FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Convegno della Fondazione Italiana Sindromi Mielodisplastiche

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Indicazioni e gestione clinica del trapianto allogenico nelle MDS e CMML: indicazioni EBMT

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Menarini StemLine					√		
Takeda					√	√	
Kyowa Kirin					√	√	
Johnson & Johnson					√		

Background

- Allogeneic SCT represents the only curative treatment option for patients with MDS and CMML
- Morbidity and mortality risks still represent major limits of allo-SCT
- Reduced-intensity and reduced-toxicity regimens have widened eligibility
- Risk-benefit ratio of allo-SCT is strongly determined by the **selection of patients** and **optimal timing of transplantation**
- **Who** to transplant and **when** to transplant are the key questions

Best results with transplantation

- ✓ Transplant-related mortality # 15%
- ✓ Relapse rate # 15%
- ✓ Overall survival # 70%

» In young, low risk and standard transplantation

Usual results with transplantation

- ✓ Transplant-related mortality # 30%
- ✓ Relapse rate # 30%
- ✓ Overall survival # 40%

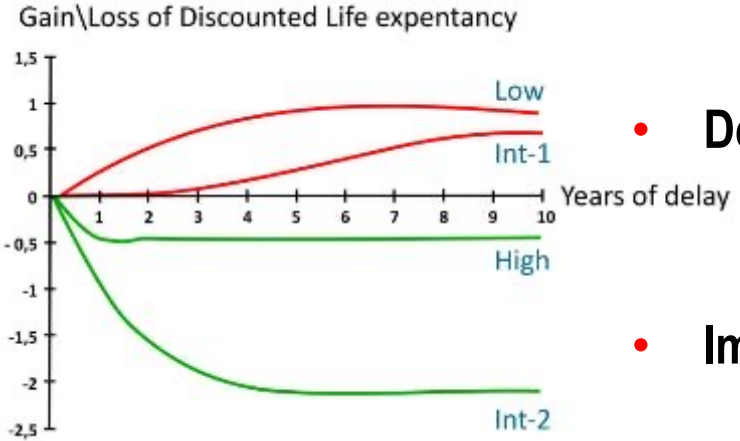
» **In older, high risk and "current" transplantation**

→ *in the majority of patients with MDS and CMML…*

Immediate vs delayed transplantation: yesterday

Context:

- MAC
- HLA-matched sibling
- Young (< 60 years)



- **Delay HSCT**
- **Immediate HSCT**

- **Patients should be transplanted before AML transformation**

Blood 2004 Cutler

Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem-Cell Transplantation in Patients With Myelodysplastic Syndromes

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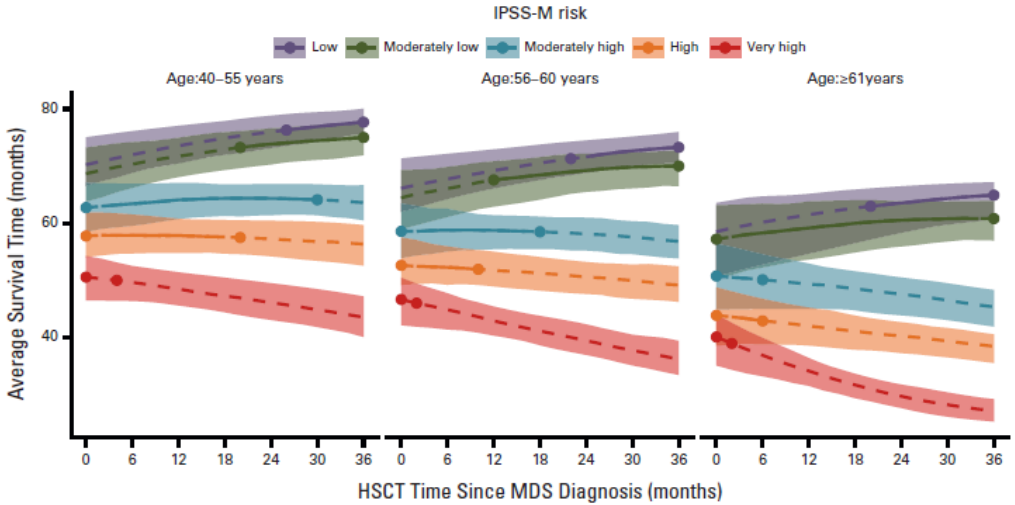
	No HSCT	HSCT
Training	3502	1878
validation	1125	613



Tentori CA et al. JCO 2024 c

Review Article

blood

Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel

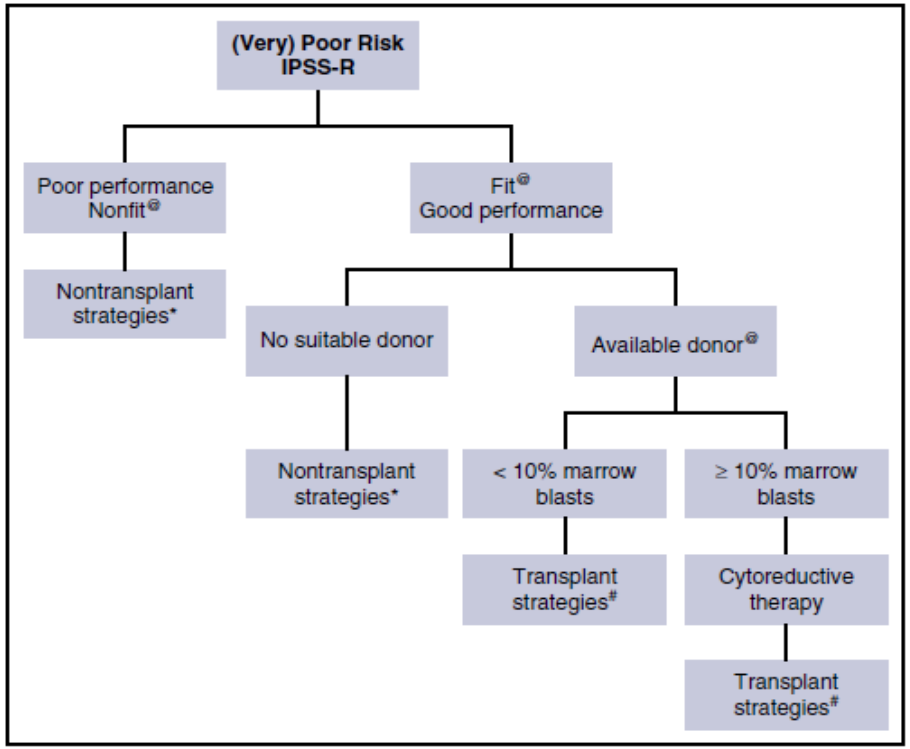
Theo de Witte,[1] David Bowen,[2] Marie Robin,[3] Luca Malcovati,[4] Dietger Niederwieser,[5] Ibrahim Yakoub-Agha,[6] Ghulam J. Mufti,[7] Pierre Fenaux,[8] Guillermo Sanz,[9] Rodrigo Martino,[10] Emilio Paolo Alessandrino,[11] Francesco Onida,[12] Argiris Symeonidis,[13] Jakob Passweg,[14] Guido Kobbe,[15] Arnold Ganser,[16] Uwe Platzbecker,[17] Jürgen Finke,[18] Michel van Gelder,[19] Arjan A. van de Loosdrecht,[20] Per Ljungman,[21] Reinhard Stauder,[22] Liisa Volin,[23] H. Joachim Deeg,[24,25] Corey Cutler,[26] Wael Saber,[27] Richard Champlin,[28] Sergio Giralt,[29] Claudio Anasetti,[30] and Nicolaus Kröger[31]

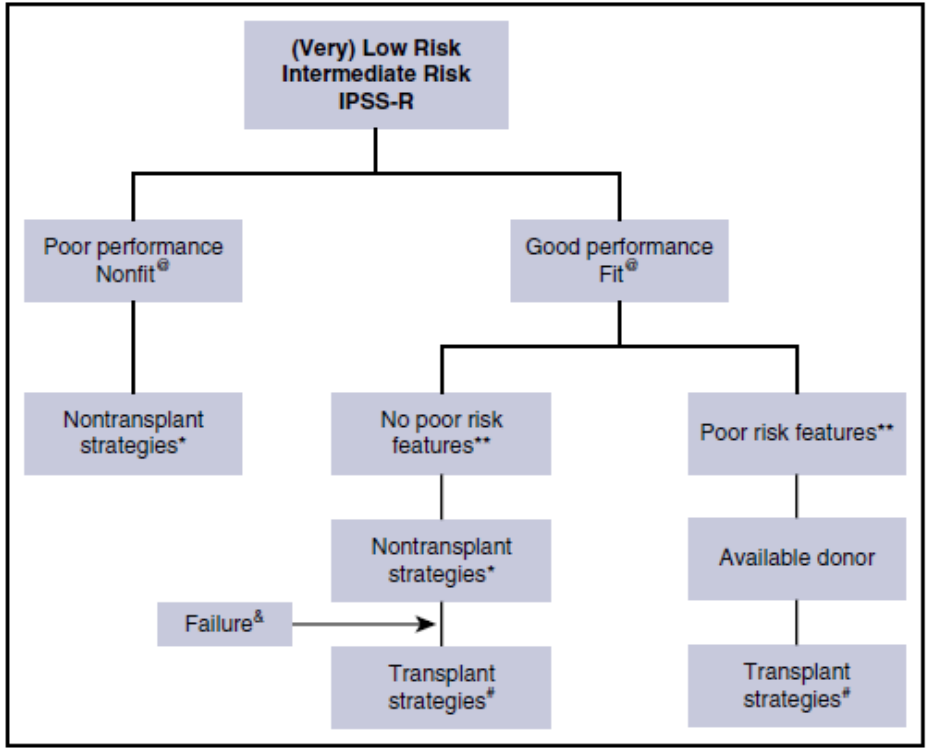
Patient Selection

- Use IPSS-R and HCT-CI to assess eligibility: fit, higher-risk patients should be considered
- Lower-risk patients: only if poor-risk genetics, severe cytopenias, or high transfusion burden
- Very-high-risk: poor outcomes with standard HSCT; favor clinical trials

de Witte T et al. Blood 2017

Transplant indications in MDS patients





**poor-risk cytogenetic characteristics, persistent blast increase [>50% or with >15% BM blasts], life-threatening cytopenias, high transfusion intensity

de Witte T et al. Blood 2017

Factors relevant for the selection of cytoreductive treatment prior to HCT

- The **percentage of bone marrow (BM) blasts at HSCT strongly influences outcomes** - patients with ≥10% blasts tend to do worse without cytoreduction.
- **HMAs and ICT** are the main options to reduce tumor burden before conditioning. There's **no definitive evidence favoring one approach outside of clinical trials**.
- Some evidence suggests **HMAs may be less toxic than ICT** with comparable post-HSCT outcomes. Patients with stable disease after ≥6 cycles of HMA can proceed to HSCT.
- ICT → significant toxicity (TRM up to 16%). **Higher-risk MDS with poor-risk CGs may be transplanted in CR after ICT** (preferably within investigational protocols).

de Witte T et al. Blood 2017

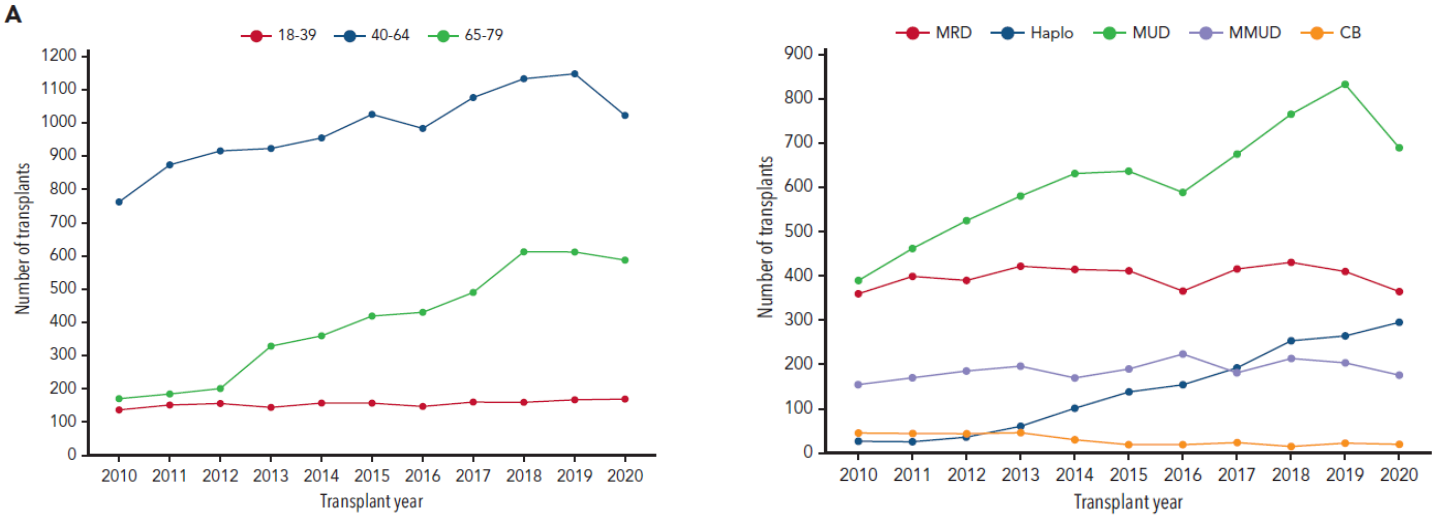
Factors relevant for the selection of cytoreductive treatment prior to HCT

- **For fit higher-risk MDS patients with >10% blasts and normal cytogenetics**: reduce tumor load, but **no clear preference between HMA and ICT**.
- For patients with **complex karyotypes**: choice is more controversial; HCT recommended but **optimal cytoreduction approach is unclear**.
- **Randomized trials** (e.g., comparing HMA vs ICT) **are needed** to clarify best strategies
- **Current recommendations emphasize proceeding to HCT once disease burden is acceptable rather than delaying for further consolidation**.

de Witte T et al. Blood 2017

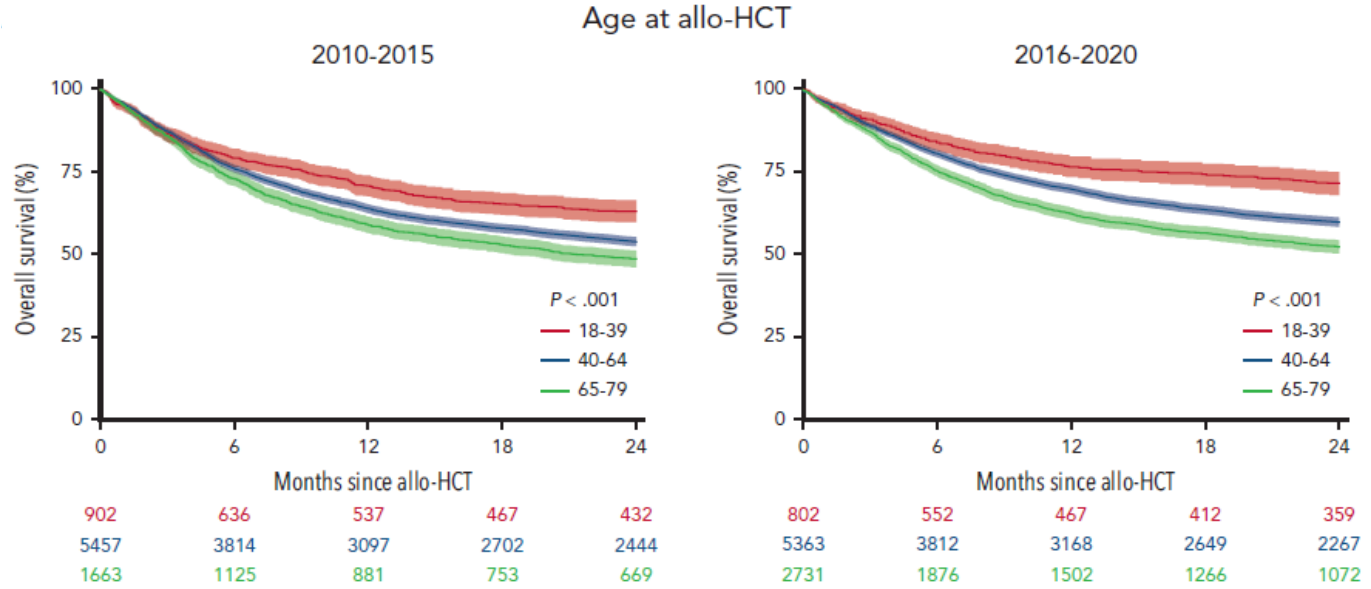
Clinical-genomic profiling of MDS to inform allo-HCT: recommendations from an international panel on behalf of the EBMT

Carmelo Gurnari,[1,2] Marie Robin,[3] Lionel Adès,[3] Mahmoud Aljurf,[4] Antonio Almeida,[5] Fernando Barroso Duarte,[6] Elsa Bernard,[7] Corey Cutler,[8] Matteo Giovanni Della Porta,[9] Theo De Witte,[10] Amy DeZern,[11] Joanna Drozd-Sokolowska,[12] Eric Duncavage,[13] Pierre Fenaux,[3] Nico Gagelmann,[14] Guillermo Garcia-Manero,[15] Claudia Haferlach,[16] Torsten Haferlach,[16] Robert Hasserjian,[17] Eva Hellström-Lindberg,[18] Meagan Jacoby,[19] Austin Kulasekararaj,[20] R. Coleman Lindsley,[8] Jaroslaw P. Maciejewski,[2] Hideki Makishima,[21] Luca Malcovati,[22] Moshe Mittelman,[23] Anders E. Myhre,[24] Seishi Ogawa,[25] Francesco Onida,[26] Elli Papaemmanuil,[27] Jakob Passweg,[28] Uwe Platzbecker,[29,30] Lisa Pleyer,[31] Kavita Raj,[32] Valeria Santini,[33] Anna Sureda,[34] Magnus Tobiasson,[18] Maria Teresa Voso,[1] Ibrahim Yakoub-Agha,[35] Amer Zeidan,[36] Matthew Walter,[19] Nicolaus Kröger,[14] Donal P. McLornan,[32,*] and Mario Cazzola[22,*]



Gurnari C et al. Blood 2024

Allo-HCT in MDS: Contemporary practice in Europe



OS by age at HCT: 2010-2015

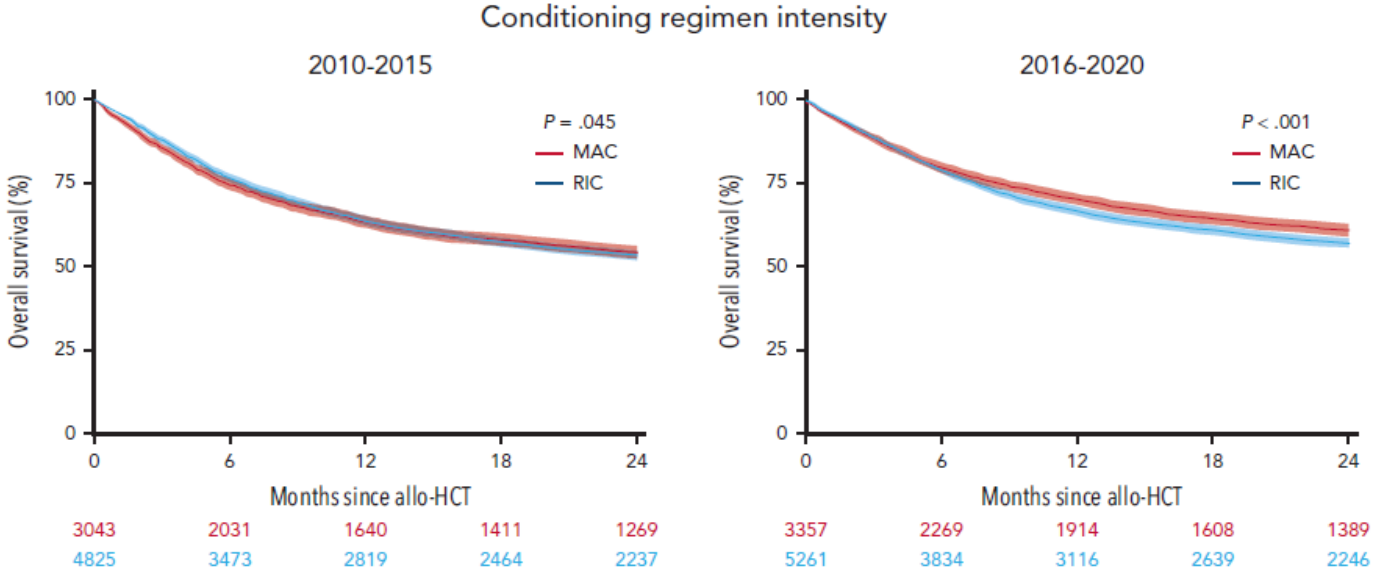
Variable	Groups	N	24 months	48 months	P
Age at HCT	18-39	902	63% (60-66%)	59% (55-62%)	< .001
	40-64	5457	54% (52-55%)	46% (44-47%)	
	65-79	1663	49% (46-51%)	40% (37-42%)	

OS by age at HCT: 2016-2020

Variable	Groups	N	24 months	48 months	P
Age at HCT	18-39	802	71% (68-75%)	65% (61-69%)	< .001
	40-64	5363	60% (58-61%)	51% (50-53%)	
	65-79	2731	52% (50-54%)	42% (40-45%)	

Gurnari C et al. Blood 2024

Allo-HCT in MDS: Contemporary practice in Europe



OS by conditioning: 2010-2015

Variable	Groups	N	24 months	48 months	P
Conditioning	MAC	3043	54% (52-56%)	47% (45-49%)	.045
	RIC	4825	53% (52-55%)	45% (44-46%)	

OS by conditioning: 2016-2020

Variable	Groups	N	24 months	48 months	P
Conditioning	MAC	3357	61% (59-63%)	53% (51-55%)	< .001
	RIC	5261	57% (56-58%)	48% (47-50%)	

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Table 3. IPSS-M risk score, risk categories, and clinical outcomes

Risk category	IPSS-M score	Median leukemia-free survival (y)	Median OS (y)	AML transformation by 1 y (%)
Six-category risk schema				
Very low (14% of all patients)	Less than or equal to −1.5	9.7	10.6	0
Low (33%)	More than −1.5 to −0.5	5.9	6.0	1.7
Moderate low (11%)	More than −0.5 to 0	4.5	4.6	4.9
Moderate high (11%)	>0 to 0.5	2.3	2.8	9.5
High (14%)	>0.5 to 1.5	1.5	1.7	14.3
Very high (17%)	>1.5	0.7	1.0	28.2
Lower-risk vs higher-risk MDS				
Lower-risk MDS (58%)	≤0 (negative value)	6.0 (95% CI, 5.7-6.7)	6.3 (95% CI, 5.8-7.2)	2.0
Higher-risk MDS (42%)	>0 (positive value)	1.2 (95% CI, 1.1-1.3)	1.5 (95% CI, 1.4-1.6)	18.9

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Risk-Based Timing

- Higher-risk IPSS-M → immediate transplant if eligible
- Lower-risk IPSS-M → consider early transplant if:

  - ✓ Transfusion-dependent & unresponsive
  - ✓ Germline predisposition
  - ✓ Therapy-related MDS
  - ✓ VEXAS with severe inflammation

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Patient Fitness

- Favor age <80 years
- Karnofsky score ≥80%
- HCT-CI: 0–2 (low/intermediate risk)
- Frailty index <0.3
- Consider biological vs chronological age

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Cytoreduction & Conditioning

- ≥10% BM blasts → cytoreductive therapy may help
- No clear consensus on optimal regimen
- Conditioning intensity:
  - ✓ MAC for fit, high-risk patients
  - ✓ RIC for older/comorbid patients

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Donor selection

- HLA-matched related or unrelated preferred
- Haploidentical donors with PTCy acceptable
- Younger donor age favored
- Match donor type to GVHD prophylaxis strategy

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MRD Monitoring & Relapse

- Use genomic profiling for MRD post-HCT
- Positive MRD → consider DLI, HMAs, or tapering IS
- Second HCT possible for select relapsed patients
- Maintenance strategies under investigation

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Shared Decision-Making

- Discuss disease course, transplant risks, and benefits
- Explain donor options & conditioning plan
- Cover psychosocial support & QoL impact
- Ensure patient-centered, informed consent

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CMML: a disease with largely unmet medical needs

Table 1. Recently completed CMML-specific clinical trials

Therapeutic agent	Mechanism	Phase	Patient population	Subjects enrolled (n)	Outcome	References
Decitabine (vs Hydroxyurea)	HMA	3	Untreated, advanced proliferative CMML	170 (decitabine, 84)	EFS HR, 0.83, (95% CI, 0.59-1.16), OS HR 1.08 (95% CI, 0.76-1.54)	DACOTA study[13]
Ruxolitinib	JAK 1/2 inhibitor	1/2	CMML (prior therapy allowed, not required)	50	ORR, 38%*	16
Lenzilumab	Recombinant anti-GM-CSF monoclonal antibody	1	CMML; R/R, intolerant, or ineligible for prior treatment	15	ORR, 33%*	17
Tipifarnib	Farnesyltransferase inhibitor	2	CMML and MDS/MPN	44 (CMML, 37)	ORR, 21.9%* in patients with CMML	18
Tagraxofusp	CD123-directed cytotoxin (IL-3 fused to diphtheria toxin)	1/2	CMML; R/R and 1L	36	11% bone marrow morphologic CR; 42% spleen response†	19

Table 2. Key considerations for drug development in CMML

- Clinical trials specifically targeting the patient population with CMML are the gold standard.
- Increased commitment to preclinical research investigating CMML is required to identify biologically rationale therapies for clinical investigation in this unique disease.
- All patients with CMML should be treated in clinical trials, when possible.
- Careful consideration should be taken regarding study design and selection of the target population. Studies should be simple and enroll as broad of a population as is appropriate (unique for each investigational agent) to promote successful accrual.
- Early phase studies should use adaptive study designs.
- Early phase studies should identify the optimal biologic dose.
- MDS/MPN-specific response criteria should be used to assess efficacy.
- PRO measures should be incorporated into all studies.
- The use of HMAs in the clinical trial setting is complex given the lack of data supporting a disease-modifying effect in CMML. Thoughtful consideration is required regarding the role of HMA in requirements for prior therapy, backbones for combination therapy, and selection of comparator arms, and should not be considered paradigmatic.
- Close collaboration is necessary among the CMML community in executing clinical trials and collecting real-world data.
- Investigators should consult with the FDA early in study development.

…currently ~ 70 trials are ongoing and recruiting (clinicaltrials.gov, June 2025)

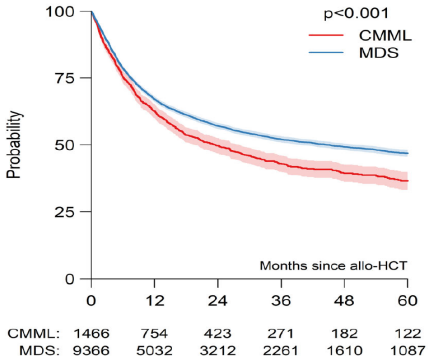
Hunter AM et al. Blood 2024

ALLO-HCT in CMML

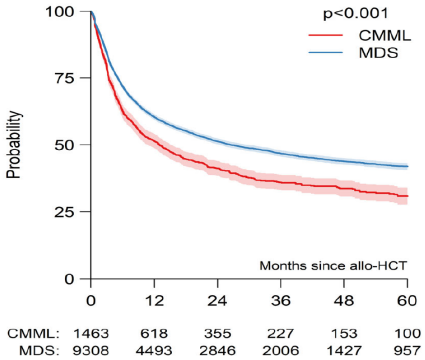
Reference	N	Median age (range)	Stage	Donor	Conditioning	RR & TRM	Survival outcomes
Kroger (2002)	50	44 (19-61)	CMML-1: 62% CMML-2: 38%	MRD 86% MUD 14%	MAC 100%	RR 28% TRM 52%	5-yr OS: 21% 5-yr DFS: 18%
Eissa (2011)	85	51 (1-69)	CMML-1: 50% CMML-2: 50%	MRD 45% MUD 55%	MAC 68% RIC 32%	RR 27% TRM 35%	10-yr OS: 40% 10-yr DFS: 40%
Park (2013)	73	53 (27-66)	CMML-1: 58% CMML-2: 42%	MRD 56% MUD 44%	MAC 41% RIC 59%	RR: 35%	3-yr OS: 32% 3-yr DFS: 29%
Itonaga (2016)	141	49 (NR)	NR	MRD 48% MUD 38% / Cord 14%	MAC 72% RIC 28%	NR	3-yr OS: 47%
Symeonidis (2015)	513	53 (18-75)	CMML-1: 41% CMML-2: 15% 7 - sAML: 44%	MRD 56% MUD 44%	MAC 52% RIC 48%	RR 32% TRM 41%	4-yr OS: 33% 4-yr DFS: 27%
Liu HD (2017)	209	57 (23-74)	CMML-1: 67% CMML-2: 25%	MRD 36% MUD 47% 7/ mMUD 17%	MAC 51% RIC 49%	RR 52% TRM 28%	5-yr OS: 30%
Pophali (2020)	70	58 (18-73)	Chronic phase 66% Blastic transf 34%	MRD 40% MUD 45% mMUD/haplo 9%	MAC 46% RIC 54%	RR 27% TRM 28%	5-yr OS: 51% (CP) 19% (BT)
Rovó (AJH 2024)	1466	60.5 (IQR 54-65)	CMML-1: 52% CMML-2: 48% Missing in 68%	MRD 28% MUD/mMUD 63% haplo 8%	MAC 36% RIC 64%	RR 38% TRM 31%	5-yr OS: 37% 5-yr PFS: 31%

Allo-HCT: CMML vs MDS

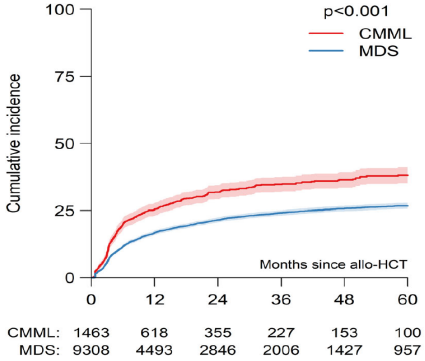
EBMT 2010-2018: **1466 CMML pts / 9366 MDS pts**
(transformed to AML excluded)



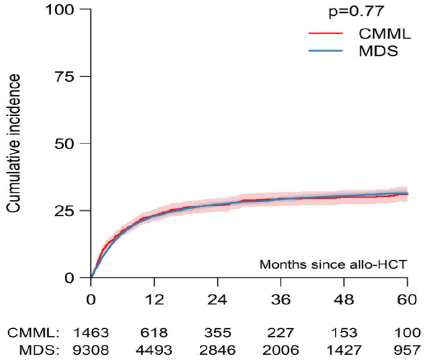
CMML 5-yr OS: 37%



5-yr DFS: 31%



5-yr Rel: 37%



5-yr NRM: 32%

Rovò A et al. Am J Hematol 2024

Prognostic scoring systems in CMML

Prognostic score	Variables	Risk-group median surv. (months) LOW	INT-1	INT-2	HIGH
MDAPS (2002)	Hb, ALC, IMC, BM-blast%	24	15	8	5
MDASC (2008)	PS, Age, Hb, PLT, WBC, BM-blast%, CGs, previous transfusions	54	25	14	6
Mayo Score (2013)	AMC, IMC, Hb, PLT	32	18.5		10
GFM Score (2013)	Age, WBC, PLT, Hb, ASXL1 mut.	NR	38.5		14.4
CPSS (2013)	**FAB-subtype, WHO-subtype, CGs transfusional requirement**	**72**	**31**	**13**	**5**
Molecular Mayo Score (2014)	AMC, IMC, Hb, PLT, ASXL-1 mut.	97	59	31	16
CPSS-Mol (2016)	**FAB-subtype, WHO-subtype, Genetics, transfusional requirement**	**NR**	**64**	**37**	**18**
BLAST±mol (2025))	**Circulating blast, Leukocyte count, Anemia + molecular (high and intermediate-risk)**	**74**	**23**		**12**

EHA/ELN 2018 Recommendations: molecular genetics

Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults

Recommendations From the European Hematology Association and the European LeukemiaNet

Raphael Itzykson[1], Pierre Fenaux[1], David Bowen[2], Nicholas C.P. Cross[3], Jorge Cortes[4], Theo De Witte[5], Ulrich Germing[6], Francesco Onida[7], Eric Padron[8], Uwe Platzbecker[9], Valeria Santini[10], Guillermo F. Sanz[11,12], Eric Solary[13,14], Arjan Van de Loosdrecht[15], Luca Malcovati[16], on behalf of the European Hematology Association, the European LeukemiaNet

- **Analysis of 4 genes (ASXL1, NRAS, RUNX1, SETBP1) is mandatory for risk assessment** according to accepted risk scoring systems in patients eligible for transplant.

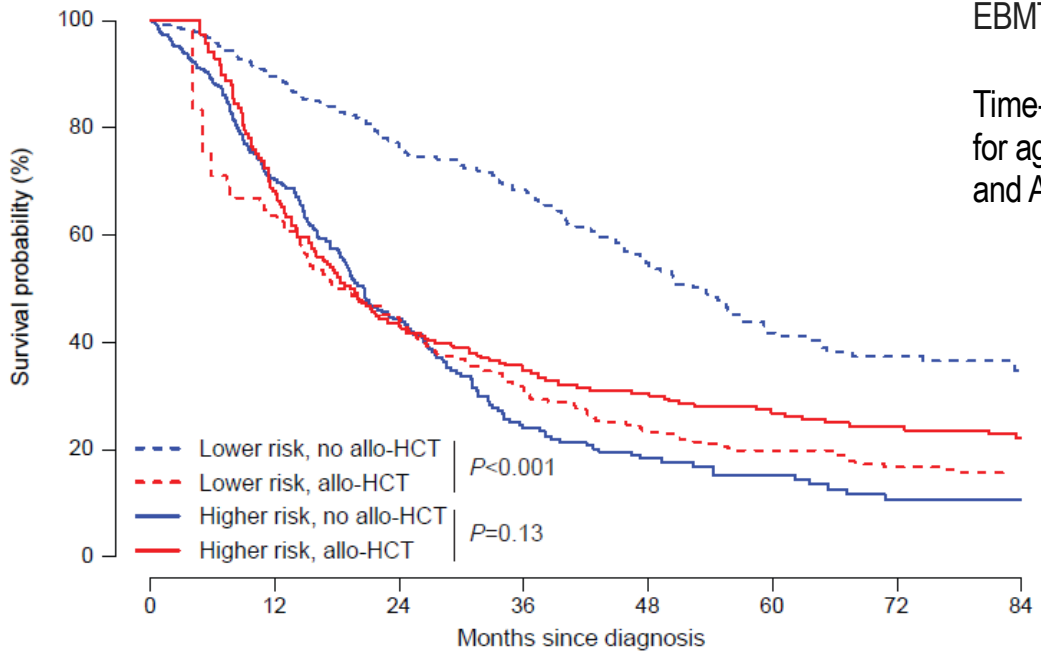
- **Analysis of a minimum of 20 genes is recommended** for patients being considered **for active treatment, including transplantation**.

Recommended minimal Next Generation Sequencing panel in CMML

Gene	Frequency, %	Pathway
TET2	29–61	Epigenetic modifiers
ASXL1	32–44	
DNMT3A	2–12	
EZH2	5–13	
IDH1[a]	1–2	
IDH2[a]	6–7	
BCOR	6–7	
SRSF2	29–52	Spliceosome
U2AF1	4–10	
SF3B1	6–10	
ZRSR2	4–8	
CBL	8–22	Signaling
KRAS	7–16	
NRAS	4–22	
NF1	6–7	
JAK2	1–10	
RUNX1	8–23	Other
SETBP1	4–18	
NPM1[b]	1–3	
FLT3[a,b]	1–3	

Itzykson E et al. HemaSphere 2018

Role of allo-SCT in CMML: an international collaborative analysis



Risk group	N at risk							
Lower-risk, no allo-HCT	386	285	200	145	100	61	45	38
Lower-risk, allo-HCT	0	62	79	76	62	45	31	24
Higher-risk, no allo-HCT	344	184	96	44	29	17	11	8
Higher-risk, allo-HCT	0	113	94	75	62	45	34	29

International CMML Dataset (n=730)
EBMT registry (n=384)

Time-dependent models and a multi-state model (accounting for age, sex, CMML prognostic scoring system at diagnosis, and AML transformation) were applied

Lower-risk : CPSS low or intermediate-1
Higher-risk: CPSS intermediate-2 or high

Performing allo-HCT before AML transformation decreases life expectancy in lower risk patients but may be considered in higher risk patients.

Robin M et al. Blood 2022

Allo-HCT in CMML: current state of the art

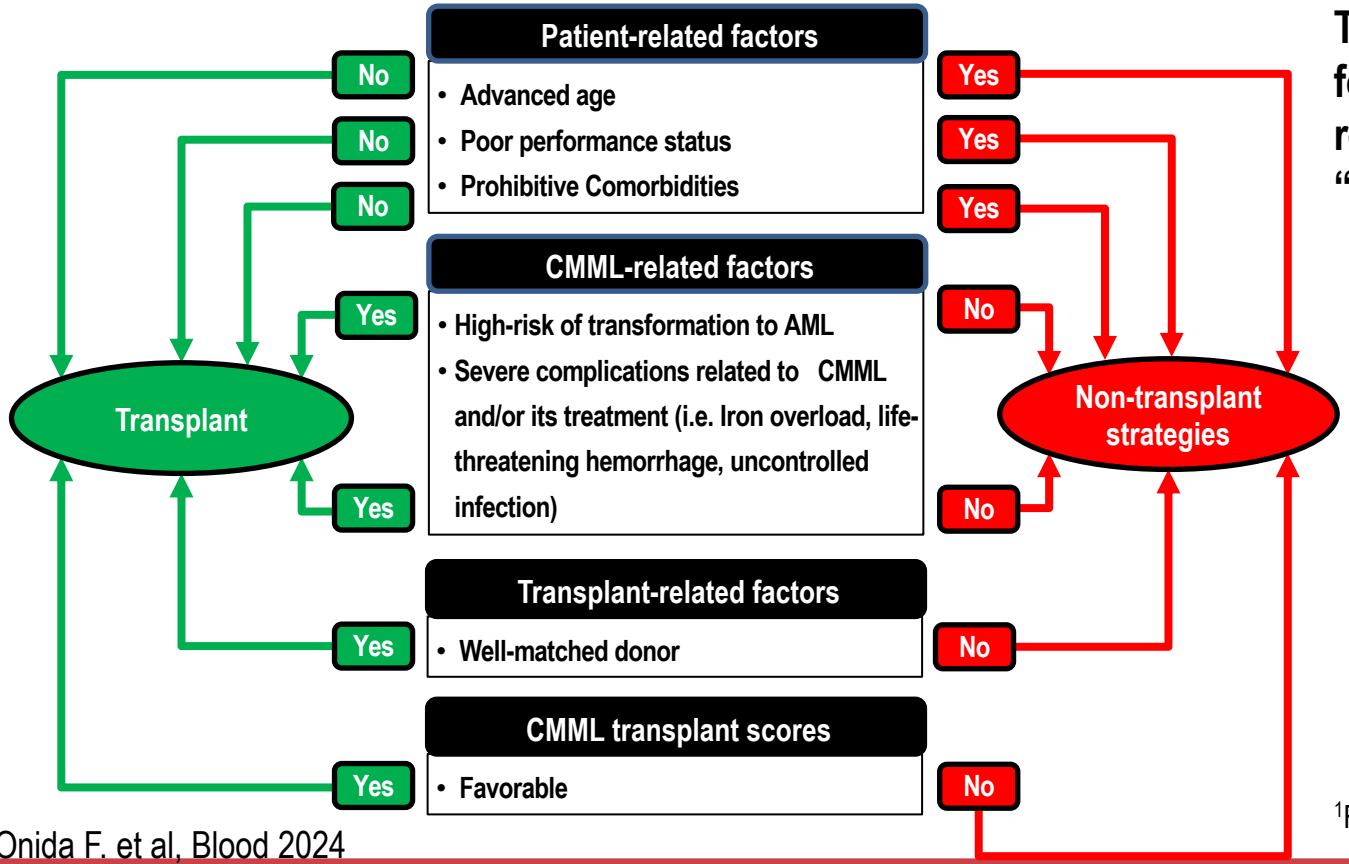
- No prospective clinical trials for allo-HCT in CMML
- High rates of post-HCT relapse rate and NRM in retrospective studies
- Treatment guidelines for CMML are mostly extrapolated from MDS data
- An EBMT survey in 2020 demonstrated large heterogeneity among Centres unveiling the need of practice harmonisation in the field.

Management of adult patients with CMML undergoing allo-HCT: recommendations from the EBMT PH&G Committee

Francesco Onida,[1,2] Nico Gagelmann,[3] Yves Chalandon,[4,5] Guido Kobbe,[6] Marie Robin,[7] Argiris Symeonidis,[8] Theo de Witte,[9] Raphael Itzykson,[10,11] Madlen Jentzsch,[12] Uwe Platzbecker,[12] Valeria Santini,[13] Guillermo Sanz,[14,15] Christof Scheid,[16] Eric Solary,[17,18] Peter Valent,[19,20] Raffaela Greco,[2,21] Isabel Sanchez-Ortega,[2] Ibrahim Yakoub-Agha,[2,22] and Lisa Pleyer[23-26]

- Who are candidates for allo-HCT?
- Do we need to pretreat patients before allo-HCT?
- How do we perform allo-HCT?
- How to manage patients post-allo-HCT?

CMML patient selection for allo-HCT – Fit for transplant?



Onida F. et al, Blood 2024

The panel considers the following factors to be required in patients deemed "fit for transplant":

- Age ≤70 years (in selected cases ≤75)
- ECOG-PS <2 or Karnofsky index ≥70%
- HCT-CI <3
- Lack of any comorbidity that the transplant specialist judges to be incompatible with IC[1]

[1]Ferrara F et al, Leukemia 2013, 27(5): 997-999

CMML Transplant Score

A prognostic score including mutation profile and clinical features for patients with CMML undergoing stem cell transplantation

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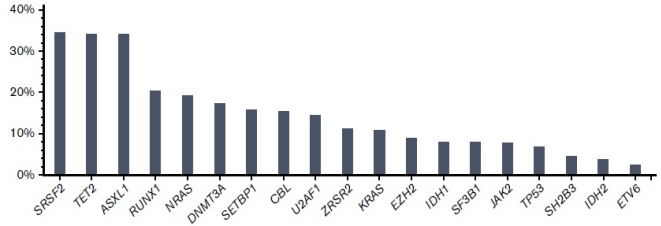
Total cohort = 240 pts
Median age = 59 (19-74)
WHO 0/1/2 = 10%/50%/40%



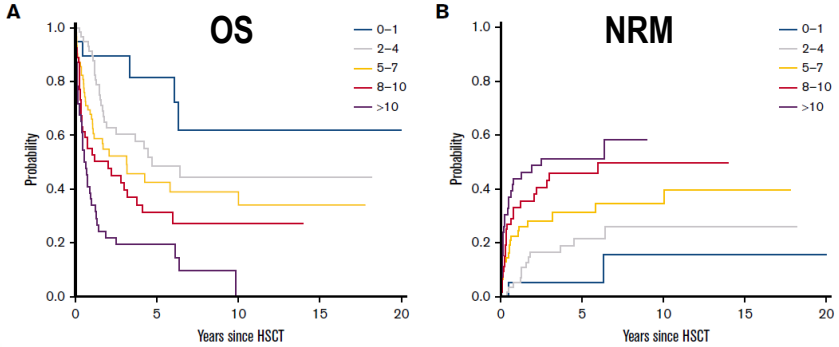


Table 4. Multivariate analysis

Factor	Beta	HR	95% CI	*P*	Points
Continuous comorbidity index	0.15	1.16	1.07-1.25	<.001	1
>2 BM blasts, %	0.53	1.70	1.11-2.61	.02	4
Genotype					
ASXL1- and/or *NRAS*-mutated	0.49	1.63	1.15-2.31	.006	4

Concordance index: 0.68; corrected: 0.67.

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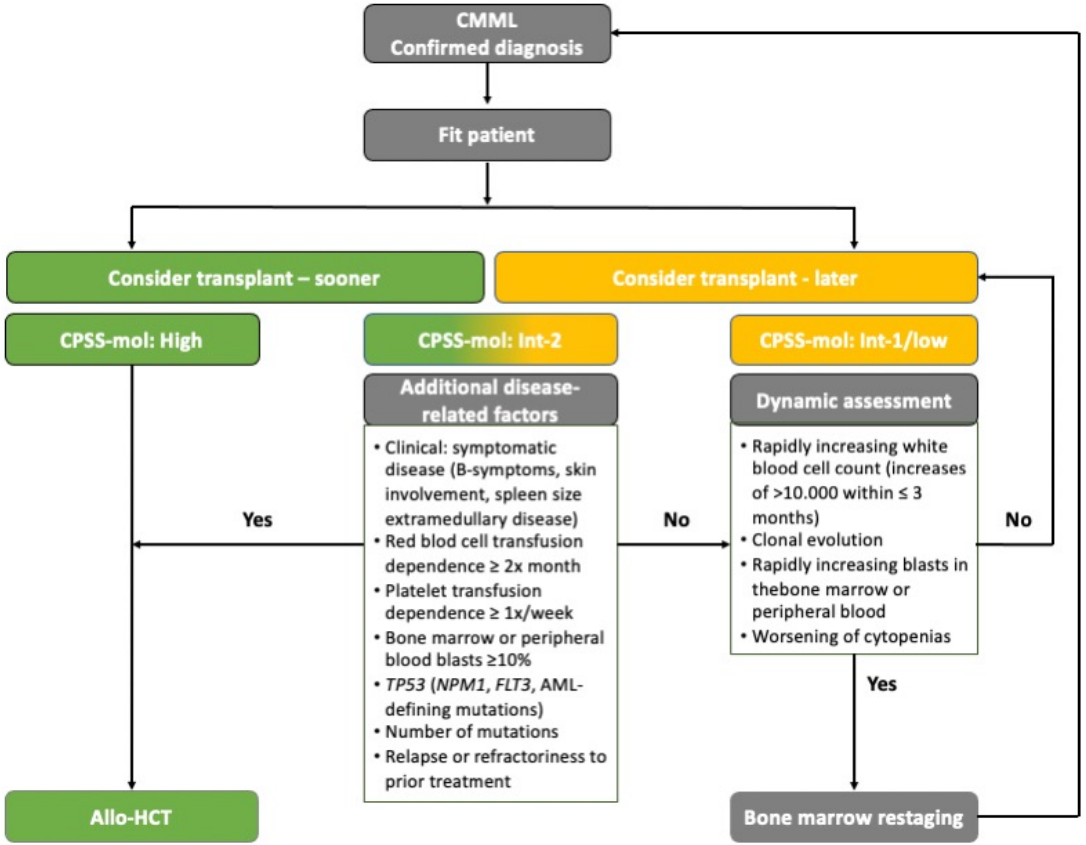
Recommendations: Pt selection and best timing for allo-HCT in CMML



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Role of debulking strategies in CMML

- In absence of data from RCT, remains unclear whether debulking and/or CR status is advantageous for allo-HCT outcomes
- Pre-HCT debulking strategies may result in worsening cytopenias, increased transfusion dependence with ensuing complications and/or infections that may preclude proceeding to transplant
- The primary goal should be to bring eligible patients to transplant in a good general condition, while achieving CR before transplant may be of subordinate importance
- **Upfront transplantation without prior disease-modifying treatment should be preferred whenever possible irrespective of BM blast count** (to maximize chances of reaching allo-HCT)

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Role of pre-transplant therapy

- In the rare cases where pre-transplant treatment is unavoidable (e.g. no matching donor available; rapid disease progression), the use of HMAs is recommended, with allo-HCT performed after establishing the best possible response status

- HMAs might be an option (as bridging strategy or instead of allo-HCT) for selected patients >60 years, with TP53 mutations and/or with complex or monosomal karyotypes

- All patients should be included within clinical trials whenever possible

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Pre-transplant management of disease symptoms

- **Pre-transplant management of (hyper)leukocytosis**: HU-based cytoreduction (with an empiric target of <10.000 WBC/μL) is recommended ≤6 weeks prior to transplant
- **Pre-transplant management of iron overload**: All transplant-eligible CMML patients (ferritin >1000 μg/L) should be considered for iron chelation therapy both pre and post-transplantation
- **Pre-transplant management of massive splenomegaly:** a transplant-coordinated approach including splenectomy, splenic irradiation, or reduction of spleen size with JAK inhibitors is recommended

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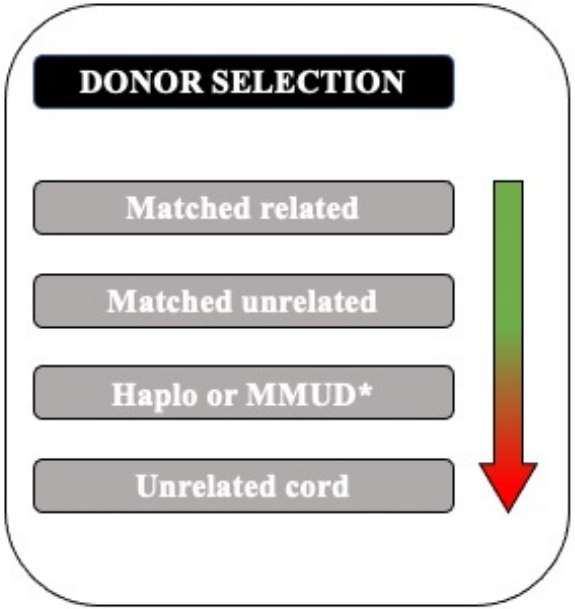
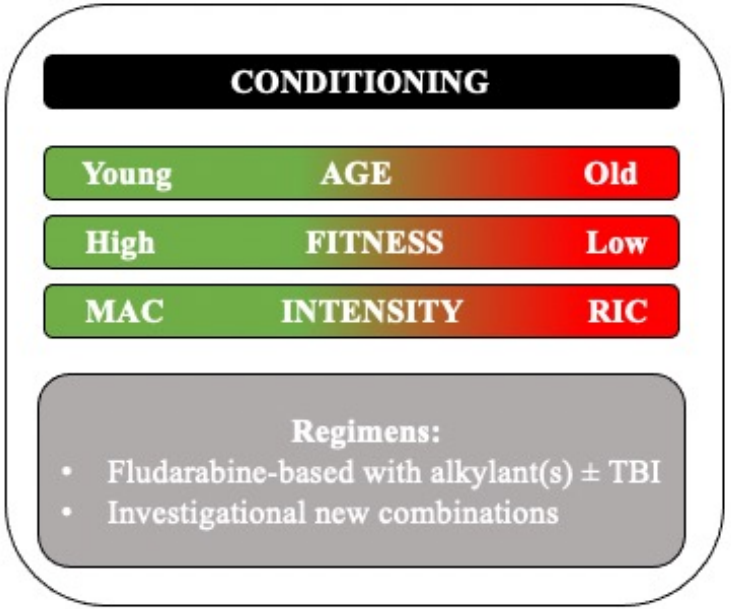
Recommendations for Transplant Modalities





SC Source: PB recommended for MRD and MUD; no recommendation for MMRD

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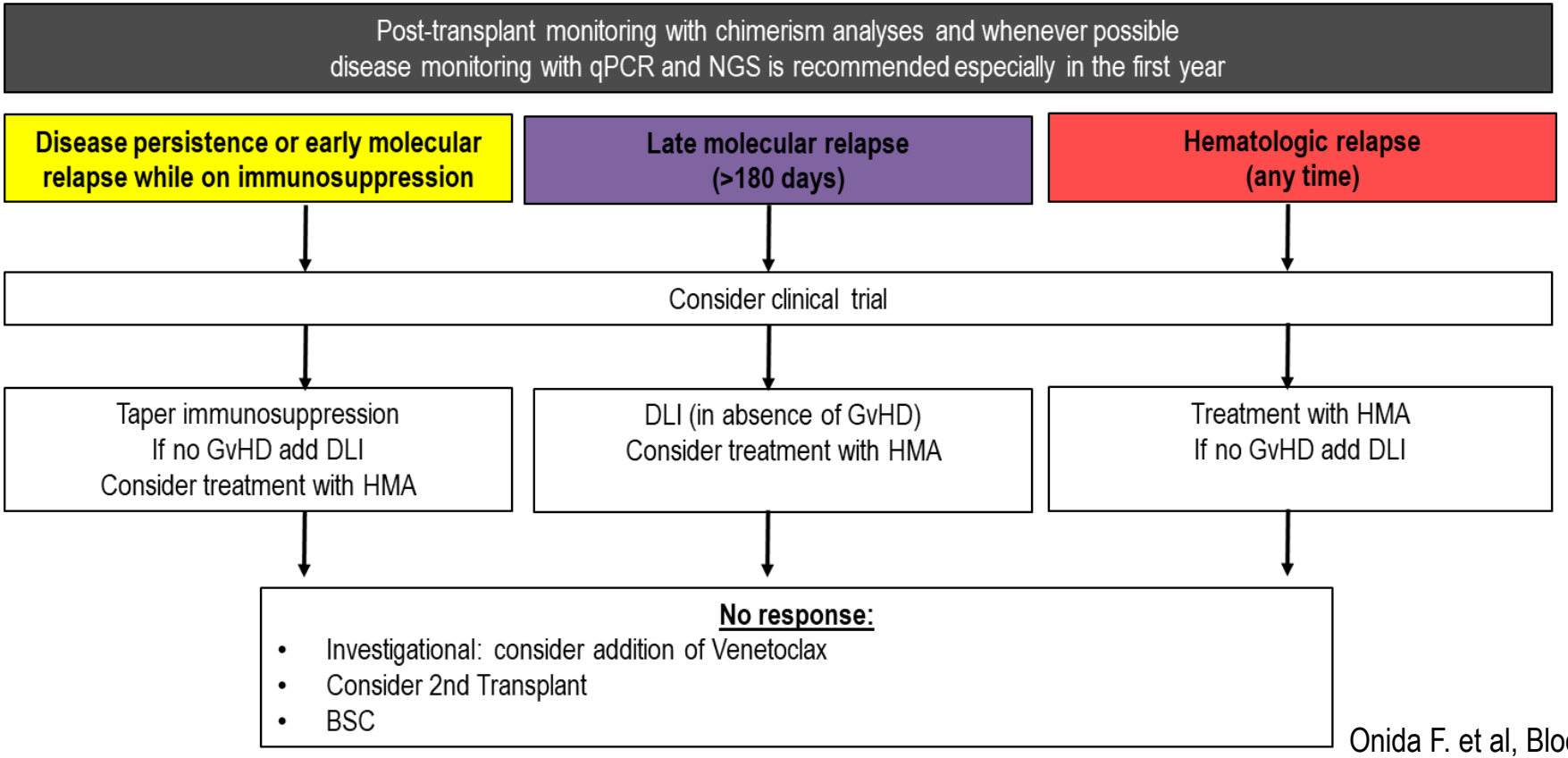
Recommendations for post transplant management in CMML



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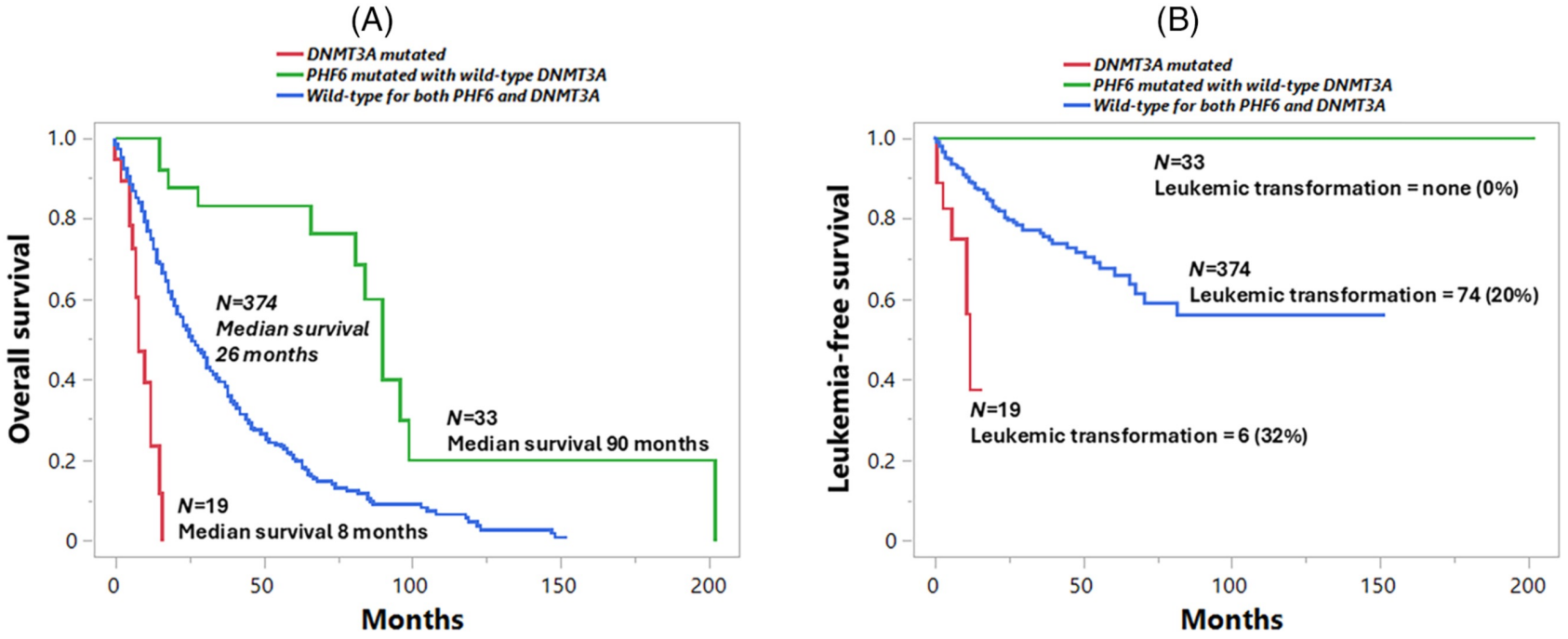
PHF6 mutations in CMML: a distinct phenotype and superior prognosis



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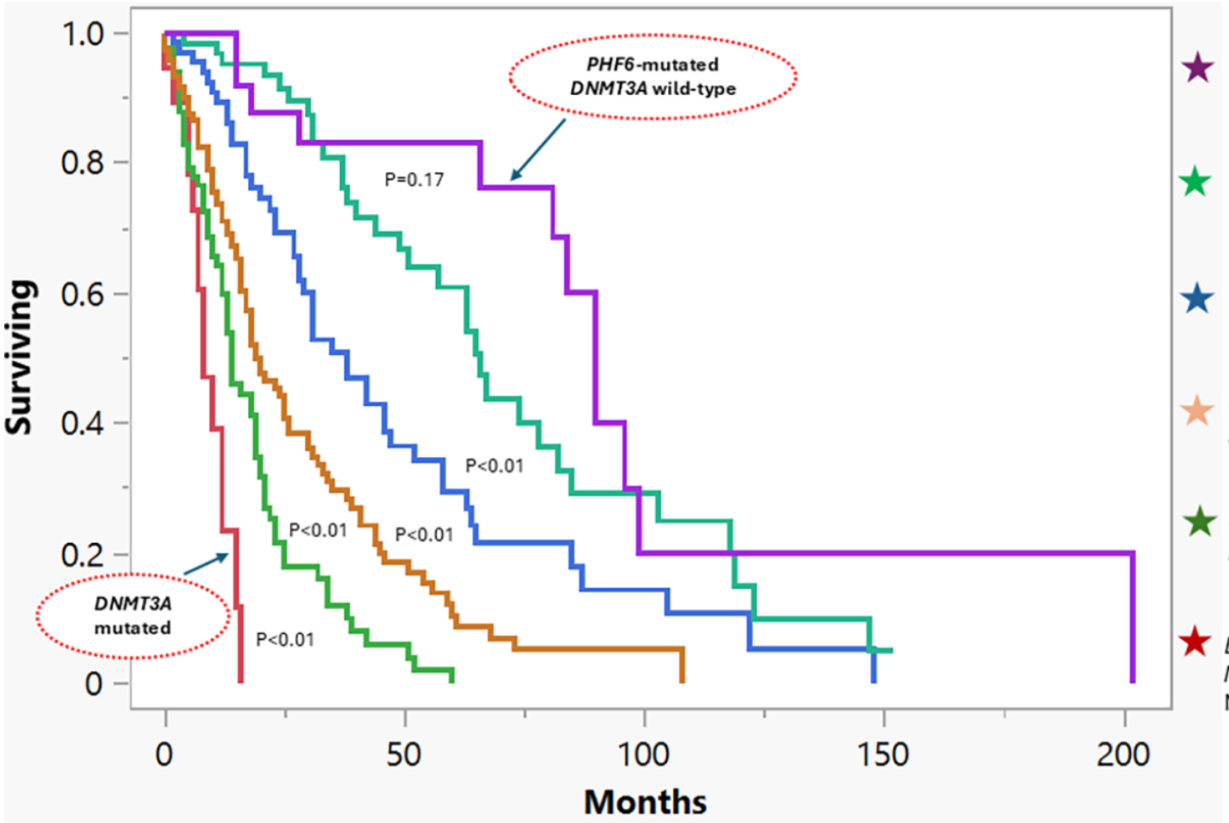
PHF6 mutations in CMML: a distinct phenotype and superior prognosis



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BLAST: A Globally Applicable and Molecularly Versatile Survival Model in Chronic Myelomonocytic Leukemia (CMML)

Context of Research

Allogeneic stem cell transplantation (ASCT) is currently the only treatment that is capable of prolonging survival in CMML but is associated with significant mortality and morbidity.

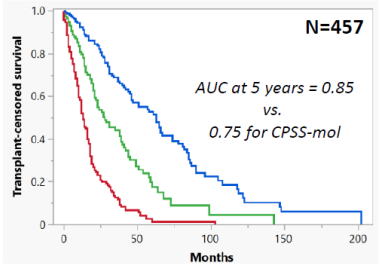
Aim of This Study

The objective was to develop a simple, globally applicable, and molecularly adaptive risk model in CMML that would facilitate patient selection for ASCT.

Findings

BLAST: A Clinical Model

*Circulating **B**lasts ≥2% (1 point),*
__L__eukocyte count ≥13 x 10^9/L (1 point), and
__A__nemia severe (2 points); moderate (1 point)
*based risk **S**tratification __T__ool*



Molecular risk category:

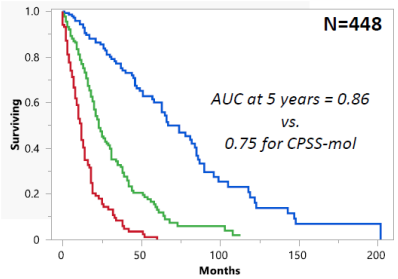
Low: *Favorable without unfavorable mutations/karyotype*
Intermediate: *Neither low nor high*
High: *Unfavorable without favorable mutations/karyotype*

Favorable mutations: *TET2, PHF6*
Unfavorable mutations: *DNMT3A, U2AF1, BCOR, SETBP1, PTPN11, NRAS, RUNX1, ASXL1, TP53*
Unfavorable karyotype: *Abnormal other than LOY or +8*

Low-risk (0 points) N=167 Median 63 months	Low-risk (0-1 points) N=149 Median 74 months
Intermediate-risk (1 point) N=120 Median 28 months	Intermediate-risk (2-3 points) N=149 Median 23 months
High-risk (2-4 points) N=170 Median 13 months	High-risk (4-6 points) N=119 Median 12 months

BLAST-mol: A Clinical-Molecular Model

High molecular risk (2 points)
Intermediate molecular risk (1 point)
Severe anemia (2 points)
Moderate anemia (1 point)
Circulating blasts ≥2% (1 point)
Leukocyte count ≥13 x 10^9/L (1 point)



Conclusions: BLAST is a new and externally validated risk model in CMML which employs easily accessible clinical risk factors and with predictive performance comparable to that of the molecularly-enhanced CMML-specific scoring system (CPSS-mol). The molecular version of BLAST (BLAST-mol) was also externally validated and integrates prognostically relevant genetic information.

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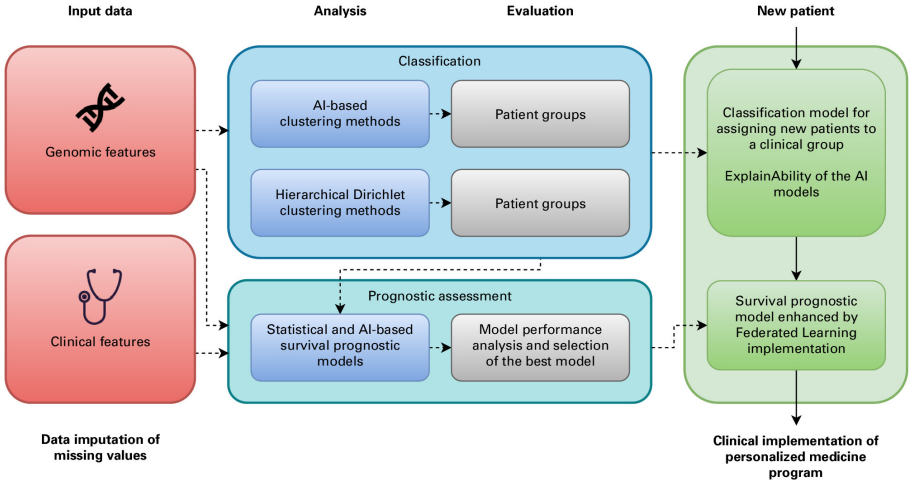
A Molecular-Based Ecosystem to Improve Personalized Medicine in Chronic Myelomonocytic Leukemia

Luca Lanino, AM Hunter, N Gagelmann, M Robin, C Sala, D Dall'Olio, C Gurnari, L Dall'Olio, YH Wang, L Pleyer, B Xicoy, G Montalban-Bravo, LY Shih, T Haque, O Abdel-Wahab, K Geissler, A Bataller, A Bazinet, M Meggendorfer, I Casetti, E Sauta, E Travaglino, L Palomo, L Zamora, D Quintela, A Jerez, E Cornejo, PG Martin, Marina Diaz-Beya, Alejandro Avendano Pita, Veronica Roldan, Dolly Viviana Fiallo Suarez, Estefania Cerezo Velasco, Marisa Calabuig, Esperanza Such, Guillermo Sanz, AS Kubasch, C Castilla-Llorente, C Bulabois, L Souchet, H Awada, M Bernardi, P Chiusolo, A Curti, L Giaccone, F Onida, LM Borin, F Passamonti, E Diral, V Vucinic, GM Bergonzi, MT Voso, HA Hou, WC Chou, CY Yao, CC Lin, HF Tien, A Campagna, M Ubezio, A Russo, G Todisco, G Maggioni, CA Tentori, A Buizza, G Asti, M Zampini, E Riva, M Delleani, A Consagra, F Ficara, A Santoro, L Carota, T Sanavia, C Rollo, A Kiwan, J VanOudenhove, P Fariselli, NH Al Ali, D Sallman, W Kern, G Garcia-Manero, S Thota, EA Griffiths, M Yung Follo, C Finelli, U Platzbecker, F Sole, M Diez-Campelo, J Maciejewski, R Bejar, FR Thol, N Kroger, P Fenaux, R Itzykson, TA Graubert, M Fontenay, AM Zeidan, RS Komrokji, V Santini, T Haferlach, U Germing, S D'Amico, G Castellani, MM Patnaik, E Solary, **E Padron, MG Della Porta**



An innovative AI-based framework for multi-modal analysis, classification and personalized prognostic assessment in hematology

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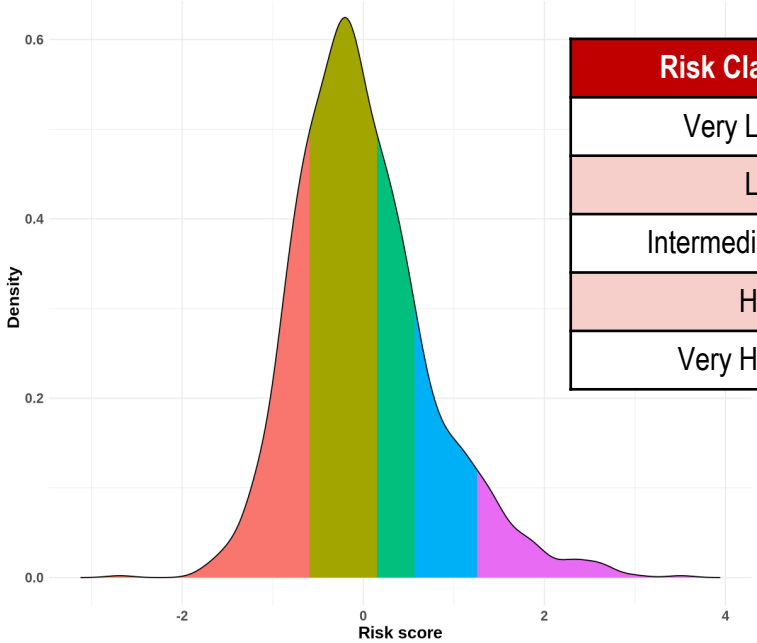
Development of the International CMML Prognostic Score (iCPSS)

- **Laboratory parameters:**
  - WBC
  - Hb
  - PLT
  - BM Blasts
- **CPSS cytogenetic stratification**
- **Mutational status (n=9)**
  - *ASXL1*
  - *DNMT3A*
  - *EZH2*
  - *RUNX1*
  - *SETBP1*
  - *STAG2*
  - *TET2*
  - *TP53*
  - *U2AF1*



Risk Class	Risk Score	%
Very Low	< -0.594	21%
Low	[-0.594, 0.147]	43%
Intermediate	[0.147, 0.566]	18%
High	[0.566, 1.258]	12%
Very High	≥1.258	7%

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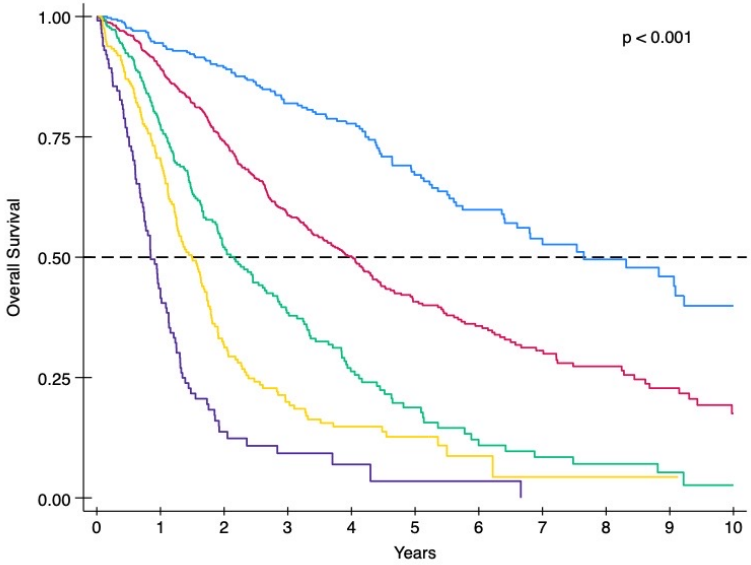
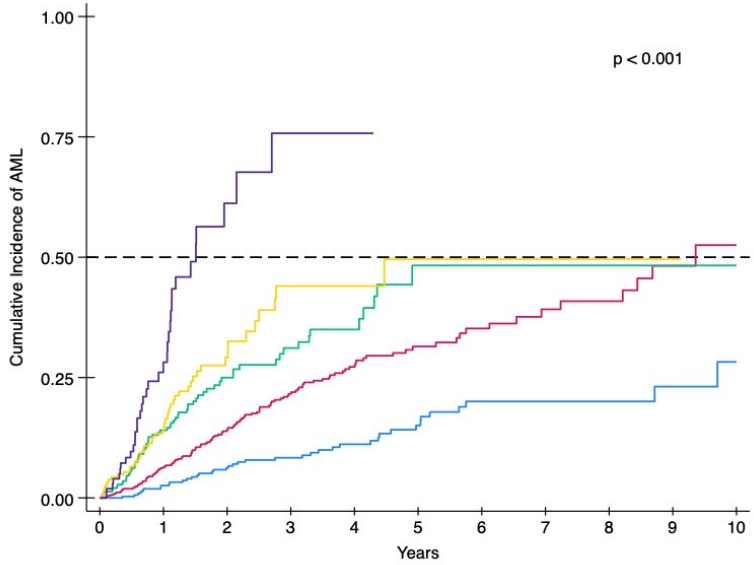
iCPSS performances





Very Low Low Intermediate High Very High

	C-INDEX
iCPSS	0.75
CPSS-mol[1]	0.63
GFM[2]	0.60
MMM[3]	0.61

By courtesy of M. Della Porta

	C-INDEX
iCPSS	0.71
CPSS-mol[1]	0.62
GFM[2]	0.59
MMM[3]	0.58

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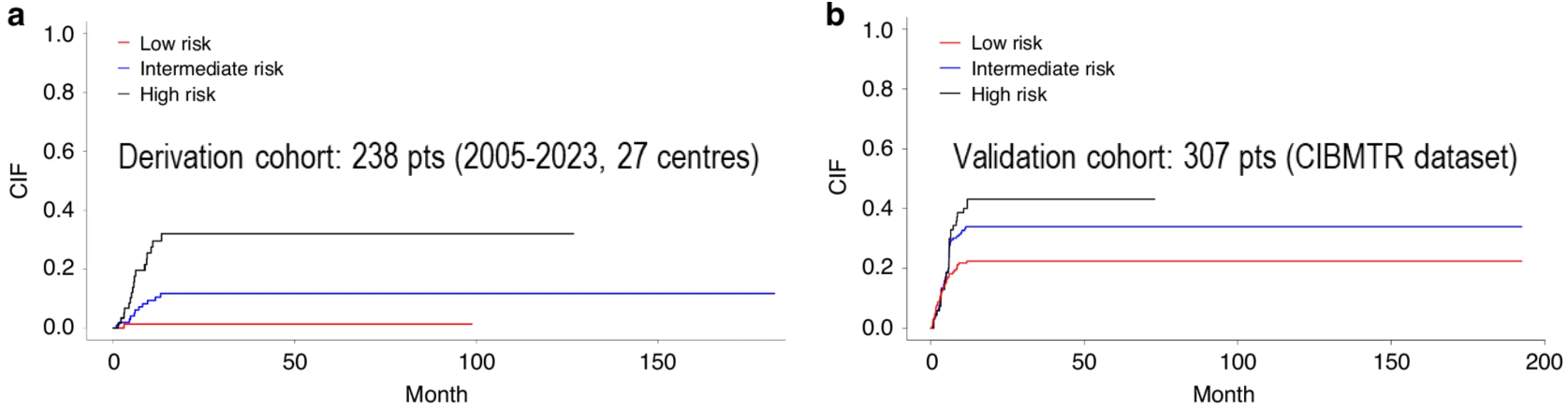
Prediction scoring system for early relapse in CMML patients after allo-HCT

Variables	Multivariate regression coefficient	HR	95% CI	*P*	Point
Bone marrow blasts before transplantation >10%	1.450	4.262	1.334, 13.617	0.014	1
Age >60 years	1.828	6.221	1.655, 23.390	0.007	1.5
Hemoglobin level before transplantation <100 g/L	1.307	3.695	1.512, 9.031	0.004	1
Non TET2	1.231	3.425	1.241, 9.450	0.017	1

low-risk: risk score 0–1; intermediate-risk score 1.5–2; high-risk score >2



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Unanswered questions and further research to do

- Lack of dynamic evaluation methods for patient selection for allo-HCT
- Role of gene mutations in selecting patients and in predicting post-HCT outcomes
- Role of new drugs and combinations as pre-transplant strategies
- Impact of disease burden at allo-HCT
- Management of splenomegaly before transplantation
- Role of haplo-identical donors
- Role of TBI in conditioning
- Post-transplant MRD monitoring (NGS?)
- Management of molecular and hematological relapse
- Possible role of post-transplant prophylactic treatment

EBMT

A new proposal:
Observational Non-Interventional Study on the Role of Allogeneic Hematopoietic Cell Transplantation (allo-HCT) in Chronic Myelomonocytic Leukemia (CMML)

"ChroMM-Allo Study"

F.Onida, M. Robin, D. Mc Lornan et al. EBMT-CMWP

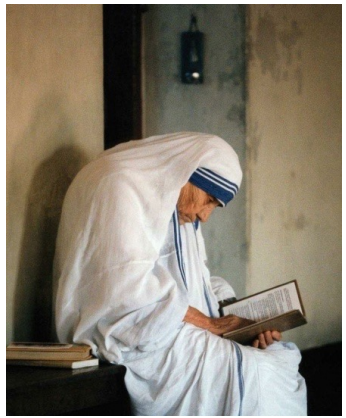
Acknowledgements

Thanks!

Any questions?

- **FISiM**
- **EBMT-CMWP**
- **MDACC Leukemia Dept**
- **International CMML Consortium**
- **MDS/MPN-IWG**
- **EHA-ELN**
- **International CMML Working conference**

"I would rather make mistakes in kindness and compassion than work miracles in unkindness and hardness"



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