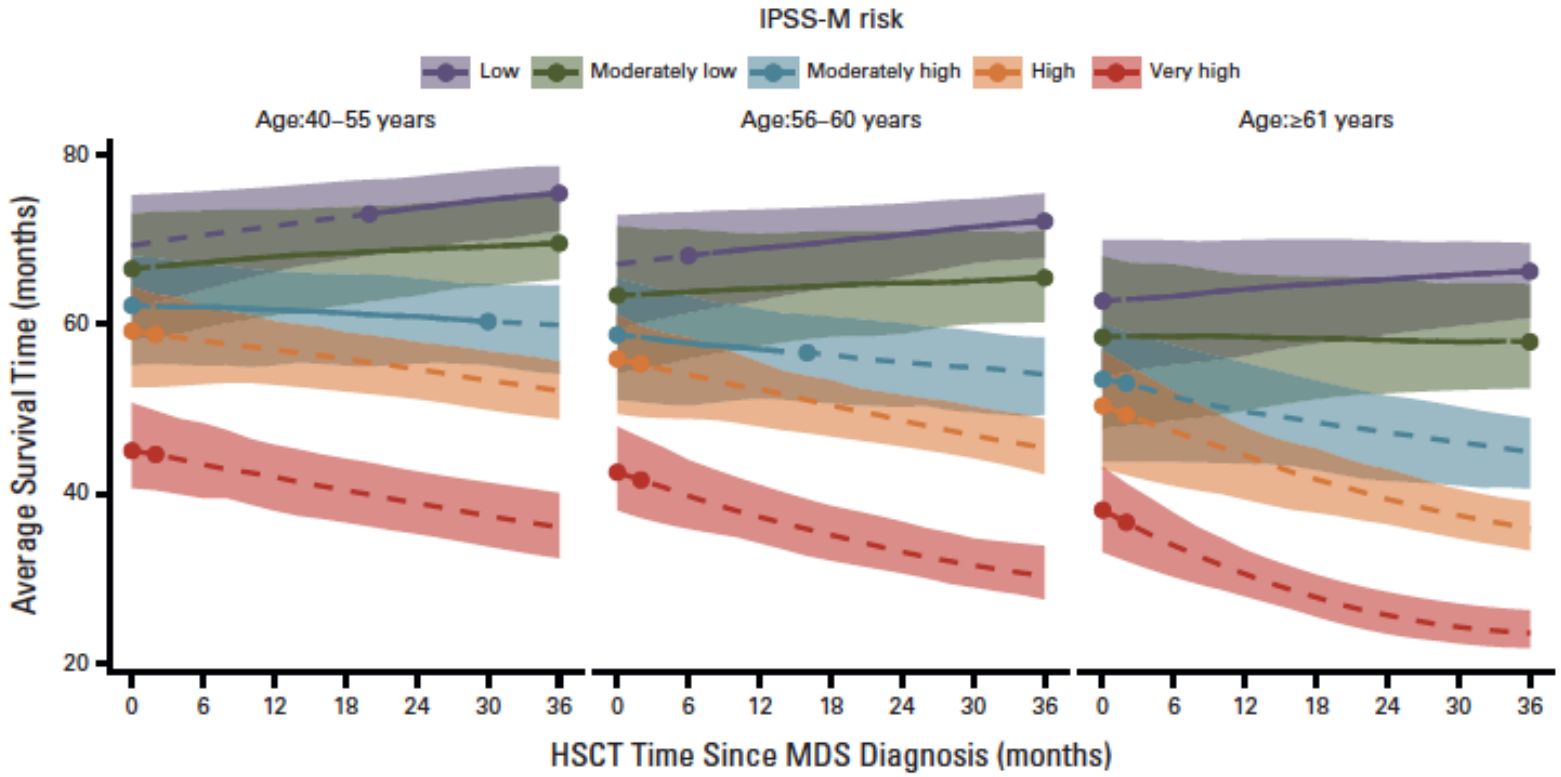
Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{Sq}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231



Bernard E et al, NEJM Evid 2022; 1 (7)

Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allo HCT

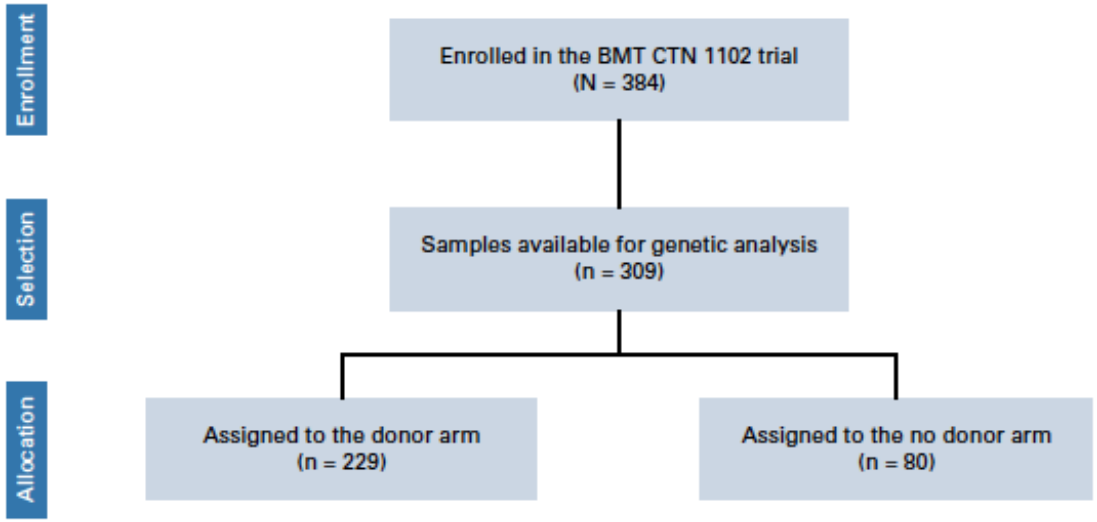


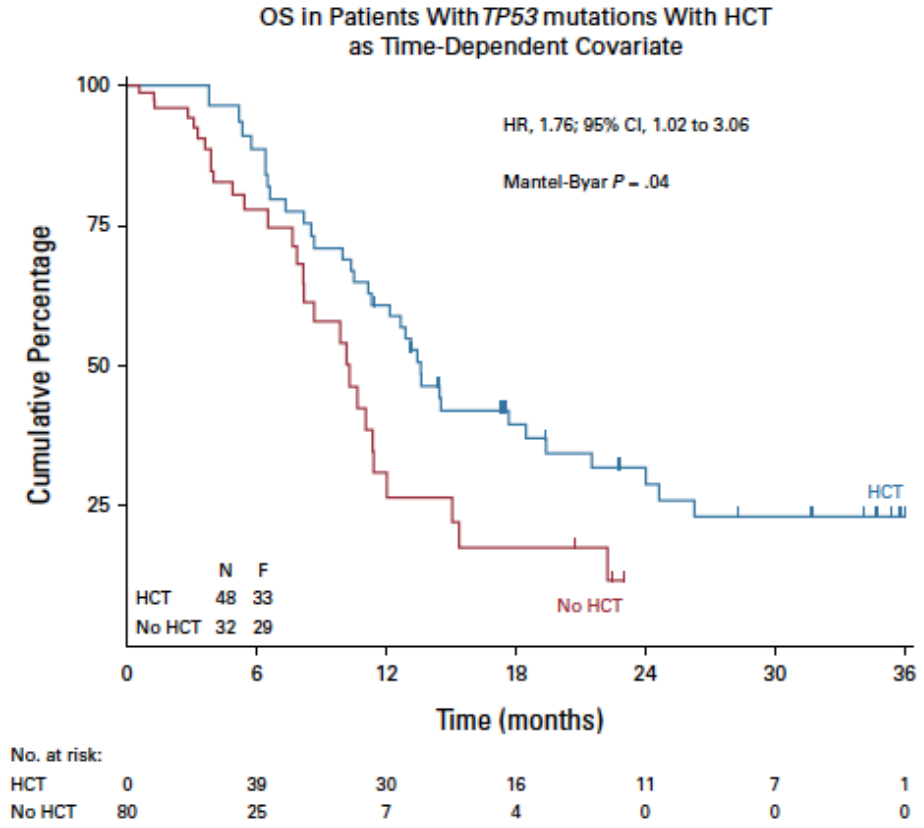


Tentori CA et al. J Clin Oncol; 2024: 42:2873-2886

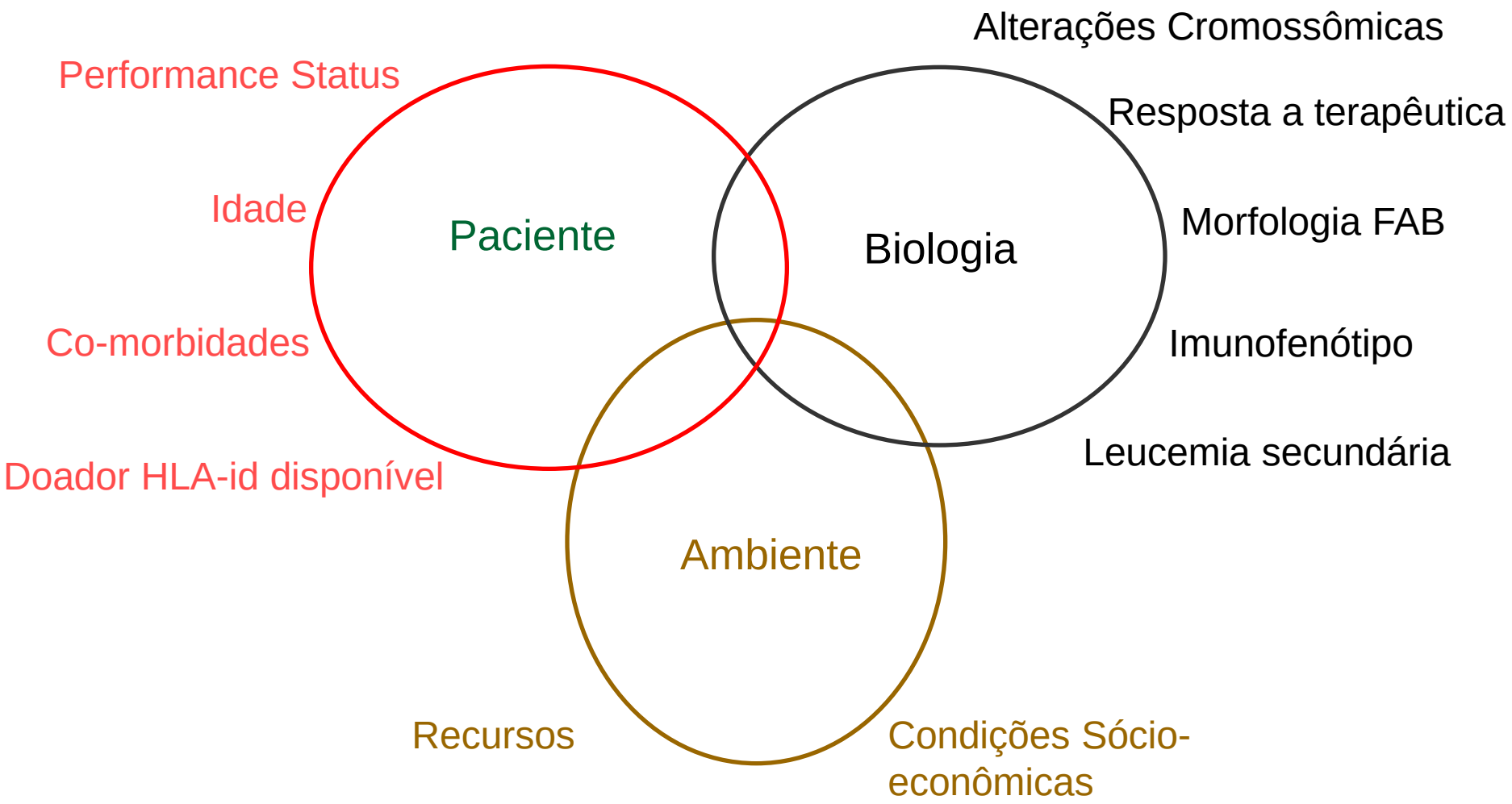
Allogeneic HCT in High-Risk MDS - BMT CTN 1102 Study

- *multicenter trial*
- *(RIC) HCT x hypomethylating therapy*
- *50-75 years*
- *IPSS intermediate-2 or high-risk de novo MDS*



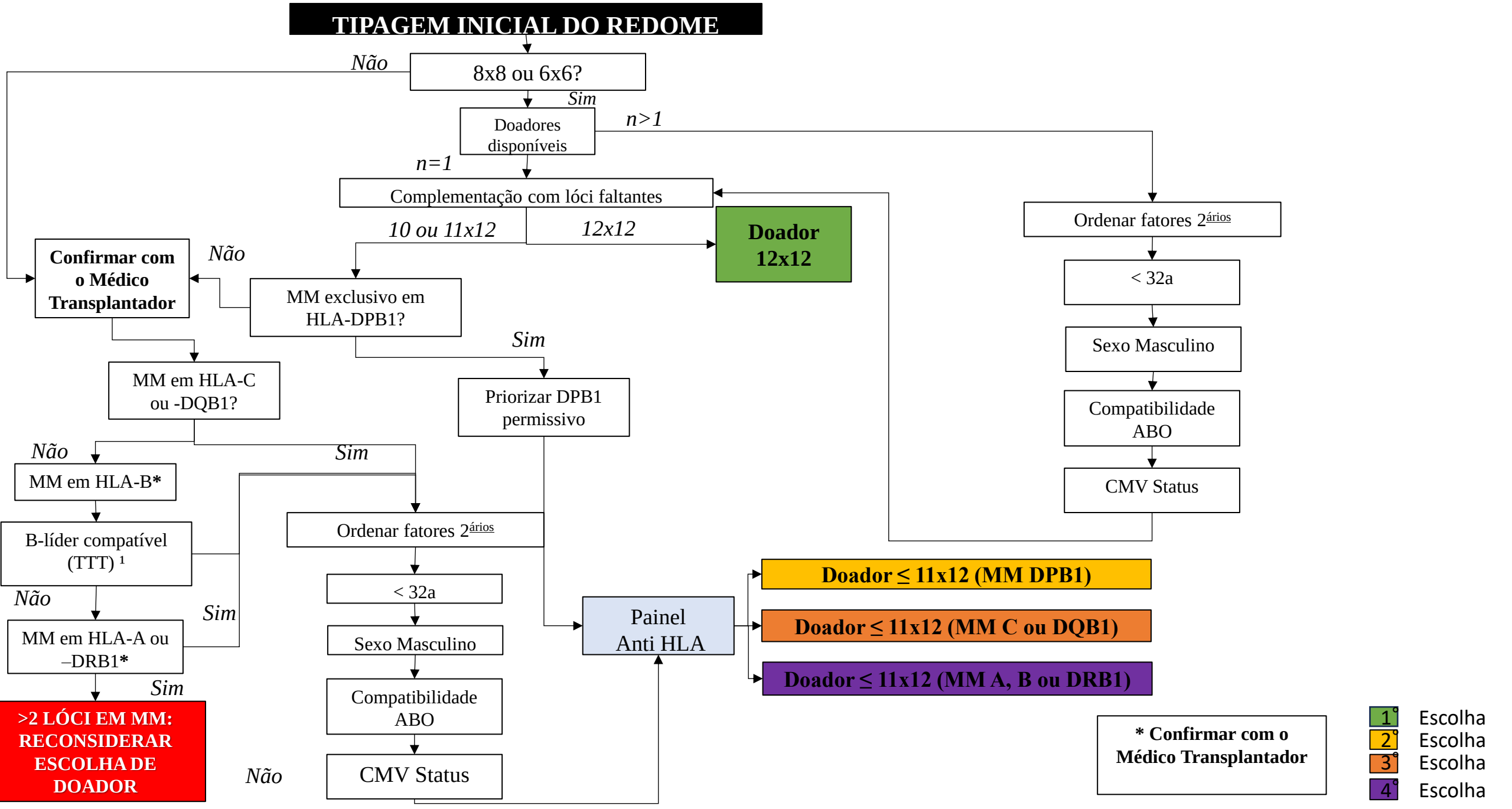


LMAs – Fatores Prognósticos



Fagundes, E et al, 2000

ALGORITMO 1 - HLA DOADORES NÃO APARENTADO



Obrigado!

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