Trattamento delle sindromi mielodisplastiche ad alto rischio e focus sul trapianto

con il patrocinio di SIE - Società Italiana di Ematologia

FISiM FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE



CONVEGNO FISiM

Firenze, CSF Montedomini - "Il Fuligno"

23-24 ottobre 2026

Disclosures Emanuele Angelucci

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Vertex							DMC
BMS							DMC
Sanofi			X				
Johnson & Johnson			X				
Pharmacosmos			X			X	

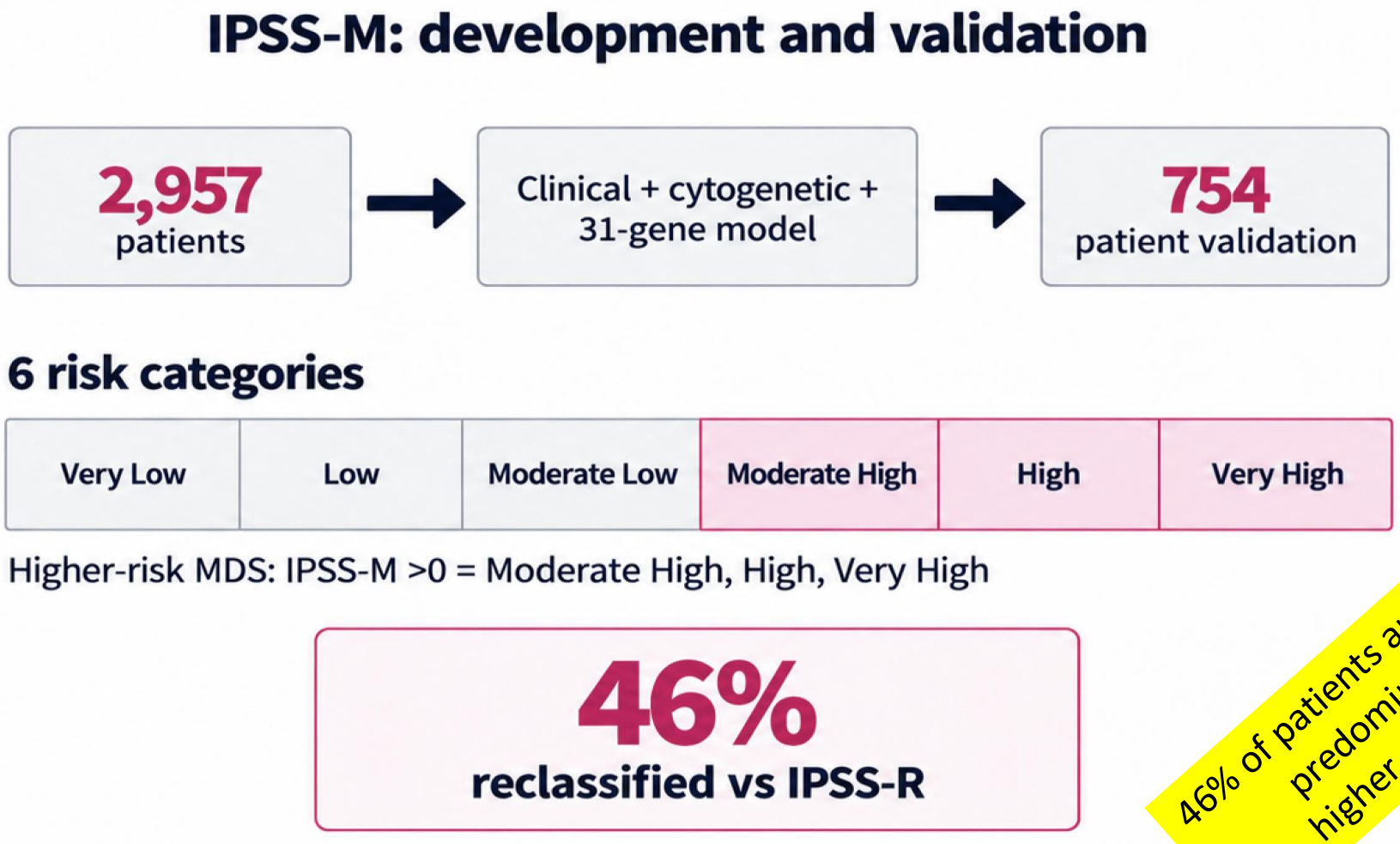
Higher-Risk MDS

Prognostic system	Higher-risk MDS
IPSS-R	>3.5: High, Very High
IPSS-M	>0: Moderate High, High, Very High

Molecular risk assessment refines conventional IPSS-R–based risk stratification

Zeidan AM et al. Blood. 2023

Molecular Risk Stratification: IPSS-M



Bernard E et al. NEJM Evid 2022

Background – Higher risk Clinical

- Defined by IPSS-R / IPSS-M intermediate-high, high, very high risk
- Median OS with standard therapy: ~18–24 months
- Allogeneic HCT: only curative option, feasible in a minority (!!??) of patients

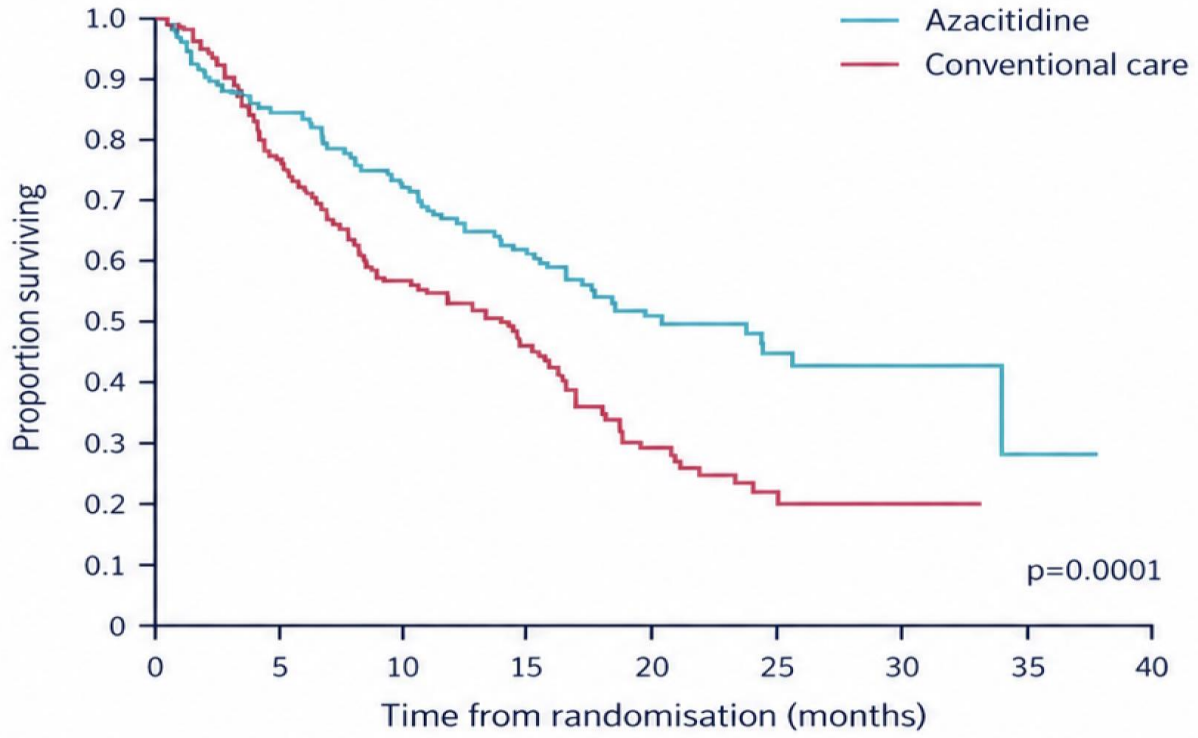
Treatment Landscape (2025)

- Hypomethylating agents (HMA):
- Overall response rates: ~40–50%
- CR rates: ~15–20%
- Primary resistance and early relapse remain major unmet needs
- Combination strategies under investigation

Rationale for HMA-Based Combinations

- Enhance depth and durability of response
- Delay AML progression
- Increase bridge-to-transplant rate
- Target molecular high-risk subgroups (e.g. TP53, ASXL1, IDH-1, ….)

Hypomethylating Agents in High-Risk MDS



Number at risk

Azacitidine	179	152	130	85	52	30	10	1	0
Conventional care	179	132	95	69	32	14	5	0	0

AZA-001, phase III randomized trial
ITT population, n=358

Median OS

24.5 months vs 15.0 months

HR 0.58 (95% CI 0.43–0.77)

stratified log-rank *P*=0.0001

2-year OS

50.8% vs 26.2%

Fenaux P et al. Lancet Oncol. 2009;10:223–232

Phase III Studies in Untreated High-Risk MDS

Study	Experimental arm	N	Primary endpoint	Key result
STIMULUS-MDS2	Sabatolimab + AZA vs PBO + AZA	530*	OS	**22.31** vs 18.83 mo; HR 0.85 (95% CI 0.67–1.07); *P*=0.0825 → **not met**
ENHANCE	Magrolimab + AZA vs PBO + AZA	539	CR + OS	CR 21.3% vs 23.6%; median OS 15.9 vs 18.6 mo; HR 1.203 (95% CI 0.947–1.528) → **not met**
VERONA	Venetoclax + AZA vs PBO + AZA	509	OS	22.18 vs 21.68 mo; HR 0.908 (95% CI 0.733–1.126); *P*=0.38 → **not met**

*STIMULUS-MDS2 included 492 patients with MDS and 38 with CMML-2.

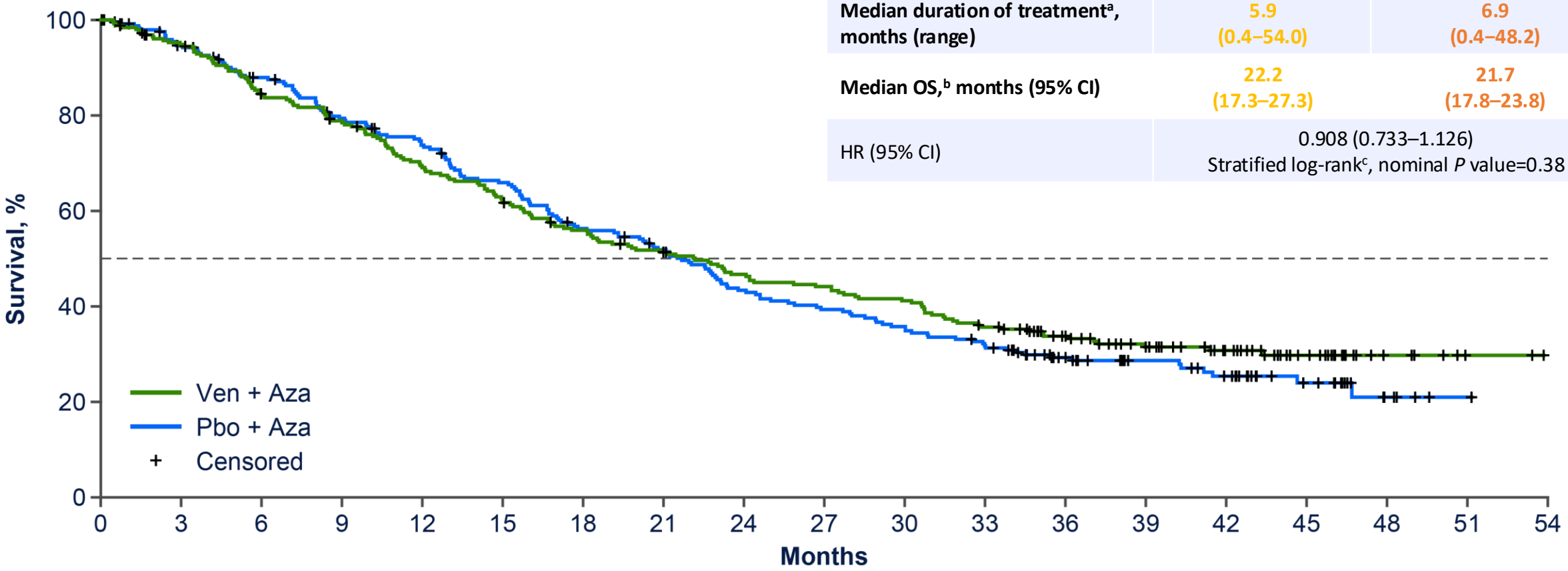
VERONA: mOR 76.6% vs 57.7%, despite no improvement in OS

Zeidan AM et al. HemaSphere. 2024;8(S1):Abstract S180; Sallman DA et al. J Clin Oncol. 2026;44:2529–2542; Garcia-Manero G et al. Clin Lymphoma Myeloma Leuk. 2025;25(Suppl 1):S644–S645. Abstract MDS-1497

VERONA Trial: No significant difference in OS was observed between Ven + Aza and Pbo + Aza in patients with higher-risk MDS

Median follow-up: 41.2 months (range, 0.03–53.9)

	Ven + Aza (N=256)	Pbo + Aza (N=253)
Median duration of treatment[a], months (range)	5.9 (0.4–54.0)	6.9 (0.4–48.2)
Median OS,[b] months (95% CI)	22.2 (17.3–27.3)	21.7 (17.8–23.8)
HR (95% CI)	0.908 (0.733–1.126) Stratified log-rank[c], nominal *P* value=0.38	



Patients at Risk

256	239	210	194	169	151	135	122	110	104	97	83	66	50	37	22	7	2	0
253	228	207	185	170	151	128	116	97	88	80	70	48	36	29	16	5	1	0

[a]Duration of treatment is from (date of the first dose in the last cycle + 27 days, date of death, cutoff date) - date of the first dose in first cycle + 1. [b]Overall survival is defined as the time from the date of randomization to the date of death. The data were censored at the date when a patient was last known to be alive on or before the cutoff date. [c]Stratified by IPSS-R (intermediate, high, very high) and HSCT eligibility (eligible, ineligible) from IVRS/IWRS.

VERONA trial: clinical interpretation

Improved disease control and response depth

- OS benefit possibly diluted by:
  - Post-protocol therapies
  - Heterogeneous population

Subgroup analyses suggest benefit in selected molecular profiles

Toxicity: increased cytopenias and infections, manageable with dose adjustments

Background – Higher risk Clinical

- Defined by IPSS-R / IPSS-M intermediate-high, high, very high risk
- Median OS with standard therapy: ~18–24 months
- **Allogeneic HCT: only curative option, feasible in a minority (!!??) of patients**

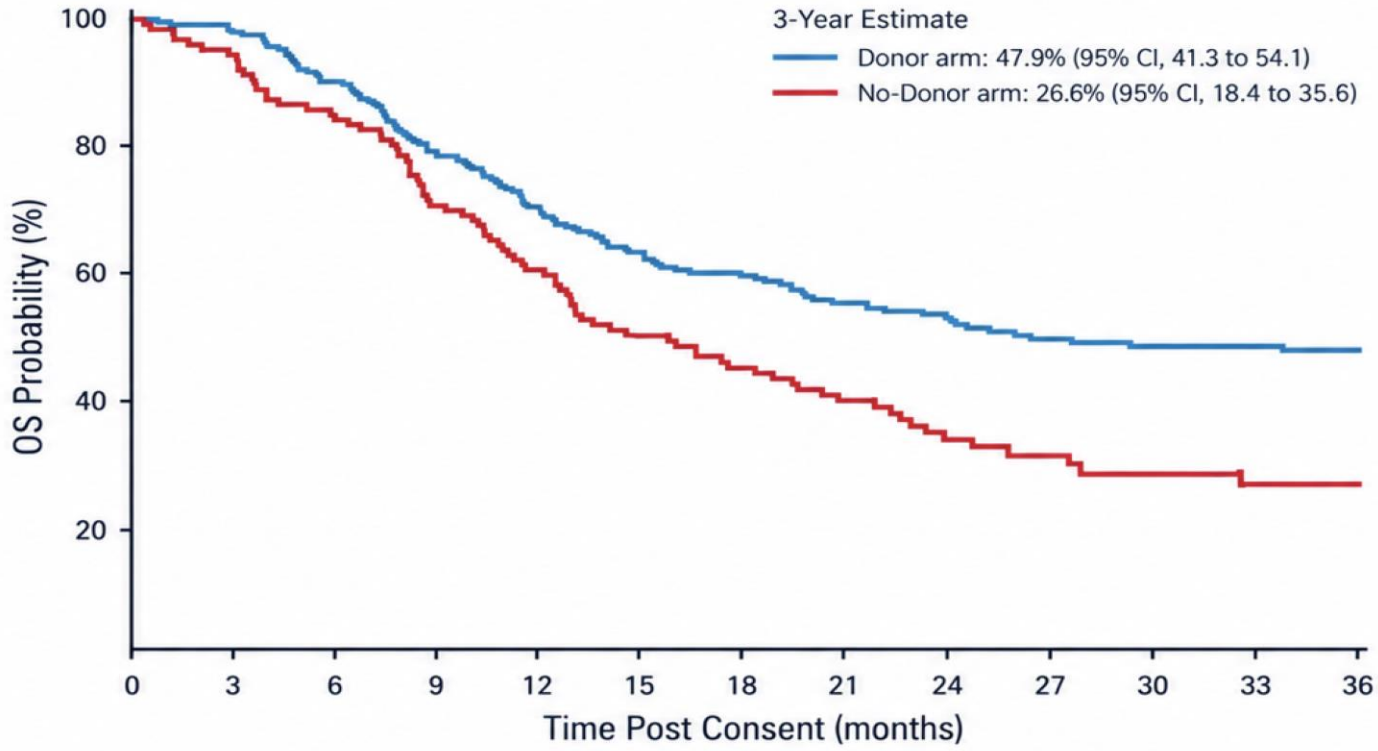
Treatment Landscape (2025)

- Hypomethylating agents (HMA):
- Overall response rates: ~40–50%
- CR rates: ~15–20%
- Primary resistance and early relapse remain major unmet needs
- Combination strategies under investigation

Allogeneic HCT in High-Risk MDS (50-75 years)
Analyses intention to treat

BMT CTN 1102

Adjusted overall survival, intention-to-treat analysis



Study design

Prospective multicenter biologic-assignment study
n = 384 | age 50–75 years | 34 centers
Donor arm: *n* = 260
No-donor arm: *n* = 124

Assignment based on availability of an HLA-matched donor within 90 days

This was not a randomized study. Patients in the donor arm were candidates for RIC-HCT; patients in the no-donor arm received non-transplant/supportive therapy.

Outcome

Adjusted 3-year OS

47.9% vs 26.6%

P = .0001

Absolute difference: **21.3%**

3-year LFS: 35.8% *vs* 20.6%; *P* = .003

Nakamura R et al. J Clin Oncol. 2021

HCT in Higher Risk MDS

Large registry analysis presented at ASH 2025 (data from EBMT).

Findings:

- Allogeneic HCT remains the only curative option for higher-risk MDS.
- Analysis of **18,710 adult MDS transplant recipients (2000–2022)**
  - **OS improved from ~44% to >50% over the past two decades**, despite older and higher-risk patients being transplanted in recent years.
  - Donor type (fully matched related donors) remained a strong positive prognostic factor.
  - Reduced-intensity conditioning lowered transplant-related mortality but was associated with a slightly increased relapse risk.
- Relapse rates remained stable while NRM decreased.

Abstract 375. Marie Robin et al.: Trends in transplantation for patients with myelodysplastic syndrome across recent decades: A registry-based study on behalf of the chronic malignancies working of the EBMT Category: 700s.

Transplant Evaluation in Higher-Risk MDS

Clinical Genomic Profiling of MDS for Decision Making in Allogeneic Hematopoietic Cell Transplantation: EBMT Recommendations





Assessment of allo-HCT eligibility at the time of MDS diagnosis



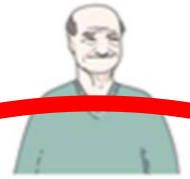
- **Disease-related factors** (IPSS-M, *TP53* allelic state, and genetic germ line predisposition)
- **Patient-related risk factors** (performance status, comorbidities, and frailty)
- **Donor availability**
- **Patient's values and wishes**

Gurnari C et al. Blood. 2025

Transplant Evaluation in Higher-Risk MDS

Clinical Genomic Profiling of MDS for Decision Making in Allogeneic Hematopoietic Cell Transplantation: EBMT Recommendations





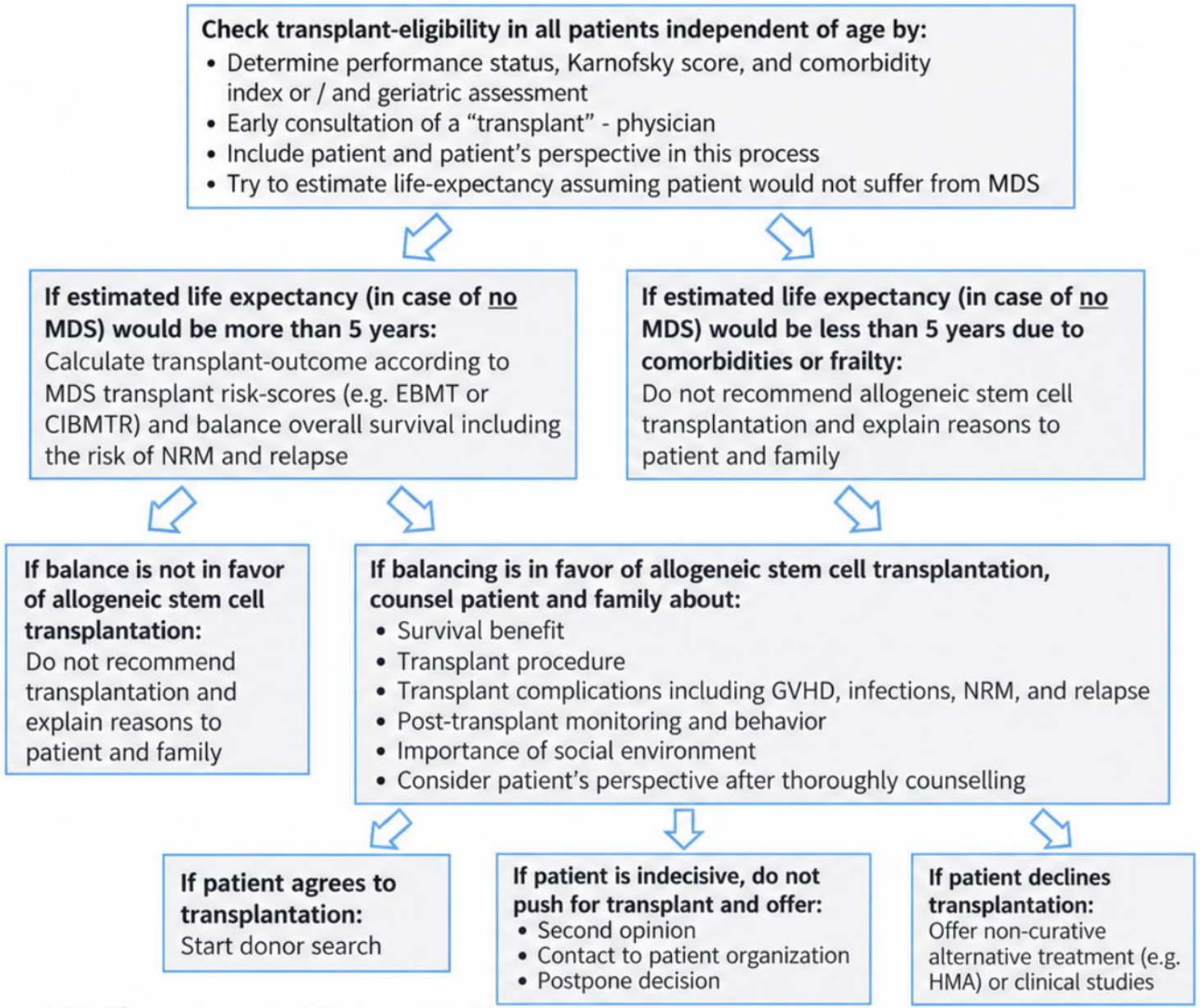
Assessment of allo-HCT eligibility at the time of MDS diagnosis



- **Disease-related factors** (IPSS-M, *TP53* allelic state, and genetic germ line predisposition)
- **Patient-related risk factors** (performance status, comorbidities, and frailty)
- **Donor availability**
- **Patient's values and wishes**

Gurnari C et al. Blood. 2025

Transplant Eligibility and Counselling in Higher-Risk MDS



Transplant eligibility
should be assessed **early**

Chronological age
should not be used alone

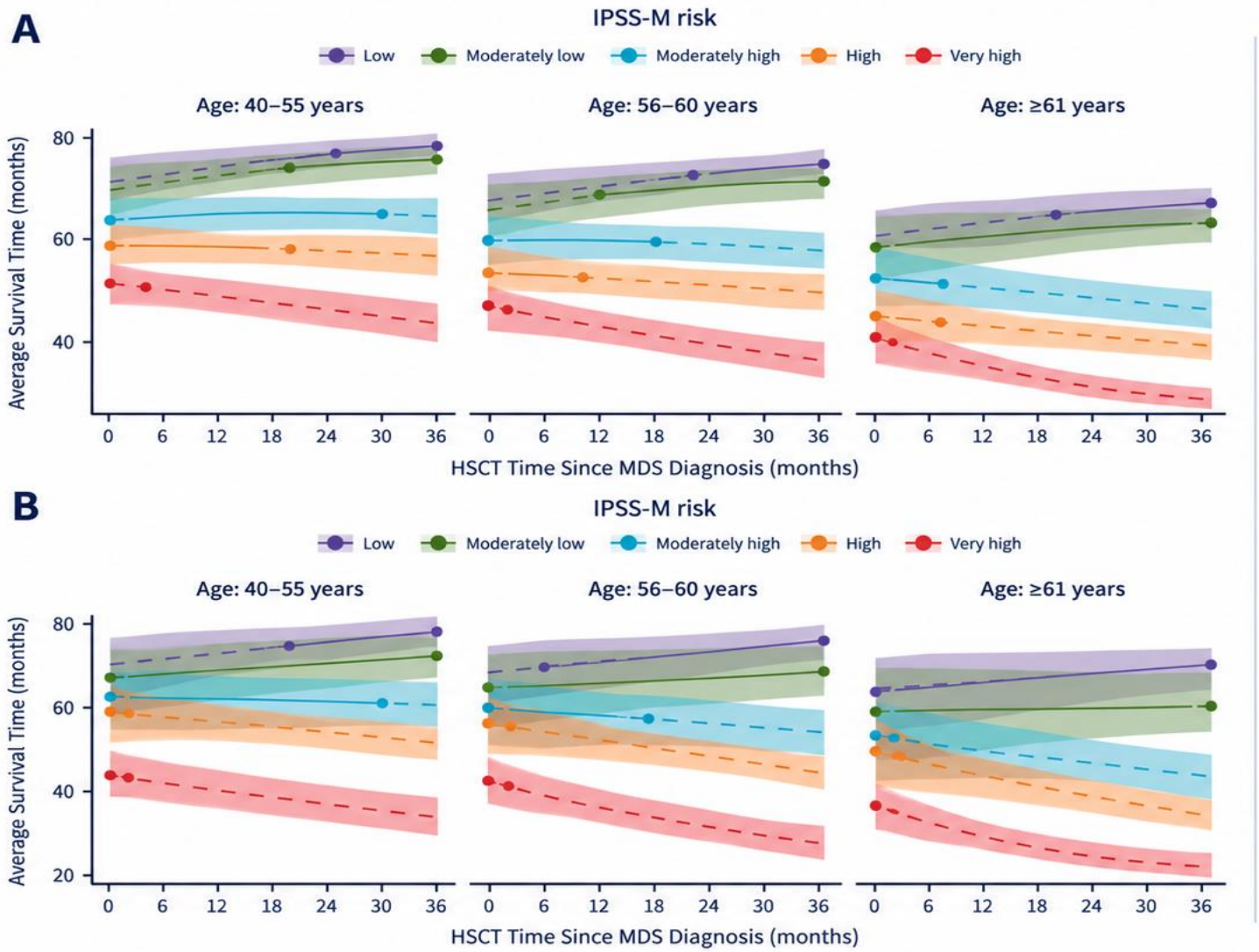
Decision-making
multidimensional assessment
disease risk + patient fitness + transplant risk + patient preference

Proposed clinical framework — not a validated transplant-eligibility score

Kröger N. Haematologica. 2025;110:339–349.

IPSS-M and Timing of Allogeneic HCT

Restricted Mean Survival Time (RMST) – 8 y.



Retrospective decision analysis, n = 7,118

Training and validation cohorts

Outcome: 8-year RMST

Model-based analysis of alternative transplant timing strategies

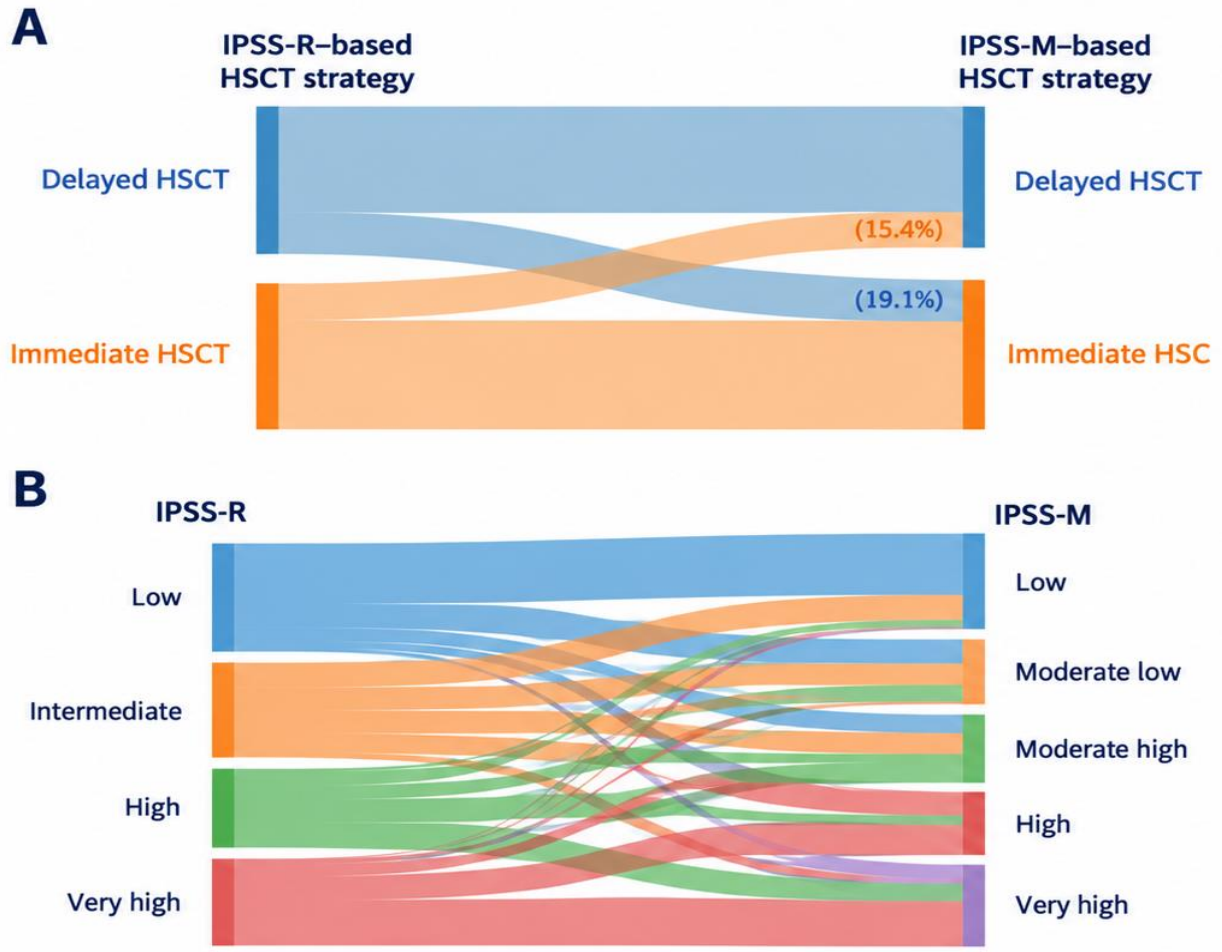
Tentori CA et al. J Clin Oncol. 2024

IPSS-R versus IPSS-M for transplant timing

Restricted Mean Survival Time (RMST) – 8 y.

A proportion of patients classified for immediate transplantation based on the IPSS-R are shifted to a deferred strategy, and vice versa; in the model, a policy based on the IPSS-M is associated with an average gain in RMST of 1.2 years.

Molecular information is particularly useful when the morphological burden is still low.



Potential HCT candidates: n = 3,172

Transplant policy changed in 17% of patients

15%: immediate by IPSS-R → delayed by IPSS-M

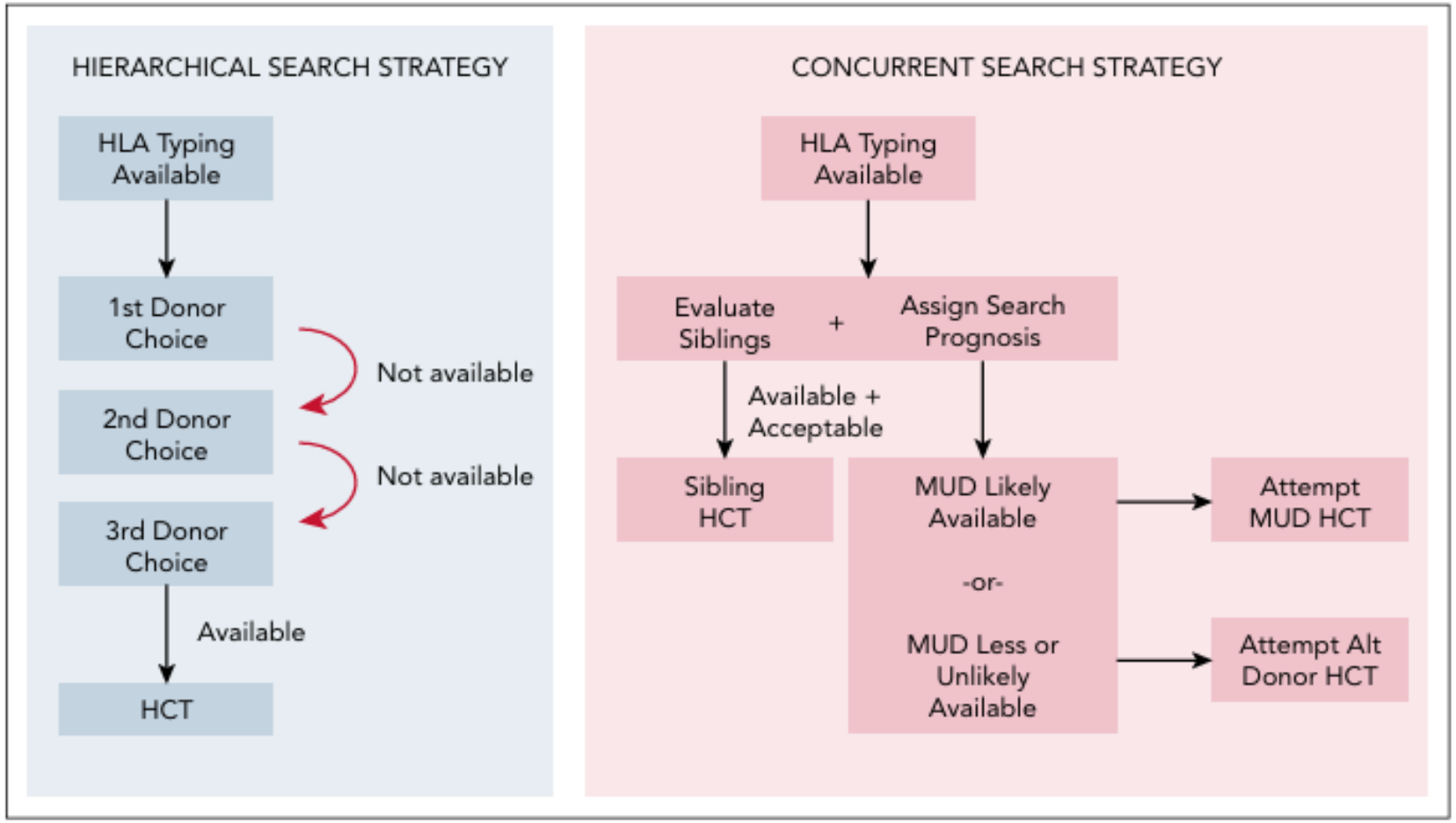
19%: delayed by IPSS-R → immediate by IPSS-M

RMST gain with IPSS-M–based policy: 1.2 years; P = .001

BM blasts <10%: RMST gain 1.8 years; P < .001

Tentori CA et al. J Clin Oncol. 2024

The search for a donor: the "time-to-transplant" paradigm. Hierarchical strategy vs. concurrent strategy



Shaffer B et al. Blood 2026

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK 1702: LONG-TERM OUTCOMES OF ALTERNATIVE DONOR ALLOGENEIC TRANSPLANTATION. Lee et al. JCO 2025, Lee et al. JCO 2025; Pidala J. et al. Transplantation and Cellular Therapy 2026

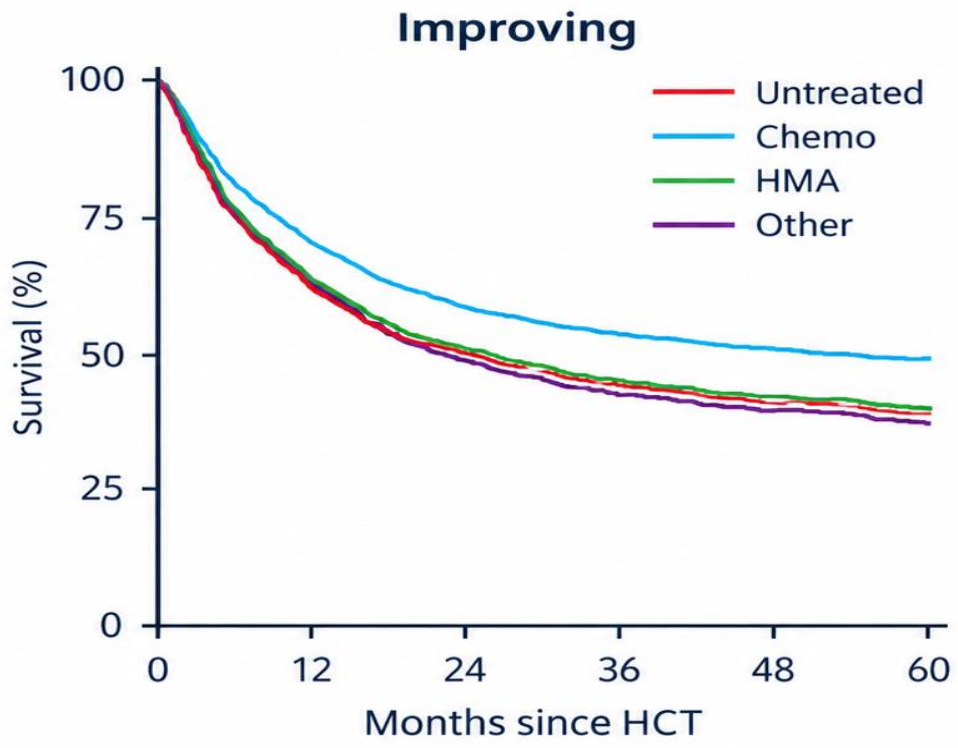
Pre-Transplant Therapy

Pre-Transplant Therapy

1. **No prospectively designed randomized study** has compared pre-HCT systemic therapy with upfront allo-HCT in MDS[1]
2. **Cytoreductive therapy may be considered** in patients with MDS and ≥10% bone marrow blasts before allo-HCT[2]
3. **Pre-HCT cytoreductive therapy has not demonstrated** a consistent overall survival benefit compared with upfront allo-HCT[3]
4. **Progression or death during pre-HCT therapy** may prevent some patients from reaching transplantation[4]

[1] DeFilipp Z et al. Transplant Cell Ther. 2023; [2] Gurnari C et al. Blood. 2025; [3] Wang H et al Leuk Res. 2021; [4] Kröger N. JCO 2021

Disease Status Before Allo-HCT



EBMT registry — n = 1,482

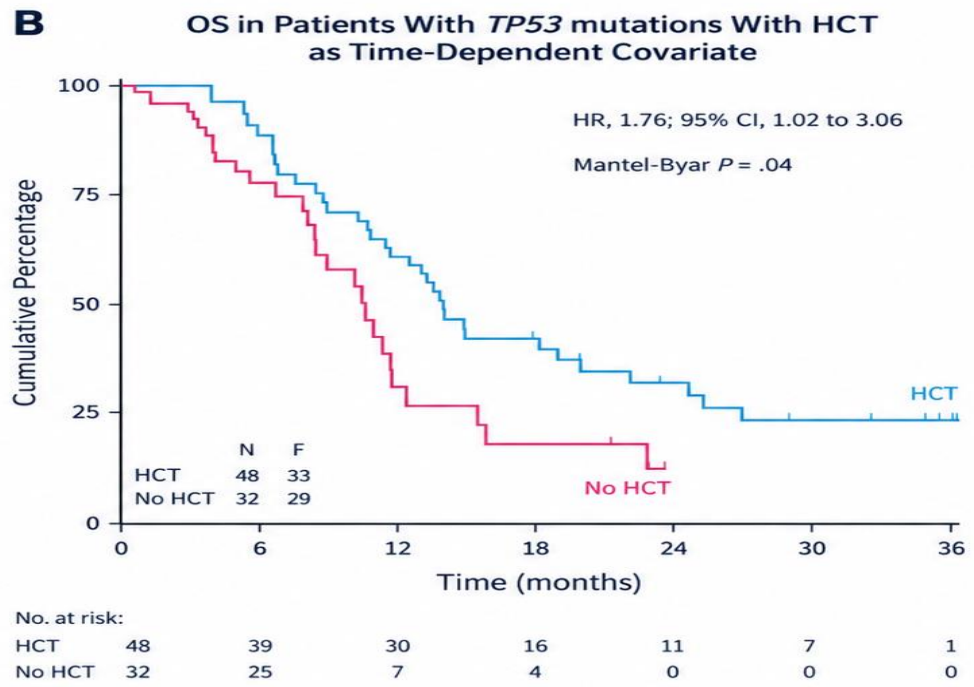
- IPSS-R improvement after HMA was not associated with improved post-HCT outcome
- Improvement after chemotherapy was associated with better outcome, although the analysis was retrospective

IPSS-M — 2026 data

- Improvement in IPSS-M before allo-HCT was not associated with better RFS, OS or GRFS

Scheid C et al. Blood. 2024; Richardson T et al. Bone Marrow Transplant. 2026

TP53-Mutated MDS and Allogeneic HCT



BMT CTN 1102 genetic analysis

3-year OS

23% with HCT vs 11% without HCT

P = .04

TP53 allelic state

3-year OS

Single-hit **22%** vs multihit **20%;** *P* = .31

3-year relapse/progression

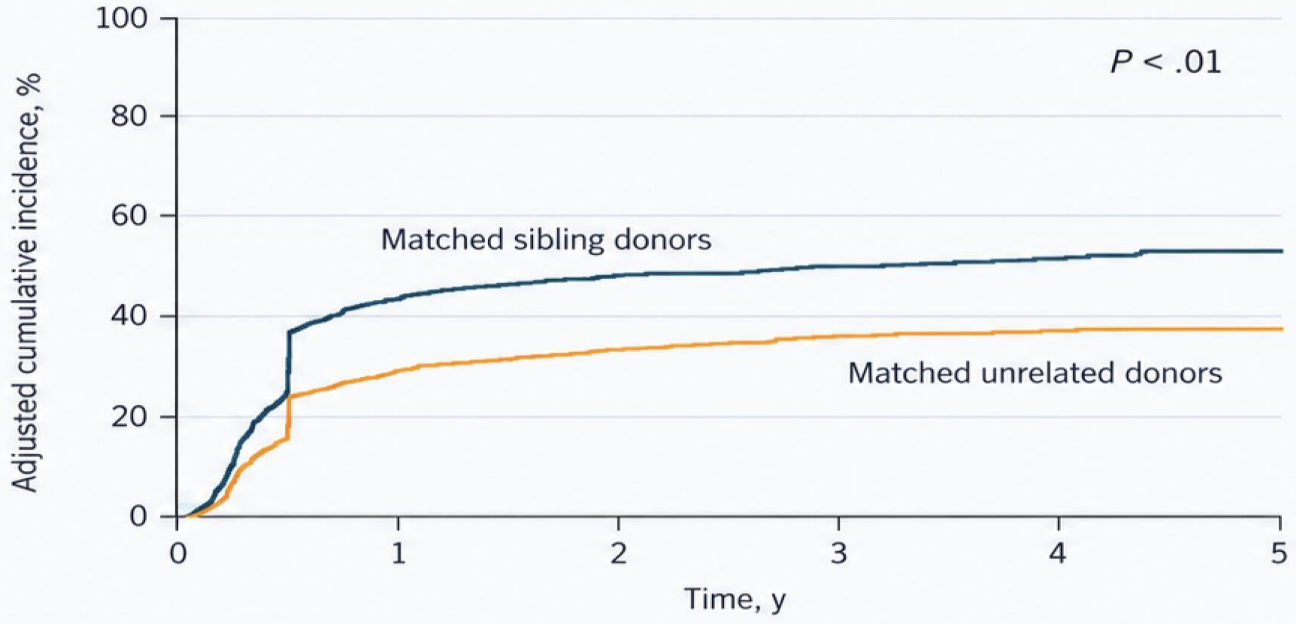
Single-hit **62%** vs multihit **74%;** *P* = .03

Versluis J et al. J Clin Oncol. 2023;

Donor Selection in MDS

Cumulative incidence of relapse

CIBMTR retrospective cohort, n = 1,761



No. at risk						
Matched unrelated donors	1110	535	366	254	162	98
Matched sibling donors	644	265	185	133	96	54

Younger MUD vs older MSD

Relapse at 5 years

37.3% vs 49.6%

Relapse — multivariable analysis

Older MSD vs younger MUD

HR 1.62

95% CI 1.32–1.97

P < .001

Disease-free survival

Older MSD vs younger MUD

HR 1.17

95% CI 1.02–1.34

P = .02

Overall survival

Older MSD vs younger MUD

HR 1.13

95% CI 0.98–1.29

P = .07

Older MSD: lower NRM and GVHD

Contemporary donor selection

HLA matching remains fundamental, but donor age, transplant timing/availability and GVHD prophylaxis increasingly influence donor hierarchy.

Guru Murthy GS et al. JAMA Oncol. 2022; Arrieta-Bolaños E et al. Bone Marrow Transplant. 2026

Conditioning Intensity in MDS

RIC

Fludarabine + Busulfan

Fludarabine **150** mg/m² total
Busulfan **6.4** mg/kg IV total
(or 8 mg/kg oral)

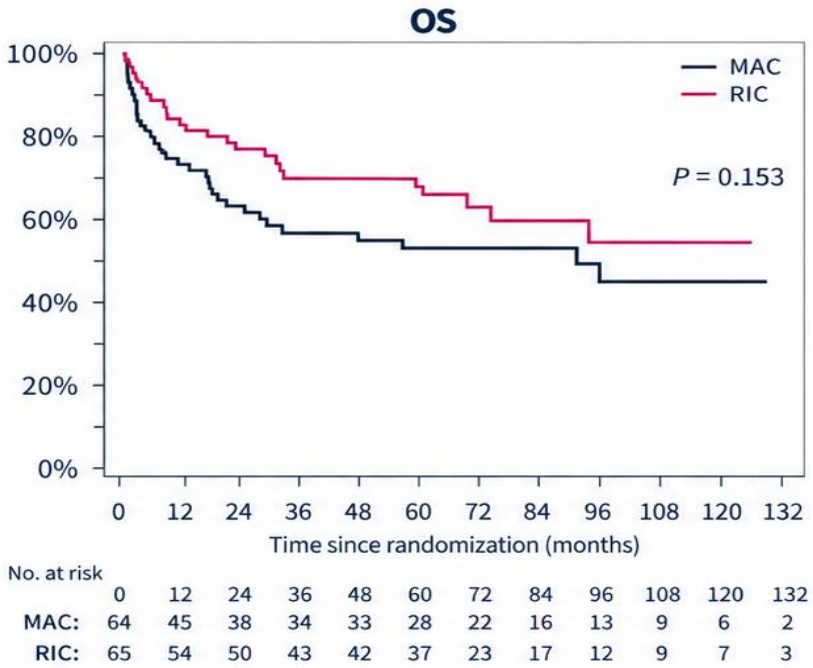
MAC

Busulfan + Cyclophosphamide

Busulfan **12.8** mg/kg IV total
(or 16 mg/kg oral)
Cyclophosphamide 120 mg/kg total

Randomized phase III
n = 129

MDS / sAML <20% blasts at HCT
patients aged 18–65 years

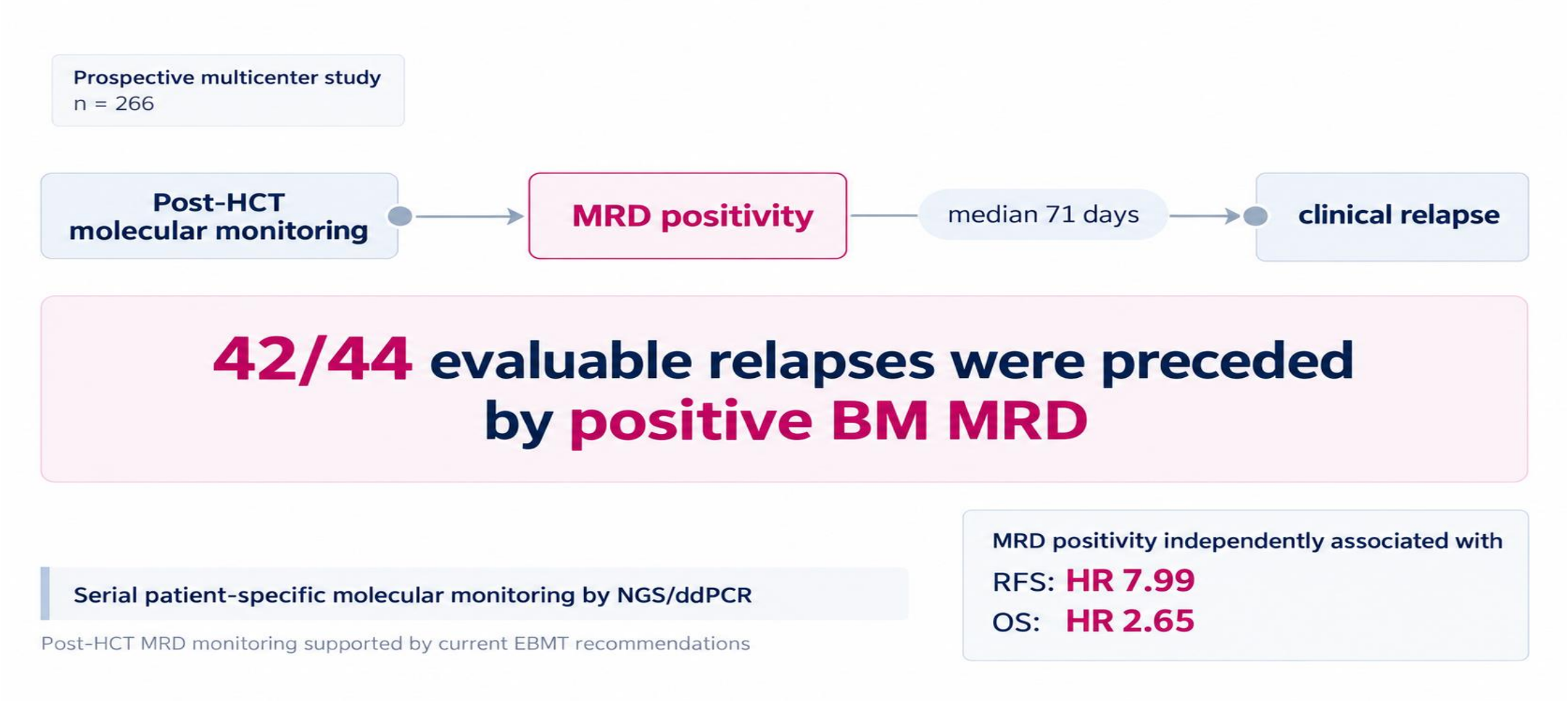


10-year OS
RIC **54.0%** vs MAC **44.4%**
P = .15

10-year RFS
RIC **43.9%** vs MAC **44.2%**
P = .78

Niederwieser C et al. Bone Marrow Transplant. 2024

Molecular MRD After Allogeneic HCT



Tobiasson M et al. J Clin Oncol. 2024; Gurnari C et al. Blood. 2025

Post-Transplant Maintenance and Pre-Emptive Therapy in MDS

Prophylactic maintenance

Oran et al. — randomized phase III

High-risk AML/MDS after allo-HCT
n = 187

Azacitidine n = 93
32 mg/m² SC, days 1–5, every 28 days
planned for 12 cycles

vs

Observation n = 94

Median RFS
2.07 vs 1.28 years
P = .43

Median OS
2.52 vs 2.56 years
P = .85

Median AZA exposure: 4 cycles
28% completed all 12 planned cycles

Oran B et al Blood Adv. 2020

MRD-guided pre-emptive therapy

RELAZA2 — prospective multicenter phase II

Advanced MDS/AML after intensive chemotherapy ± allo-HCT
Population not exclusively post-HCT or MDS

357 screened

119 MRD-positive

95 treated with azacitidine

60/95 (63%)
relapse-free at 6 months
95% CI 54–71; *P* < .0001

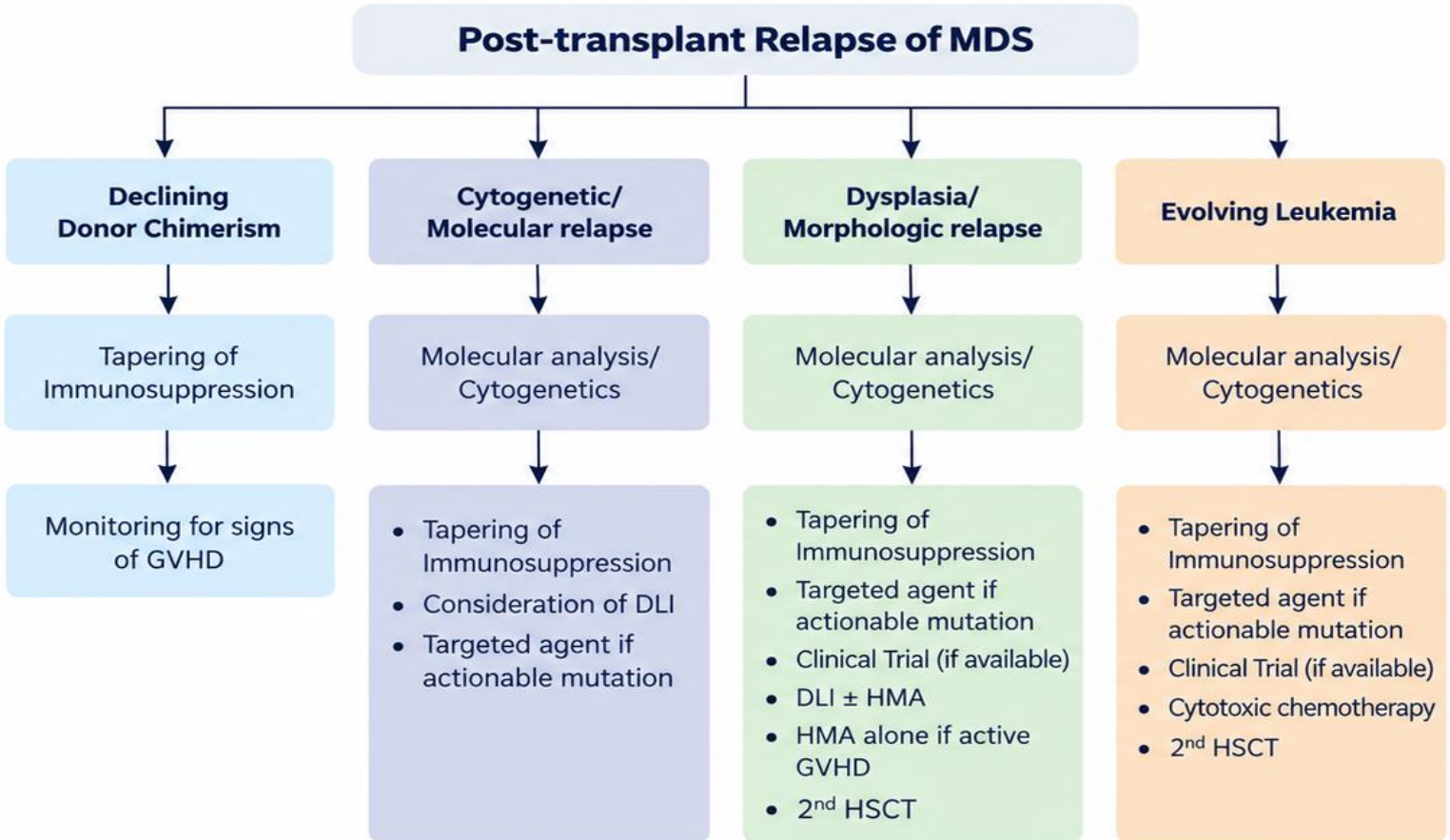
31/60 (52%)
MRD responders remained relapse-free ≥2 years

Median follow-up: 6.6 years

Platzbecker et al Blood. 2026

Post-transplant Relapse of MDS

General approach to reduce and treat posttransplantation relapse of MDS.



Early / molecular relapse

- immunosuppression tapering
- consider DLI ± HMA

Morphologic relapse

- HMA-based therapy ± DLI
- molecularly targeted therapy when applicable

Selected fit patients

- second allo-HCT may be considered

Treatment is individualized; prospective MDS-specific evidence remains limited.

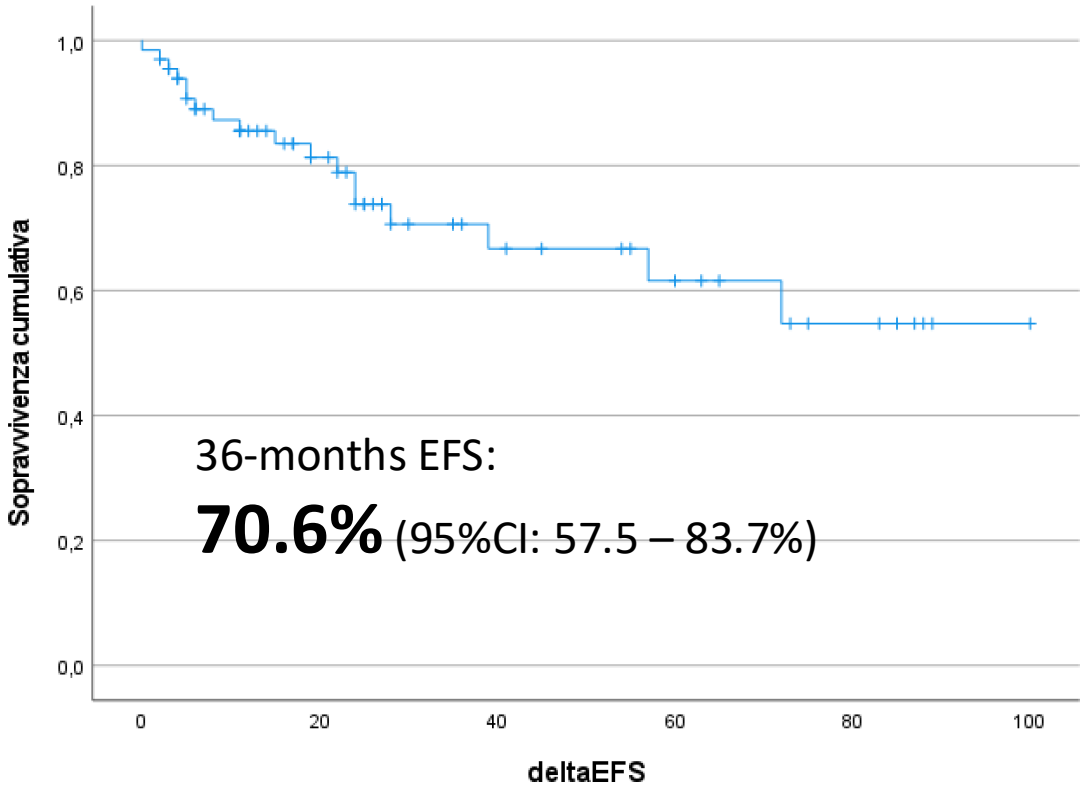
Mina A, et al Blood 2024

Genoa experience

MDS, 2018-2026, N = 67 (median age 64y, range 18-73)

MDS, 2018-2026, N = 67 (median age 64y range 18-73)

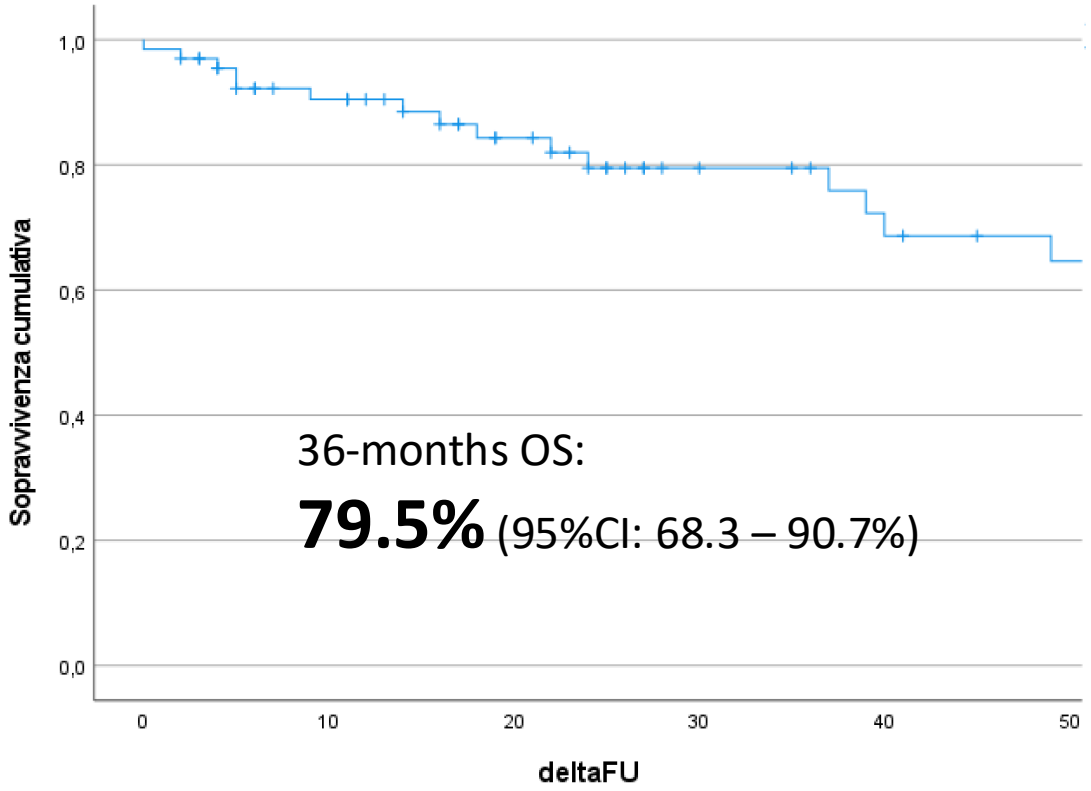
Event Free Survival



36-months EFS:

70.6% (95%CI: 57.5 – 83.7%)

Overall Survival

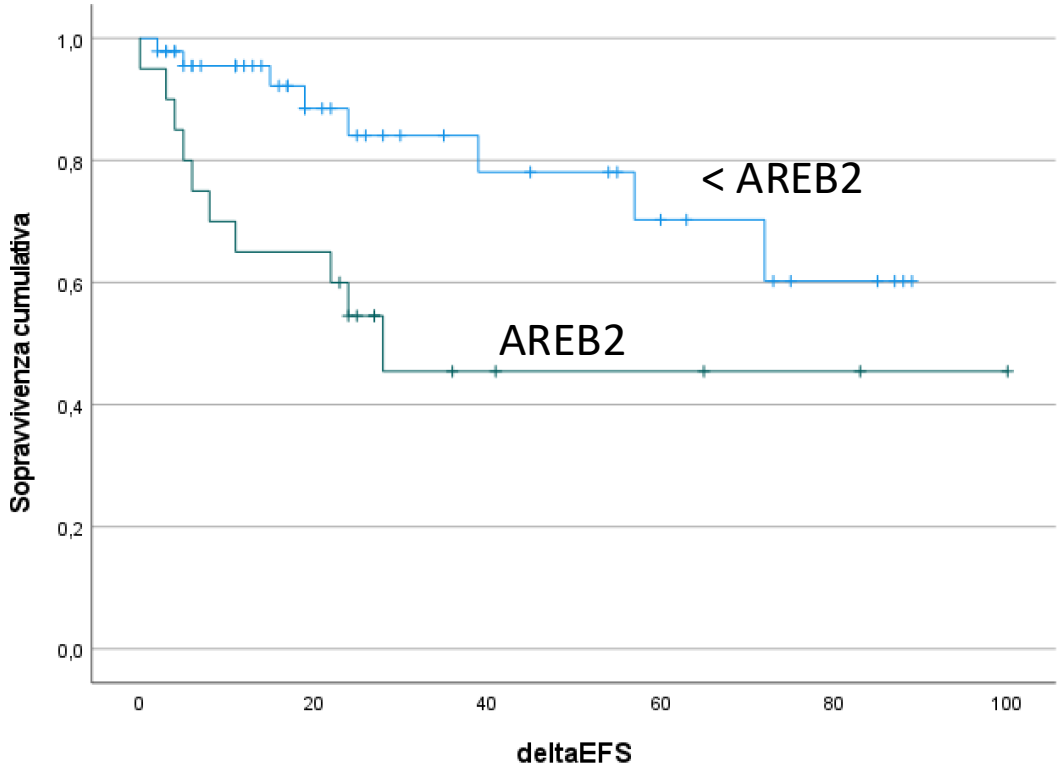


36-months OS:

79.5% (95%CI: 68.3 – 90.7%)

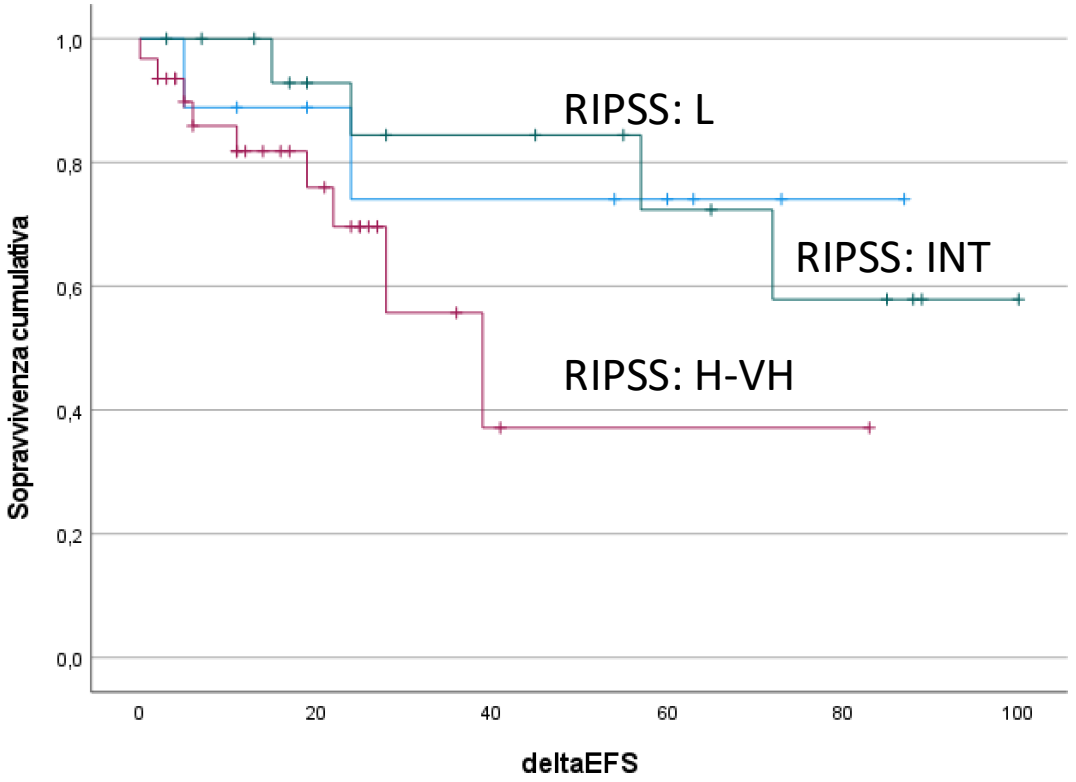
MDS, 2018-2026, N = 67 (median age 64y range 18-73)

MDS type



36-months EFS:
< AREB2: 84.1% (95% CI: 70.8 – 97.4%)
AREB2: 45.5% (95%CI: 21.0 – 70.0%)
P = 0.015

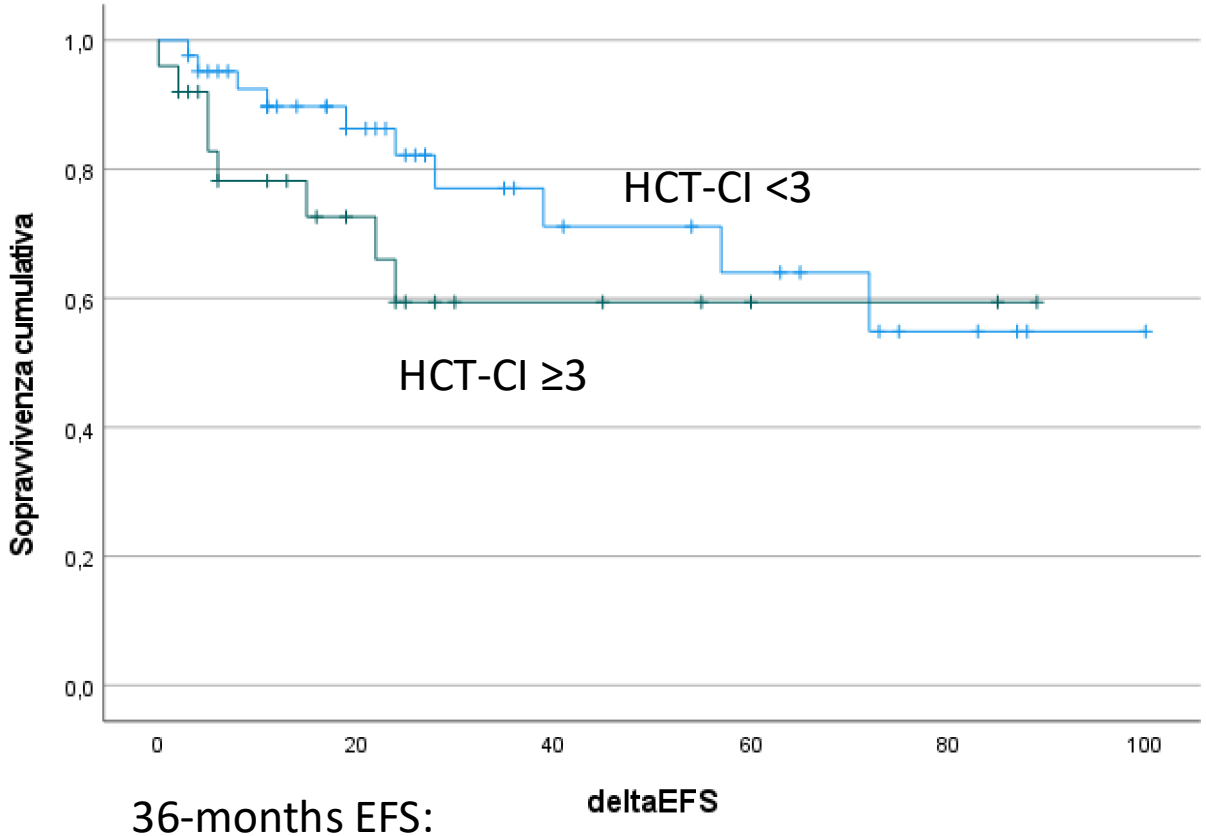
R-IPSS risk



36-months EFS:
L: 74.1% (95% CI: 42.5 – 84.9%)
INT: 84.4% (95%CI: 64.4 – 99.9%)
H-VH: 55.5% (95%CI: 42.5 – 99.9%)
P = 0.078 (H-VH vs INT)

SORROR - HCI score

MDS, 2018-2026, N = 67 (median age 64y range 18-73)



36-months EFS:

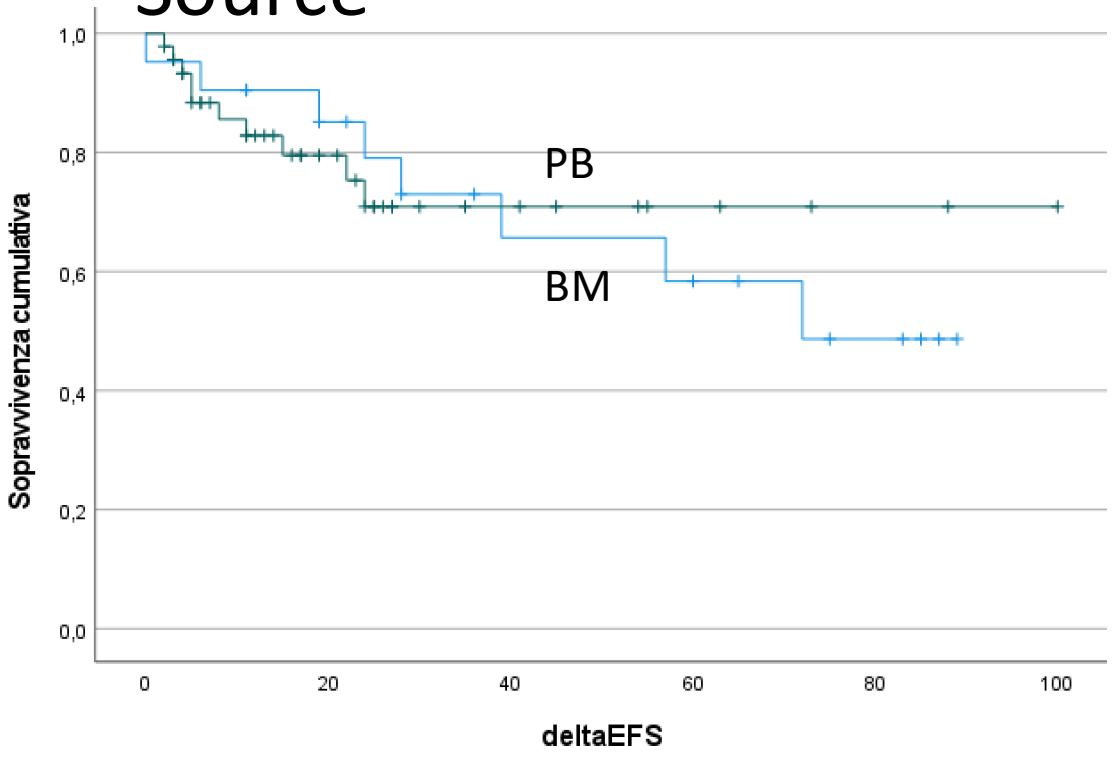
HCT-CI<3: 77.0% (95% CI: 61.1 – 92.9%)

HCT-CI≥:3 59.4% (95%CI: 36.7 – 82.1%)

P = 0.247

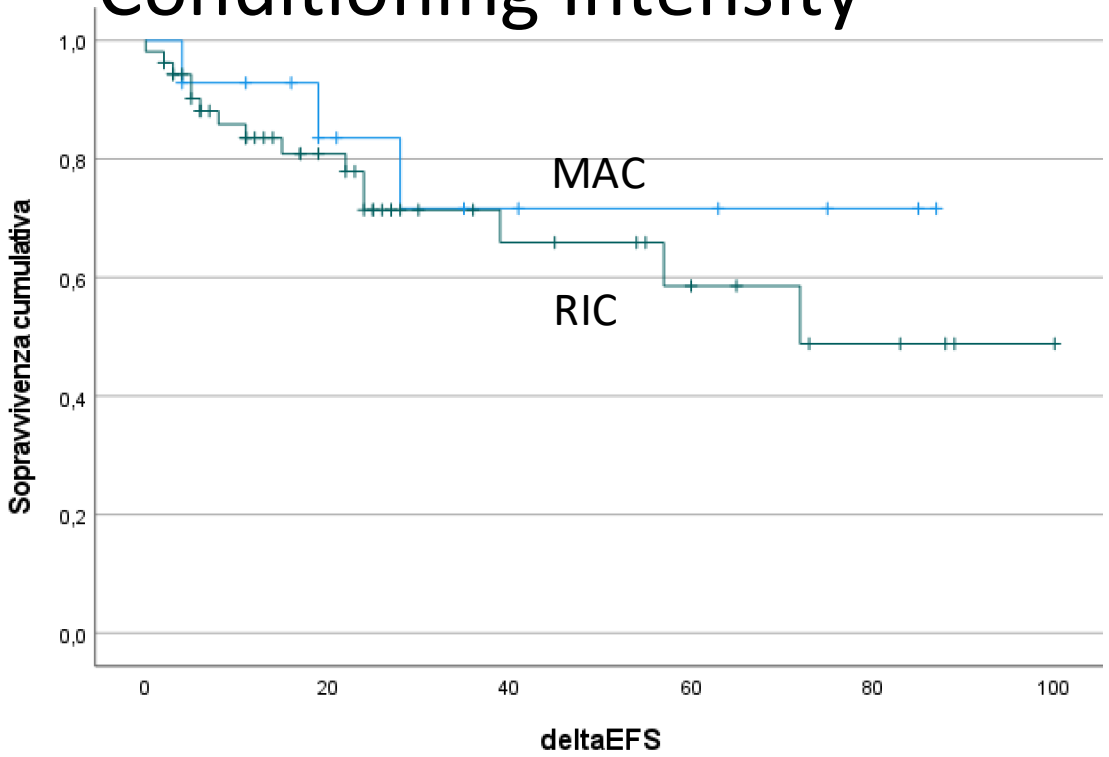
MDS, 2018-2026, N = 67 (median age 64y range 18-73)

Source



36-months EFS:
BM: 73.0% (95%CI: 52.4 – 93.6%)
PB: 70.9% (95% CI: 54.8 – 87.0%)
P = 0.898

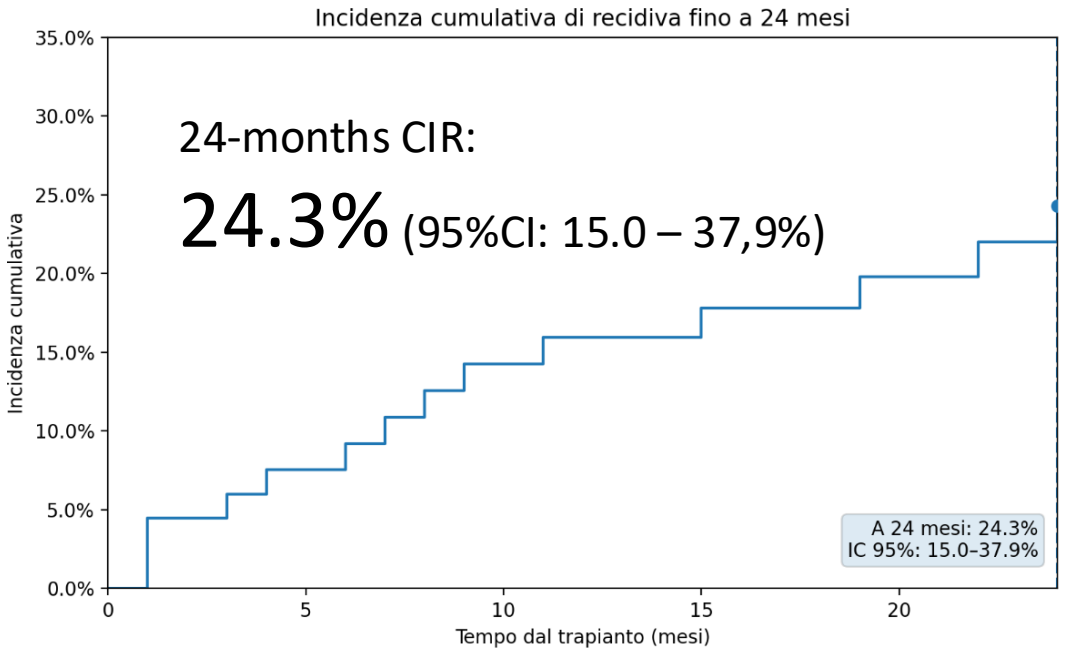
Conditioning Intensity



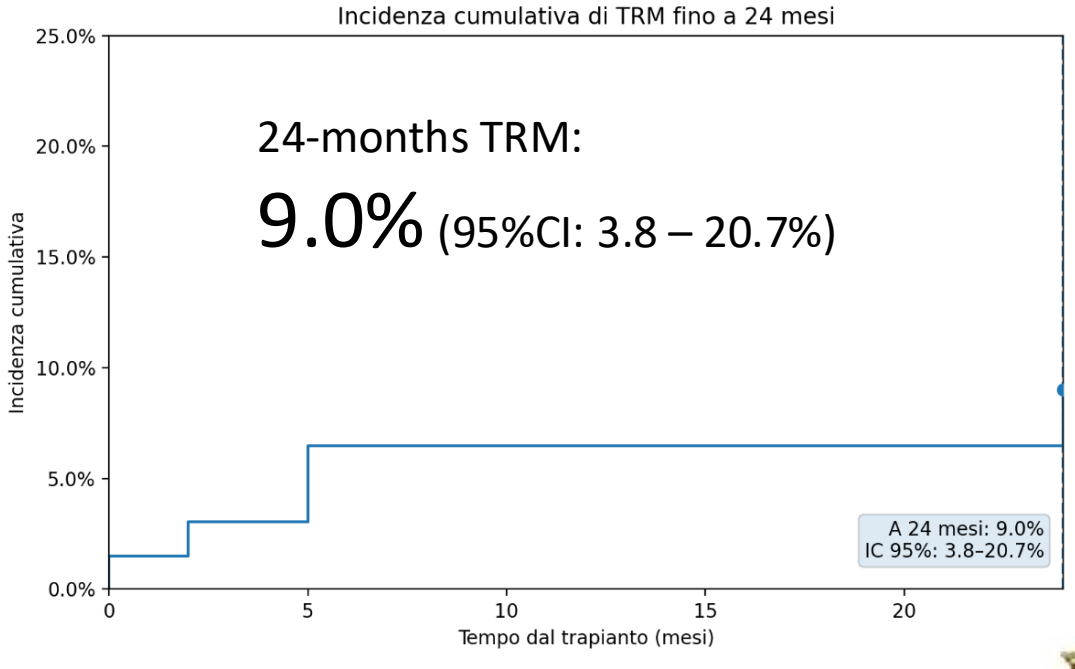
36-months EFS:
MAC: 71.6% (95% CI: 43.4 – 99.8%)
RIC: 71.4% (95%CI: 57.1 – 85.7%)
P = 0.445

MDS, 2018-2026, N = 67 (median age 64y range 18-73)

Relapse

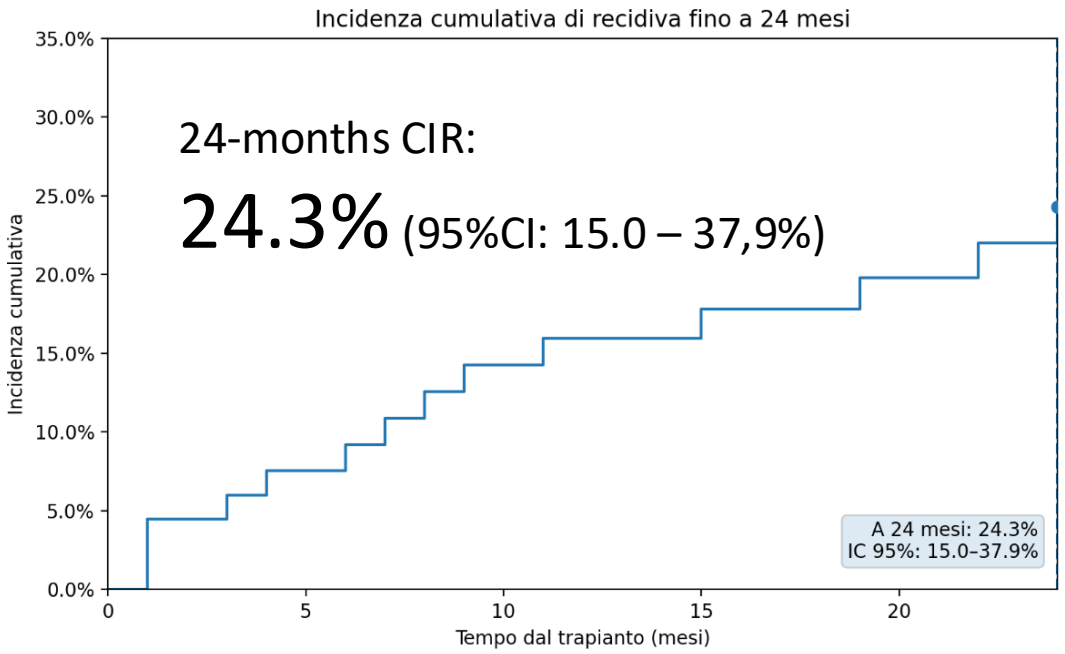


Transplant Related Mortality

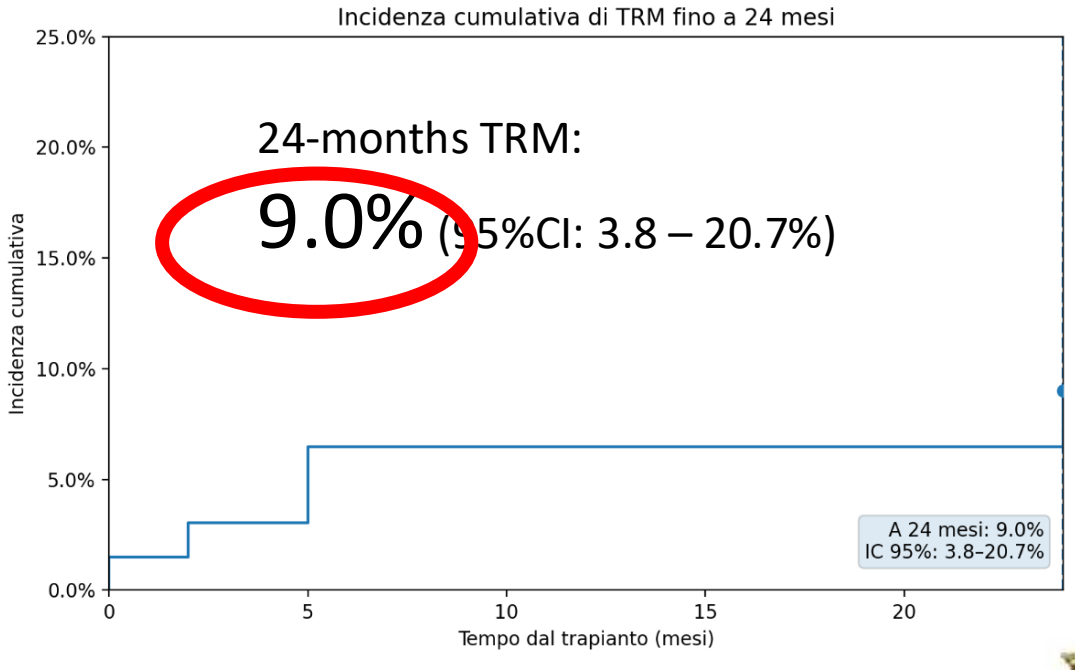


MDS, 2018-2026, N = 67 (median age 64y range 18-73

Relapse

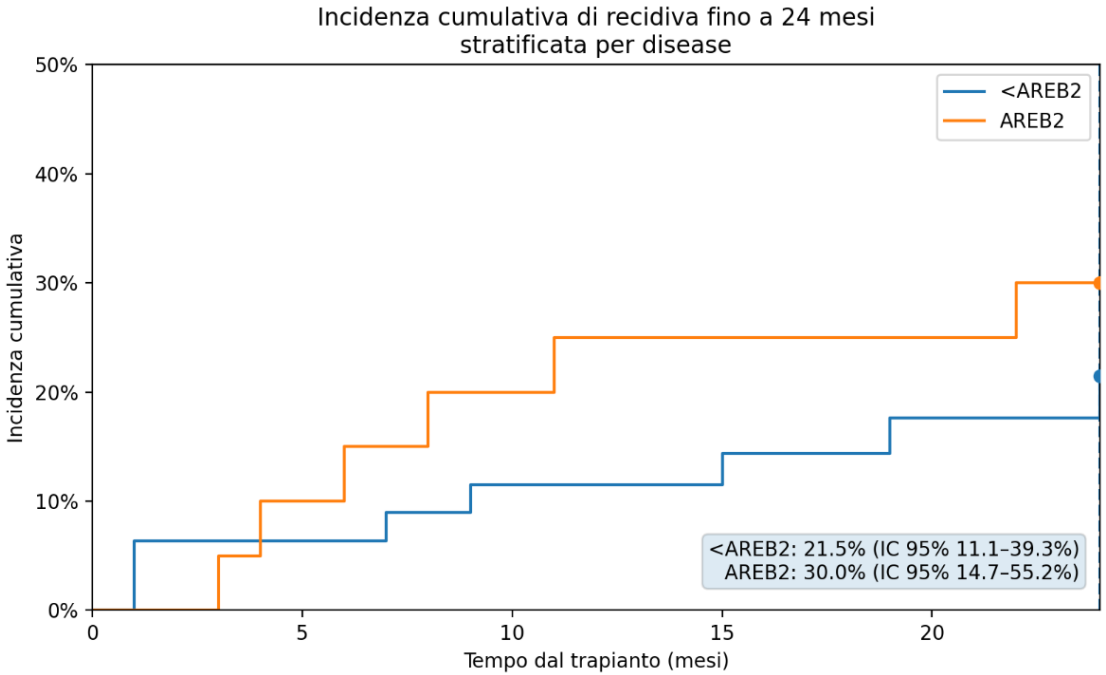


Transplant Related Mortality



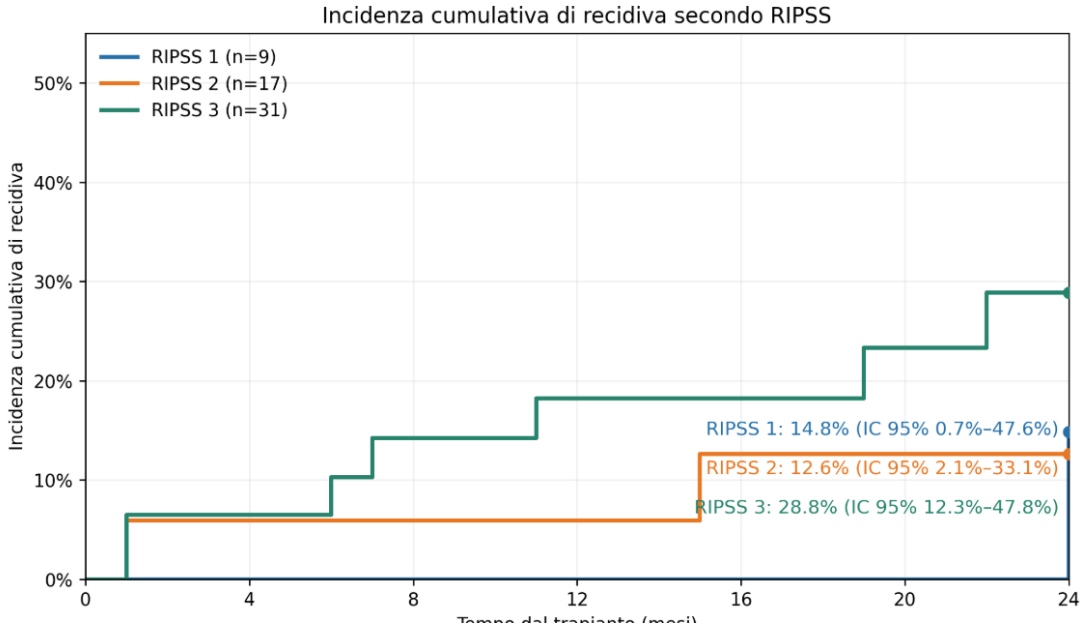
MDS, 2018-2026, N = 67 (median age 64y range 18-73

Relapse, MDS type



24-months Relapse:
< AREB2: 21.5% (95% CI: 11.1 – 39.3%)
AREB2: 30.0% (95%CI: 14.7 – 55,2%)

Relapse, R-IPSS



24-months Relapse:
L-VL: 14.8% (95% CI: 0.7 – 47.6%)
INT: 12.6% (95%CI: 2.1 – 33.1%)
H-VH: 28.8% (95%CI: 12.3 – 47.8%)

Conclusions

INDICATION & TIMING

Allo-HCT remains the only potentially curative treatment for higher-risk MDS and should be considered early in eligible patients.

IPSS-M refines prognostic stratification and may influence transplant timing.

TRANSPLANT STRATEGY

Pre-transplant cytoreduction is not mandatory and should be **individualized**; improvement in disease-risk category does not necessarily translate into better post-HCT outcomes.

Donor selection should integrate HLA matching, donor age, availability and GVHD prophylaxis.

Concurrent strategy

POST-HCT SURVEILLANCE

Post-HCT molecular **MRD** identifies patients at high risk of relapse, but standardized MRD-guided intervention strategies are not yet established.

MEDICINES CAN CURE DISEASES BUT ONLY DOCTORS CAN CURE PATIENTS.

C. G. Jung





Thank you for your kind attention

